The nosology of hereditary cerebellar ataxias: 
Development of a classification for recessive ataxias 
and phenotypical description of Spinocerebellar ataxia 
34 

Mémoire 

Marie Beaudin 

Maîtrise en épidémiologie - épidémiologie clinique - avec mémoire 
Maître ès sciences (M. Sc.) 

Québec, Canada 

© Marie Beaudin, 2019
The nosology of hereditary cerebellar ataxias
Development of a classification for recessive ataxias and phenotypical description of Spinocerebellar ataxia 34

Mémoire

Marie Beaudin

Sous la direction de :

Nicolas Dupré, directeur de recherche
Danielle Laurin, codirectrice de recherche

© Marie Beaudin 2019
Résumé

Les ataxies cérébelleuses héréditaires causent une atteinte progressive de l’équilibre et de la marche. Malgré l’amélioration de la performance et de l’accessibilité des tests génétiques, environ la moitié des patients demeurent sans diagnostic précis, ce qui a un impact sur la prise en charge. Dans ce mémoire de maîtrise, nous abordons l’enjeu du sous-diagnostic chez les patients atteints d’ataxie cérébelleuse via l’élaboration d’une nouvelle classification pour les ataxies récessives et la caractérisation détaillée de l’ataxie spinocérébelleuse 34.

Le premier chapitre est une revue systématique de la littérature concernant les ataxies récessives. Au total, 2354 références et 130 articles complets ont été révisés afin d’identifier un groupe de 45 pathologies récessives où l’atteinte cérébelleuse est au cœur du phénomène et 29 pathologies multisystémiques additionnelles où l’ataxie est un élément secondaire, mais qui devraient être incluses dans le diagnostic différentiel du patient ataxique.

Le deuxième chapitre présente les résultats d’un groupe de travail dédié à la classification des ataxies récessives. En se basant sur les résultats de la revue systématique, 12 experts internationaux se sont entendus sur des critères d’inclusion ainsi que sur deux classifications basées sur la symptomatologie clinique et les mécanismes cellulaires impliqués. Une approche clinique au patient ataxique est proposée.


Un système de classification basé sur des descriptions phénotypiques étoffées est essentiel pour les cliniciens et les chercheurs afin d’organiser adéquatement les groupes de maladies complexes. Le travail présenté constitue une avancée concrète pour améliorer l’approche diagnostique aux patients avec ataxie héréditaire.
Abstract

Hereditary cerebellar ataxias are neurodegenerative disorders associated with progressive motor incoordination and gait imbalance. Despite significant progress in the availability and performance of genetic tests, around half of patients remain without a molecular diagnosis, which has major counselling and management consequences. In this master thesis, we address the issue of underdiagnosis in patients with hereditary ataxias through the development of a novel classification system for recessive cerebellar ataxias and the in-depth characterization Spinocerebellar ataxia 34.

The first chapter is a systematic review of the literature regarding recessive cerebellar ataxias. We revised 2354 references and 130 full-text articles to identify a group of 45 recessive disorders in which cerebellar ataxia is at the core of the clinical phenotype and 29 additional complex or multisystem disorders where ataxia is a secondary feature and which should be included in the differential diagnosis of ataxia.

The second chapter presents the work of a dedicated task force on the classification of recessive cerebellar ataxias. Based on the results of the systematic review, 12 international ataxia experts agreed on revised inclusion criteria and on classifications based on clinical symptoms and pathogenic cellular mechanisms. We also propose a general clinical approach to the ataxic patient.

The third chapter shows the clinical and biochemical characterization of a rare dominant ataxia, Spinocerebellar ataxia 34 caused by ELOVL4 mutations. We studied a multi-generational family with a late-onset cerebellar syndrome associated with executive deficits, and apparent visuospatial, attention, and psychiatric dysfunction. Immunohistochemistry of dermal fibroblasts showed the first evidence of ELOVL4 protein pathology in this disorder with mislocalization and aggregation of the protein.

Classification systems based on detailed phenotypic descriptions are essential for both clinicians and researchers to understand complex groups of disorders. The work presented here advances our understanding of hereditary ataxias and constitutes a pragmatic diagnostic tool for clinicians.
Table des matières

Résumé................................................................................................................................. ii
Abstract ................................................................................................................................. iii
Table des matières................................................................................................................. iv
Liste des abréviations........................................................................................................... vi
Remerciements ....................................................................................................................... x
Avant-propos ........................................................................................................................ xi
Introduction ............................................................................................................................. 1

Chapter 1 Reviewing the evidence: a systematic scoping review of the literature on recessive
cerebellar ataxias .................................................................................................................... 7
  1.1 Résumé ............................................................................................................................ 7
  1.2 Abstract .......................................................................................................................... 8
  1.3 Background .................................................................................................................... 9
  1.4 Methods ......................................................................................................................... 10
  1.5 Results ........................................................................................................................... 11
  1.6 Discussion ...................................................................................................................... 12
  1.7 Conclusion ...................................................................................................................... 14
  1.8 Tables ............................................................................................................................ 14
  Table 1.1 Proposed new list of autosomal recessive ataxias ................................................... 14
  Table 1.2 Other complex movement or multisystem recessive disorders that have prominent
  ataxia ..................................................................................................................................... 16
  Table 1.3 Recessive disorders that may occasionally present with ataxia, but where ataxia is a
  secondary feature ............................................................................................................... 18
  1.9 Figures ........................................................................................................................... 19
  Figure 1.1 Flow diagram .................................................................................................... 19
  Figure 1.2 Clinical algorithm of autosomal recessive ataxias ............................................... 20
  1.10 Supplementary material ............................................................................................. 20
  Search strategy for MEDLINE/Pubmed ............................................................................. 20
  1.11 References .................................................................................................................. 21

Chapter 2 Building a conceptual framework: a new classification for recessive cerebellar ataxias . 30
  2.1 Résumé .......................................................................................................................... 30
  2.2 Abstract ........................................................................................................................ 31
  2.3 Introduction .................................................................................................................... 31
  2.4 Methods ........................................................................................................................ 33
  2.5 Results ........................................................................................................................... 34
  2.6 Discussion ...................................................................................................................... 39
  2.7 Conclusion ...................................................................................................................... 41
  2.8 Tables ............................................................................................................................ 41
  Table 2.1 Primary recessive cerebellar ataxias .................................................................... 41
Table 2.3 Other metabolic or complex recessive disorders that have ataxia as an associated feature ................................................................. 45
2.9 Figures .................................................................................. 48
- Figure 2.1 Clinical classification of autosomal recessive ataxias .................................................................................. 48
- Figure 2.2 Graphical summary of the clinical approach to a patient presenting with ataxia ........................................ 49
- Figure 2.3 Classification of autosomal recessive ataxias according to molecular pathogenesis ........................................ 50
2.10 References ........................................................................... 51

Chapter 3 Contributing to the evidence: the phenotypical description of a cerebellar ataxia in the French-Canadian population ................................................................. 64
3.1 Résumé .................................................................................. 64
3.2 Abstract ............................................................................... 65
3.3 Introduction ......................................................................... 66
3.4 Methods ............................................................................... 68
3.5 Results ................................................................................ 70
3.6 Discussion ........................................................................... 73
3.7 Conclusion .......................................................................... 75
3.8 Tables .................................................................................. 76
- Table 3.1 Detailed neurological findings in affected individuals with ELOVL4 mutations ........................................ 76
- Table 3.2 Results of the clinical evaluation in SCA34 patients and controls ......................................................... 76
- Table 3.3 Clinical and paraclinical characteristics of patients with mutations in ELOVL4 in present and previous studies ................................................................. 77
3.9 Figures .................................................................................. 78
- Figure 3.1 Pedigree of a French-Canadian Family with the c.504 G>C mutation in ELOVL4 ........................................ 78
- Figure 3.2 Dermatologic lesion in a SCA34 patient ........................................ 78
- Figure 3.3 Neuroimaging findings in patients with the c.504 G>C mutation in ELOVL4 ........................................ 79
- Figure 3.4 Impaired copy of the RCFT in three patients with the c.504 G>C mutation in ELOVL4 ........................................ 80
- Figure 3.5 Immunofluorescence staining of dermal fibroblasts from a SCA34 patient compared with fibroblasts from a healthy control ........................................ 81
3.10 Supplementary Material ............................................................... 82
3.11 References .......................................................................... 83

Conclusion .................................................................................. 86

Bibliographie ............................................................................ 92
Liste des abréviations

ACPHD ataxia, combined cerebellar and peripheral with hearing loss and diabetes mellitus
ALS Amyotrophic lateral sclerosis
AOA ataxia with oculomotor apraxia; ARCA autosomal recessive cerebellar ataxia
ARSACS autosomal recessive spastic ataxia of Charlevoix-Saguenay
AT ataxia-telangiectasia
ATLD ataxia-telangiectasia-like disorder
AVED ataxia with vitamin E deficiency
BVVLS2 Brown-Vialetto-Van Laere syndrome type 2
CA Cayman ataxia
CAMOS cerebellar ataxia mental retardation optic atrophy and skin abnormalities
CAMRQ cerebellar ataxia mental retardation with or without quadrupedal locomotion
CCAS cerebellar cognitive-affective syndrome
CDG congenital disorder of glycosylation
CI confidence interval
CLN neuronal ceroid lipofuscinosis
CMT Charcot-Marie-Tooth
COACH cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis
DCMA dilated cardiomyopathy with ataxia
DES disequilibrium syndrome
DTR deep tendon reflexes
EOAH early-onset ataxia with oculomotor apraxia and hypoalbuminemia
EKV erythrokeratodermia variabilis
EPM progressive myoclonic epilepsy
FAHN fatty acid hydroxylase-associated neurodegeneration
FDG-PET [18F]-fluorodeoxyglucose positron emission tomography
FRDA Friedreich ataxia
GMS Galloway-Mowat syndrome
IMNEPD infantile-onset multisystem neurologic, endocrine, and pancreatic disease
IOSCA infantile onset spinocerebellar ataxia
LIKNS Lichtenstein-Knorr syndrome
MC3DN2 mitochondrial complex III deficiency, nuclear type 2
MGCA5 3-methylglutaconic aciduria type 5
MIRAS mitochondrial recessive ataxia syndrome
MCSZ microcephaly seizures developmental delay
MMSE Mini-Mental State Examinsation
MMYAT mitochondrial myopathy and ataxia
MoCA Montreal Cognitive Assesssment
MSS Marinesco-Sjogren syndrome
MTDPS7 mitochondrial DNA depletion syndrome 7
NBIA neurodegeneration with brain iron accumulation
PBD peroxisome biogenesis disorder
PC Purkinje cell
PCH pontocerebellar hypoplasia
PEOA3 progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant 3
PHARC polyneuropathy hearing loss ataxia retinitis pigmentosa and cataract
RCFT Rey complex figure test
SANDO sensory ataxic neuropathy with dysarthria and ophthalmoparesis
SCA spinocerebellar ataxia
SCAE spinocerebellar ataxia with epilepsy
SCAN1 spinocerebellar ataxia with axonal neuropathy 1
SCAR spinocerebellar ataxia, autosomal recessive
SPAX spastic ataxia
SeSAME seizures sensorineural deafness ataxia mental retardation and electrolyte imbalance
SNVs single nucleotide variants
SPAX spastic ataxia
SPG spastic paraplegia
UMN upper motor neuron
WES Whole exome sequencing
WGS Whole genome sequencing
À Hugo, qui me pousse à me dépasser tous les jours
À Isabelle, qui m’apprend à grandir de chaque revers
Every patient you see

is a lesson in much more

than the malady from which he suffers.

- Sir William Osler
Remerciements

Je tiens à remercier de tout cœur mon directeur de recherche, Dr Nicolas Dupré, qui m’a accompagnée dans tout le cheminement de ma maîtrise, depuis le début de mon implication en recherche jusqu’à la révision de mes articles et de ce mémoire. Merci de m’avoir guidée sur plusieurs aspects de la conciliation médecine et recherche et d’avoir été un véritable mentor pour m’initier à la recherche et à la neurologie. Un immense merci également à ma co-directrice de recherche, Dre Danielle Laurin, pour son appui soutenu et généreux dans la progression de ma maîtrise ainsi que pour ses conseils judicieux et opportuns. Merci de m’avoir accompagnée dans les imprévus de ce long processus et merci de votre grande compréhension face à mon parcours atypique. Finalement, merci à tous les collaborateurs avec lesquels j’ai travaillé pour la réalisation des projets qui composent ce mémoire de maîtrise, ce fut un grand plaisir de travailler et d’apprendre avec vous.
Avant-propos

Les travaux de ce mémoire de maîtrise ont été rendus possible grâce à une Bourse d'études supérieures du Canada au niveau de la maîtrise Frederick-Banting et Charles-Best octroyée par les Instituts de Recherche en Santé du Canada.

Le premier article inséré dans ce mémoire « Systematic review of autosomal recessive ataxias and proposal for a classification » a été soumis au journal Cerebellum & Ataxias le 22 novembre 2016, a été accepté le 17 février 2017 et a été publié dans ce journal le 23 février 2017. La version intégrée de l’article est identique à la version publiée. J’étais première auteure sur cet article et mon rôle a été de définir la méthode en élaborant la stratégie de recherche et les critères d’inclusion, de réaliser la revue systématique et d’écrire l’article. Les co-auteurs étaient Dr Christopher J. Klein, Dr Guy A. Rouleau et Dr Nicolas Dupré, qui ont tous contribué par un apport intellectuel à l’orientation de l’article et à la révision du manuscrit final. L’article est présenté tel que publié. Une bourse pour publication comme première auteure a été octroyée par la Faculté des études supérieures et postdoctorales suite à la publication de cet article.

Le deuxième article inséré dans ce mémoire « The Classification of Autosomal Recessive Cerebellar Ataxias: A consensus statement from the Society for Research on the Cerebellum and Ataxias Task Force » a été soumis au journal The Cerebellum le 30 décembre 2018 et est toujours en processus de révision. J’étais première auteure sur cet article et mon rôle a été de compléter la revue systématique jusqu’à la période d’octobre 2018 en utilisant la méthodologie préalablement développée, d’extraire les données cliniques, épidémiologiques et moléculaires, de développer les classifications et d’écrire l’article en intégrant les apports intellectuels des autres co-auteurs. Les autres co-auteurs étaient Dr Antoni Matilla-Dueñas, Dr Bing-Weng Soong, Dr Jose Luiz-Pedroso, Dr Orlando G. Barsottini, Dr Hiroshi Mitoma, Dr Shoji Tsuji, Dr Jeremy D Schmahmann, Dr Mario Manto, Dr Guy A. Rouleau, Dr Christopher Klein et Dr Nicolas Dupré qui ont tous fourni un apport intellectuel au contenu et commenté l’article final. L’article est présenté tel que soumis.

Le troisième article inséré dans ce mémoire « Characterization of the phenotype with neurocognitive impairment and protein mislocalization in ELOVL4-associated Spinocerebellar ataxia 34 » a été soumis au journal JAMA Neurology le 4 avril 2019 et est toujours en processus de révision. J’étais première auteure sur cet article et mon rôle a été de réviser la littérature pertinente, de participer à l’évaluation des patients et à la collecte de données, de réaliser les analyses statistiques portant sur les analyses cognitives, et d’écrire l’article. Les co-auteurs étaient Dre Leila
Sellami et Dr Robert Laforce qui ont réalisé les évaluations cognitives des patients, Christian Martel, Lydia Touzel-Deschènes et Dr François Gros-Louis qui ont réalisé les analyses immunohistochimiques sur les fibroblastes, Gabrielle Houle et Dr Guy A. Rouleau qui ont procédé aux analyses génétiques, ainsi que Dre Laurence Martineau, Dr Kevin Lacroix, Dre Andréane Lavallée, Dr Nicolas Chrestian qui ont contribué à l’évaluation des participants. Dr Nicolas Dupré a recruté les participants et supervisé la réalisation du projet. Tous les auteurs ont donné leurs commentaires sur le texte final. Le texte, les tableaux et les figures contenus dans le matériel supplémentaire de la publication ont été intégrés à l’article pour la présentation dans ce mémoire de maîtrise et des corrections mineures au contenu du texte ont été effectuées suite à la révision.
Introduction

Ataxia comes from the greek a-, meaning not or absence of, and taxis, meaning order or arrangement. It refers to the loss of balance and coordination affecting gait and limb movements that results from lesions to the cerebellum or, occasionally, to the sensory or vestibular pathways. Cerebellar ataxia may result from a variety of acute and chronic insults to the cerebellum, including stroke, tumor, infection, toxin, trauma, vitamin deficiencies, hypothyroidism, auto-immune processes, and hereditary genetic mutations. Hereditary cerebellar ataxias present with progressive onset of gait imbalance leading to falls, incoordination of hands and feet, eye movement abnormalities, slurred speech, and difficulty swallowing. In addition to these frequent motor symptoms, patients may present with a wide variety of neurologic and multisystem involvement, depending on the mutated gene. Hereditary ataxias are divided according to the mode of inheritance based on family history, with autosomal dominant and recessive ataxias as the most frequent forms, while X-linked and mitochondrial mutations are much rarer (1, 2).

Hereditary cerebellar ataxias are individually rare diseases, but their pooled prevalence represents a significant number of affected patients. A recent systematic review with meta-analysis of international prevalence studies evaluated the global prevalence of hereditary ataxias at 9,8 per 100 000 population (95% confidence interval (CI) 6,7 - 12,8/10^5) (3). Specifically, the estimated prevalence for autosomal dominant ataxias was 2,7 per 100 000 population (95% CI 1,5 - 4,0/10^5), and for recessive ataxias, 3,3 per 100 000 (95% CI 1,7 - 4,9/10^5). These global estimates were limited by high heterogeneity between studies with an I² value over 98,5% for all estimations. This heterogeneity was manifest in the very large range of prevalence estimates across studies, which varied between 0,0 to 5,6 per 100 000 population for dominant ataxias with highest prevalence in Portugal, Norway, and Japan, while for recessive ataxias, the prevalence varied between 0,0 to 7,2 per 100 000 population, with highest estimates in Cantabria and Alsace. This heterogeneity was attributed to different genetic backgrounds across geographical areas as well as different case ascertainment methods and inclusion criteria across studies. Hence, the prevalence of hereditary ataxias appears highly variable with clusters of higher prevalence in specific geographical areas or founder populations, but the global prevalence does represent a significant health concern.

Hereditary ataxias lead to considerable morbidity and mortality for affected patients. Studies of patients affected with dominant ataxias have shown that health-related quality of life is significantly impaired and deteriorates with time based on measurements with the EuroQol Five Dimensions Questionnaire and SF-36 General Health Questionnaire. Of interest, the severity of lost quality of
life was associated with the severity of the clinical involvement and depended on the presence of a carer (4, 5). Other studies in patients with Friedreich ataxia, the most prevalent recessive ataxia, have also shown lower health-related quality of life in children and adults affected with ataxia (6, 7). As regards mortality, according to the World Health Organization data for the European Union, the age-adjusted mortality rate attributable to hereditary ataxias was 0.50 per 1,000,000 population (95% CI 0.42 - 0.57) in the time period between 2000 and 2012. This rate was slightly superior for men than for women, and appeared to increase over the time period studied (8).

Hereditary ataxias also represent a significant economic burden for society, the health and social care sector, caregivers and patients. A recent economic analysis from the United Kingdom and Germany of patients living with Friedreich ataxia estimated that the total annual cost was 18,774 € ($≈28,500) (9). This included direct medical expenses for prescription medications, outpatient consultations, and hospitalisations, along with direct non-medical costs, notably for professional caregiver support, and finally long-term adaptation of accommodation and mobility. The most important cost associated with the disorder was that associated with long-term unemployment or work loss since Friedreich ataxia typically begins in teenage or young adulthood.

Despite major genetic advances in the last decades that led to the discovery of over 40 mutated genes involved in dominant ataxias (10), and as many in recessive ataxias, a large number of patients remain without a specific genetic diagnosis. In the systematic review of prevalence studies by Ruano et al. (3), 20 to 92% of patients with a suspected dominant hereditary ataxia and 37 to 60% with a suspected recessive ataxia remained without a molecular diagnosis after extensive evaluation and genetic testing. This proportion varied according to geographical areas, possibly secondary to clusters of specific disorders and variability in the depth of the investigation method. For example, in a population-based study from Norway with multisource ascertainment and that included only patients with a positive family history, a precise genetic diagnosis was achieved in only 25% of patients with a standard clinical and genetic evaluation (11). In a Canadian study of 69 hereditary ataxia patients from 60 different families identified through a movement disorders clinic, a genetic diagnosis was obtained in only 26.7% of families, with higher yield in patients with a positive family history (12). Finally, in a more recent genetic study of 319 undiagnosed European cerebellar ataxia patients that had undergone previous extensive work-up, whole-exome sequencing led to a molecular diagnosis in only 28.5% of patients, leaving 71.5% patients with an undefined diagnosis (13). The diagnostic yield was better for patients with certain specific clinical features and those with earlier onset.
The absence of a specific molecular diagnosis has major impacts for patients, which will receive a tentative diagnosis of familial or sporadic ataxia with early or late onset, depending on the presence of a family history and age at symptom onset (14). Although no study has specifically evaluated this phenomenon in the ataxia population, the results of a recent nationwide survey of 462 Australian children living with a rare disease provide evidence as to the impact of absent or delayed diagnosis on patients and families (15). In this study, 37% of respondents believed that diagnosis was delayed, 27% initially received a wrong diagnosis, and 7% remained undiagnosed. The most common reported consequences included anxiety, frustration, and stress. Respondents also reported worsening of symptoms, disease progression, delays in treatment and intervention, inappropriate treatments received, additional medical costs, impact on family relationships and siblings, and extra unnecessary diagnostic tests. In adult patients, data regarding the impact of a long diagnostic odyssey come from the analysis of delayed diagnosis in patients with amyotrophic lateral sclerosis (ALS), another neurodegenerative disorder associated with severe functional impairment and for which no cure is available. Patients with delayed diagnosis in ALS have reported protracted periods of uncertainty, impression of lack of knowledge by physicians, and additional costs (16). In contrast, diagnosed patients reported satisfaction at having a label for their condition as opposed to diagnostic uncertainty, easier coping mechanisms once they knew their diagnosis, clarified expectations, and facilitated help demands with a precise diagnosis (17). We can conclude that undiagnosed patients with hereditary cerebellar ataxias are faced with major uncertainty regarding the expected evolution and risk of premature death, which may cause anxiety and frustration. They may experience anguish regarding the existence of disease-modifying treatment options from which they are denied. They may be subjected to additional invasive testing or inadequate treatments. They may engage additional costs for medical opinion, tests and treatments. Finally, they cannot have adequate genetic counselling and prenatal testing when applicable.

In order for physicians to be able to diagnose effectively patients with hereditary cerebellar ataxias, they must have access to an adequate knowledge base of the individual disorders and a systematic organization that enable non-expert clinicians to navigate this complex group of diseases. In the previously discussed study by Kurynski et al. of Australian children with rare diseases, the most frequent perceived reason for delayed diagnosis was the lack of knowledge among health professionals regarding the patient’s rare condition (15). Hence, it is essential to better define the typical and atypical phenotypic presentations of rare disorders, but also to develop useful classification systems for both physicians and researchers to gain a better understanding of these disorders.
There are different ways to define and categorize disorders. Before the development of molecular genetics, most disorders were defined according to clinical syndromes or pathogenic enzymatic defects. With the discovery of the underlying genetic mutation in a growing number of patients with hereditary disorders, the diseases are now defined according to the mutated gene and compiled in large online databases. This gene-based definition of disorders offers important advantages: it can be tested in a standardized manner for the presence of a mutation and is directly related to the pathogenic defect. Nevertheless, it is important to highlight that there are important variations in the clinical presentation and penetrance among patients with different mutations in the same gene, and even among patients with the same mutation. What is more, genetic variations of unknown significance are often identified in genes associated with hereditary disorders and their clinical relevance is difficult to clarify for the clinician. With the multiplication of genes involved in complex categories of disorders such as hereditary ataxias, it has become strenuous for the non-expert and even the expert clinician to maintain sufficient mastery of each disorder to adequately order and interpret test results in order to obtain a precise molecular diagnosis. To facilitate this, clinical or phenotypical classifications categorize gene-defined disorders in a meaningful way according to the presence of specific clinical and paraclinical features to give structure to the diagnostic approach of a group of disorders. Finally, as many of these disorders are individually rare, it is difficult to obtain funding and recruit adequate numbers of patients for the development of disease-modifying therapies. Hence, a pathophysiological classification that regroups disorders with common treatment targets is useful to develop adequately powered clinical trials or drug repurposing strategies. Hence, each of these classification systems presents important advantages, serves a specific purpose, and is in fact complementary to the others.

Previous classification systems have been proposed for hereditary cerebellar ataxias. In dominant ataxias, disorders have been regrouped according to the mutation type, distinguishing polyglutamine repeat expansion and conventional mutations (18), or according to clinical presentation, separating pure cerebellar phenotypes from those with associated features (19). On the opposite, the classification of recessive ataxias has proven to be a significant challenge owing to several reasons. Indeed, contrarily to their dominant counterparts who were named in a systematic numerical pattern – with SCA 1 to 47 listed to this day (20)– that defined the included disorders, recessive ataxias remained an ill-defined group of disorders that were named according to physicians’ surnames, areas of high prevalence, or dominant clinical signs. Moreover, recessive ataxias present with complex phenotypes and frequent multisystem involvement, showing partial overlap with other disease categories that may present with ataxia, such as hereditary spastic
paraplegias or inborn errors of metabolism. Finally, many recessive congenital disorders that present with cerebellar malformations may or may not be included depending on the goal and criteria of the classification. Hence, previous tentative classifications of recessive ataxias presented only the most prevalent disorders with incomplete assessment of the literature and underrecognition of rare or geographically circumscribed disorders (21-23). Isolated tentative classifications presented a variable list of included disorders and were not uniformly adopted owing to the absence of a consensus among experts in this field. This highlighted the need for a consensus on a recessive ataxia classification that would be useful for clinicians, researchers, and learners alike.

The other central issue for adequate diagnosis of hereditary ataxias is that several disorders remain with an incomplete or partial phenotypic characterization. Indeed, some are described only in rare families with superficial characterization, such that the range of clinical involvement remains unknown and that different phenotypes with atypical features are underrecognized. There exist many examples in the literature of disorders that were described with an initial typical phenotype, but where subsequent data showed that other clinical pictures were as prevalent if not more. For example, autosomal recessive cerebellar ataxia 1 associated with SYNE1 mutations, was initially described as a pure cerebellar ataxia (24), but subsequent data showed that motor neuron involvement was found in a majority of patients and associated with very severe neuromuscular involvement in some (25). Hence, proper phenotypic characterization is essential to facilitate diagnosis and to adequately manage patients by answering questions regarding expected evolution and symptomatic involvement, searching for subtle involvement that may be amenable to treatment, and addressing symptoms that patients may not associate with their neurological disease. It also provides additional elements to understand the underlying disease mechanism with the ultimate objective to develop disease-modifying therapies.

My perspective in completing the work that composes this master’s thesis was to address the complex issue of underdiagnosis in patients with hereditary ataxias. Hence, the general objective of this master’s thesis is to expand our understanding and knowledge of the presentation of hereditary ataxias through the development of a classification for recessive cerebellar ataxias and the phenotypical characterization of a specific ataxia in the French Canadian population. More specifically, I will present three articles that have been published or that are currently under review. The first one is a systematic scoping review of the literature on recessive cerebellar ataxia that aimed to identify all cerebellar disorders that should be included in a recessive ataxia classification. The second one presents a new classification of recessive cerebellar ataxias that was endorsed by a dedicated international Task Force. Finally, the third one aims at defining the phenotypical
description of a specific cerebellar ataxia in the French-Canadian population with new atypical features and in-depth cognitive assessment.
Chapter 1 Reviewing the evidence: a systematic scoping review of the literature on recessive cerebellar ataxias

Original title
Systematic review of autosomal recessive ataxias and proposal for a classification

1.1 Résumé

Introduction
La classification des ataxies cérébelleuses autosomiques récessives représente un défi particulier vu l'hétérogénéité génétique importante et les phénomènes complexes des pathologies rencontrées. Nous avons réalisé une revue systématique de la littérature pour identifier l'ensemble des ataxies récessives pralablement décrites afin de proposer une classification clinique de ce groupe de pathologies et de mieux définir ce champ de recherche à l'ère des technologies de séquençage de nouvelle génération.

Méthodes
Nous avons interrogé Pubmed et Embase afin d'identifier les articles originaux portant sur la description d'ataxies à transmission autosomique récessive chez l'humain pour lesquelles un gène avait été identifié. Nous avons également révisé les listes de références des articles sélectionnés ainsi que les bases de données publiques, notamment OMIM et GeneReviews. Pour chaque pathologie considérée, nous avons révisé la description clinique pour déterminer si l'ataxie cérébelleuse était un élément central du phénotype et avons évalué la qualité de l'évidence supportant l'association avec le gène impliqué. Les pathologies incluses étaient regroupées en trois catégories: les ataxies récessives primaires, les maladies complexes ou multisystémiques fréquemment associées à l'ataxie, et les maladies pouvant occasionnellement présenter un tableau ataxique.

Résultats
Après le retrait des doublons, 2354 références ont été révisées sur la base du titre et du résumé pour évaluer leur éligibilité. Au final, 130 articles ont été révisés en entier et inclus dans cette analyse qualitative. La nouvelle liste des ataxies récessives primaires inclut 45 pathologies génétiques pour lesquelles l'ataxie cérébelleuse est au cœur du phénotype clinique. Vingt maladies complexes ou multisystémiques fréquemment associées à l'ataxie ont également été identifiées, ainsi que neuf maladies pouvant occasionnellement présenter un tableau ataxique. Un algorithme clinique basé sur les symptômes associés est également proposé.
Conclusion
Cette revue systématique de la littérature des ataxies cérébelleuses récessives a permis de définir et de classifier ce groupe de maladies tout en mettant en évidence la complexité des phénomètes et la diversité des atteintes associées. Cette revue systématique devrait être instrumentale dans le développement d’un consensus sur la classification des ataxies récessives.

1.2 Abstract

Introduction
The classification of autosomal recessive ataxias represents a significant challenge because of high genetic heterogeneity and complex phenotypes. We conducted a comprehensive systematic review of the literature to examine all recessive ataxias in order to propose a new classification and properly circumscribe this field as new technologies are emerging for comprehensive targeted gene testing.

Methods
We searched Pubmed and Embase to identify original articles on recessive forms of ataxia in humans for which a causative gene had been identified. Reference lists and public databases, including OMIM and GeneReviews, were also reviewed. We evaluated the clinical descriptions to determine if ataxia was a core feature of the phenotype and assessed the available evidence on the genotype-phenotype association. Included disorders were classified as primary recessive ataxias, as other complex movement or multisystem disorders with prominent ataxia, or as disorders that may occasionally present with ataxia.

Results
After removal of duplicates, 2354 references were reviewed and assessed for inclusion. A total of 130 articles were completely reviewed and included in this qualitative analysis. The proposed new list of autosomal recessive ataxias includes 45 gene-defined disorders for which ataxia is a core presenting feature. Twenty complex or multisystem recessive disorders that have prominent ataxia were also identified along with nine recessive disorders that may occasionally present with ataxia, but where ataxia is a secondary feature. We propose a clinical algorithm based on the associated symptoms.
Conclusion
We present a new classification for autosomal recessive ataxias that brings awareness to their complex phenotypes while providing a unified categorization of this group of disorders. This review should assist in the development of a consensus around a classification useful in both clinical and research applications.

1.3 Background
The classification of the hereditary ataxias has represented a challenge for decades due to the large heterogeneity of clinical presentations and the important overlap between different pathologies (1). The first to propose a global classification for this group of disorders was Greenfield in 1954, whose classification was based on pathoanatomical findings (2). This was followed by Harding’s classification in 1983, which regrouped the ataxias according to age of onset, as a proxy for mode of inheritance, and clinical findings (3). Although this clinical classification had merit, it quickly became overshadowed by a nomenclature based on gene discoveries within each specific type of ataxia starting with ATXN1 in Spinocerebellar ataxia 1 in 1993 (4) and FXN in Friedreich ataxia (5). Since then, over 40 genes have been discovered in the dominant ataxias and as many in recessive ataxias (6).

One of the main challenges in the study of recessive ataxias is the difficulty to properly circumscribe which disorders belong to the field of hereditary ataxias and which belong to other disease categories. Indeed, ataxia is a cardinal symptom in cerebellar disorders, but may also be a presenting symptom of hereditary spastic paraplegias, hereditary polynuropathies, neurodevelopmental disorders, and mitochondrial diseases, for example. Concurrently, recessive ataxias often manifest with complex phenotypes, even more so than their dominant counterparts, and may present diverse associated features including neuropathy, pyramidal and extrapyramidal involvement, oculomotor abnormalities, cognitive involvement, seizures, retinopathy, hypogonadism, and many others. This explains the high variability in the list of included disorders in recent literature reviews on recessive ataxias(7, 8).

Nevertheless, the advent of next generation sequencing techniques requires to properly determine which disorders belong to each disease category in order to design thoughtful targeted panels and facilitate the interpretation of whole exome and whole genome sequencing data. Indeed, targeted panel sequencing is a highly effective method for the diagnosis of neurological disorders, but it requires insightful categorization of disease phenotypes to respond to the specific needs of clinicians (9, 10). Similarly, the interpretation of unknown variants in the analysis of whole exome
or whole genome sequencing data poses a significant challenge for clinicians who must determine if the gene is associated with the suspected disease category and if the phenotype correlates with what has previously been described. As next generation sequencing techniques become increasingly available and the ability to detect DNA repeat expansion diseases improves (11), the proper classification of diseases will represent a useful tool in the interpretation of test results. Hence, this calls for a systematic effort to review recessive diseases in which ataxia is a prominent feature in order for experts in the field to collectively determine which disorders should be included in a recessive ataxia classification.

Therefore, the purpose of this article is to review the literature on recessive diseases presenting with ataxia in order to present a new classification. The goal is to bring together experts for the development of a much-needed consensus that fulfills research and clinical needs.

1.4 Methods

We conducted a systematic scoping review to identify articles relevant to the classification of autosomal recessive ataxias. We searched Pubmed and Embase from inception to September 2016 in order to identify original articles on disorders presenting with ataxia. The search strategy was large and targeted both recessive and sporadic ataxias, since recessive inheritance may appear sporadic in certain circumstances (full search strategy is provided in Additional file 1). We also reviewed reference lists of relevant articles and public databases including OMIM and GeneReviews to identify other relevant articles.

We reviewed the titles and abstracts of all identified references to select original articles on recessive forms of ataxia in humans for which a causative gene was identified. We evaluated the articles from a clinical perspective to determine if cerebellar ataxia was a prominent feature in the reported patients or rather a secondary finding in other movement or multisystem diseases. Diseases reporting only on cerebellar atrophy or cerebellar malformations without any clinical correlate were not included. For each listed disorder, we reviewed the evidence for a genotype-phenotype association using the US National Human Genome Research Institute guidelines (12). Major considerations included the exclusion of previously described genes, the number of unrelated individuals described with similar genotype-phenotype correlations, the evidence of segregation with the disease, the absence of the variant in large control cohorts, and the presence of biochemical or animal-model functional validation. For the primary ataxias, we identified two relevant references from different research groups when possible. All relevant articles were fully reviewed to be included in this classification of recessive ataxias.
Identified disorders were classified in three categories: the first included the primary autosomal recessive ataxias, the second included other movement or multisystem recessive diseases that have prominent ataxia, and the final group was composed of recessive disorders that may occasionally present with ataxia, but where ataxia is a secondary feature.

We also developed a clinical algorithm for the primary recessive ataxias based on the most frequent phenotype and cardinal symptoms associated with each disorder. The objective of this algorithm is to rapidly summarize the main discriminatory features between different ataxias to serve in a clinical setting, but also as a pedagogical and research tool.

1.5 Results

3750 references were identified through the literature search in Pubmed and Embase, and 49 additional references were identified through reference lists or public databases. After removal of duplicates, 2354 references were reviewed on the basis of title and abstract. Finally, 130 articles were selected on the basis of the aforementioned criteria and completely reviewed to be included in this qualitative analysis (Figure 1.1).

Figure 1.1 Flow diagram

The proposed new list of autosomal recessive ataxias is presented in Table 1.1 in chronological order of gene discovery. The disorders included in this list were evaluated as having a relatively predominant cerebellar involvement compared to the involvement of other neurologic and non-neurologic systems. Table 1.2 presents the other complex motor or multisystem disorders that have prominent ataxia. Finally, Table 1.3 presents disorders that may occasionally present with ataxia, but where ataxia is a secondary feature. Certain decisions were made in the elaboration of this classification. Notably, abetalipoproteinemia (ABL) and Refsum disease were not included in the list of primary recessive ataxias, but rather in the list of complex disorders that have prominent ataxia. Indeed, despite their important Friedreich-like neurological picture, these disorders are primary lipid metabolism disorders with multisystem involvement. Moreover, ataxic disorders that are allelic to other movement disorders, especially spinocerebellar ataxias and hereditary spastic paraplegias, were assigned to the second category to avoid any confusion with the primary recessive ataxias. The MARS2-linked autosomal recessive ataxia with leukoencephalopathy (ARSAL/SPAX3) was not included because the genetic evidence was deemed insufficient (13). Finally, some disorders described only in single families were included, despite this being a factor for weaker genetic evidence, if other major considerations were met; this was indicated in the list.
Table 1.1 Proposed new list of autosomal recessive ataxias

Table 1.2 Other complex movement or multisystem recessive disorders that have prominent ataxia

Table 1.3 Recessive disorders that may occasionally present with ataxia, but where ataxia is a secondary feature

The primary recessive ataxias were also organized in a clinical algorithm (Figure 1.2) according to the presence of key clinical clues, which include the presence of sensorimotor involvement, cognitive impairment, spasticity, and oculomotor abnormalities.

Figure 1.2. Clinical algorithm of autosomal recessive ataxias

Other disorders have been reported with ataxia, but the authors evaluated that these disorders did not need to be included in the differential diagnosis of recessive ataxias. However, clinicians may bear in mind that the following may have ataxia as an associated feature: Lafora disease (EPM2A, EPM2B), megalencephalic leukoencephalopathy with subcortical cysts (MLC1), COL18A1-linked ataxia epilepsy cognitive problems and visual problems, Perrault syndrome (HSD17B4), Zellweger-spectrum disorders (PEX2), Wolfram syndrome (WFS1), Canavan disease (ASPA), metachromatic leukodystrophy (ARSA), Galloway-Mowat syndrome (WDR73), and GLUT-1 deficiency (SCL2A1).

1.6 Discussion

We present a new classification for the autosomal recessive ataxias. This classification should allow for better categorization of recessive disorders presenting with ataxia with a clear separation between the primary recessive ataxias and disorders that may present with ataxia as an associated feature but belong to other disease categories. We also provided a clinical algorithm as a tool for diagnostic, learning, and research purposes. This comprehensive classification will allow for improved genetic diagnosis by targeted next generation sequencing applications as the ability to detect DNA repeat expansion diseases is quickly becoming a reality with prospects of treatment in the future (11, 14, 15).

As compared to previously published reports on this subject (7, 8), we systematically reviewed the literature to evaluate the available evidence on the disease-associated genes in order to include all disorders presenting with a predominant cerebellar ataxia phenotype. The systematic review methodology with a structured data search and comprehensive evaluation of all references allowed
for a complete evaluation of the literature regarding disorders presenting with ataxia to ensure that all potentially relevant disorders were included in this classification. Nevertheless, some methodological elements were not applicable to the task at hand. For example, two references were selected for each primary recessive ataxia, and articles that provided evidence for a separated genetic basis with a clinical corollary of ataxia were preferred. Therefore, some articles that provided only detailed clinical description were not included. Moreover, inclusion criteria were clearly defined but there remained a large place for interpretation to determine if cerebellar ataxia was a core feature of the phenotype and if the genotype-phenotype association was convincing. Thus, the classification of individual disorders between the three groups, i.e. as a recessive ataxia, a complex disorder with predominant ataxia or a disorder where ataxia is a secondary feature, remains a subjective appreciation and is open for discussion by a dedicated task force in order to reach a consensus. Finally, the search strategy was designed to be as sensible as possible, but ataxia is a frequent symptom in neurology, and it is possible that other ataxia-associated disorders could be considered for inclusion.

Important challenges remain to be addressed. First, the nosology of recessive ataxias is still highly confusing. Contrary to the dominantly inherited spinocerebellar ataxias, no universal acronym was adopted in the field of recessive ataxias, such that disorders were named based on the author who first described them, on regions of high prevalence, or according to clinical presentation. In the last few years, the term spinocerebellar ataxia, autosomal recessive (SCAR) was used to designate novel recessive ataxias, but this nomenclature did not include the previously described and most frequent ataxias. Moreover, as SCAR assignation was based on locus discovery, some of the included SCARs do not correspond to an identified gene. The term SPAX has also been used to designate ataxias with a strong spasticity component, irrespectively of their mode of inheritance. Recently, the International Parkinson and Movement Disorder Society Task Force for Nomenclature of Genetic Movement Disorders recommended a nomenclature with a gene suffix in order to overcome the shortcomings of the numbered locus system, which include erroneously assigned loci, the mingling of causative and risk factor genes, unconfirmed causative associations, and inconsistent phenotypic correlations (16). These concerns are justified, although numbered naming systems present definite advantages for ease of use and proper delineation of the field. The nomenclature of recessive ataxias should be discussed by a dedicated task force of international experts in order to develop a naming system that reflects the complexity of the recessive ataxia phenotypes while allowing convenient clinical use.
Finally, large phenotypic variability exists between patients from different families and even from a single family with the same mutated gene, depending on the type of mutation and on its location in the gene. Other factors that affect age at onset and clinical course probably include the presence of modifier genes and environmental exposures. Hence, one could argue that the paradigm of one gene-one disease presented here does not reflect all the phenotypic variability observed, and could as well be replaced by the concept of one patient-one disease as we identify new genetic and environmental prognostic features that characterise more precisely the age at onset, evolution, and response to treatment. Such developments are likely to modify our understanding of genetic disorders and of their classification.

1.7 Conclusion

We present herein a classification of the autosomal recessive ataxias based on a systematic scoping review of the literature. This work should serve as a framework for scientific discussion in order to bring together experts for the establishment of a much-needed consensus in this field.

1.8 Tables

Table 1.1 Proposed new list of autosomal recessive ataxias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>OMIM</th>
<th>Additional clinical features and neuroimaging findings</th>
<th>Relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX</td>
<td>CYP27A1</td>
<td>213700</td>
<td>Dementia, paesis, tendon xanthomas, atherosclerosis, cataracts, elevated cholesanol level, childhood onset, variable cerebellar atrophy, cerebral or cerebral leukodystrophy</td>
<td>(17,18)</td>
</tr>
<tr>
<td>AVED</td>
<td>TTPA</td>
<td>277460</td>
<td>Retinitis pigmentosa, head titubation, low serum vitamin E, teenage onset, spinal cord atrophy, absence of cerebellar atrophy</td>
<td>(19, 20)</td>
</tr>
<tr>
<td>AT</td>
<td>ATM</td>
<td>208900</td>
<td>Telangiectasias, oculomotor apraxia, photosensitivity, immunodeficiency, predisposition for cancer, elevation of α-foetoprotein, infantile onset, cerebellar atrophy</td>
<td>(21, 22)</td>
</tr>
<tr>
<td>FRDA</td>
<td>FXN</td>
<td>229300</td>
<td>Bilateral Babinski sign, square-wave jerks, scoliosis, hypertrophic cardiomyopathy, sensory involvement, teenage onset, spinal cord atrophy, absence of cerebellar atrophy</td>
<td>(5, 23)</td>
</tr>
<tr>
<td>ATLD</td>
<td>MRE11</td>
<td>604391</td>
<td>Oculomotor apraxia, childhood onset, cerebellar atrophy</td>
<td>(24, 25)</td>
</tr>
<tr>
<td>ARSACS</td>
<td>SACS</td>
<td>270550</td>
<td>Spastic paraparesis, retinal striation, pes cavus, infantile or childhood onset, anterior superior cerebellar atrophy, occasional T2-weighted linear hypointensities in pons</td>
<td>(26, 27)</td>
</tr>
<tr>
<td>AOA1/EAOH</td>
<td>APTX</td>
<td>208920</td>
<td>Oculomotor apraxia, cognitive impairment, hypoalbuminemia, hypercholesterolemia, childhood onset, cerebellar atrophy</td>
<td>(28, 29)</td>
</tr>
<tr>
<td>SCAN1</td>
<td>TDP1</td>
<td>607250</td>
<td>Peripheral axonal sensorimotor neuropathy, distal muscular atrophy, hypercholesterolemia, teenage onset, cerebellar atrophy</td>
<td>(30, 31)</td>
</tr>
<tr>
<td>Cayman ataxia</td>
<td>ATCAY</td>
<td>601238</td>
<td>Psychomotor retardation, hypotonia, ataxia, neonatal onset, cerebellar hypoplasia</td>
<td>(32, 33)</td>
</tr>
<tr>
<td>SANDO or MIRAS/SCAE</td>
<td>POLG1</td>
<td>607459</td>
<td>Sensory ataxia, ophthalmparesis, myoclonus, ptosis, adult onset, variable cerebellar atrophy, cerebellar white matter lesions, stroke-like lesions In MIRAS, cerebellar and sensitive ataxia, epilepsy, migraine, myoclonus, childhood or teenage onset, signal abnormalities in cerebellum and thalamus</td>
<td>(34, 35)</td>
</tr>
<tr>
<td>AOA2</td>
<td>SETX</td>
<td>606002</td>
<td>Polyneuropathy, pyramidal signs, oculomotor apraxia, head tremor,</td>
<td>(36, 37)</td>
</tr>
</tbody>
</table>
chorea, dystonia, elevation of α-foetoprotein, teenage onset, cerebellar atrophy

CAMRQ1, DES  VLDLR  224050  Non-progressive cerebellar ataxia, mental retardation, hypotonia, strabismus, occasional quadripedal gait, congenital onset, inferior cerebellar hypoplasia, cortical gyral simplification (38, 39)

IOSCA/MTDPS7  C10orf2  271245  Athetosis, hypotonia, optic atrophy, ophthalmoplegia, hearing loss, epilepsy, hypogonadism, liver involvement, infantile onset, moderate atrophy of brainstem and cerebellum with advancing disease (40, 41)

MSS  SIL1  248800  Cataracts, mental retardation, myopathy, short stature, childhood onset, cerebellar atrophy (42, 43)

DCMA/MGCA5  DNAJC19  610198  Dilated cardiomyopathy, non-progressive cerebellar ataxia, mental retardation, testicular dysgenesis, anemia, increased urinary 3-methylglutaconic acid, infantile onset (44, 45)

ARCA1  SYNE1  610743  Pure cerebellar ataxia, cognitive impairment, occasional pyramidal signs, late onset, cerebellar atrophy (46, 47)

ARCA2  ADCK3  612016  Exercise intolerance, epilepsy, myoclonus, cognitive impairment, childhood onset, cerebellar atrophy, occasional stroke-like cerebral lesions (48, 49)

SeSAME syndrome  KCNJ10  612780  Epilepsy, sensorineural deafness, mental retardation, tubulopathy and electrolyte imbalance, infantile onset, absence of cerebellar atrophy (50, 51)

CAMRQ3  CA8  613227  Mild mental retardation, occasional quadripedal gait, congenital onset, cerebellar atrophy, white matter abnormalities (52, 53)

Salih ataxia/SCAR15 (1 family)  KIAA0226  615705  Epilepsy, mental retardation, childhood onset, absence of cerebellar atrophy (54, 55)

PHARC  ABHD12  612674  Sensorimotor neuropathy, cataract, hearing loss, retinitis pigmentosa, teenage onset, variable cerebellar atrophy (56, 57)

SPAX4 (1 family)  MTPAP  613672  Spastic paraparesis, optic atrophy, cognitive involvement, infantile onset (58, 59)

ARCA3  ANO10  613728  Cognitive impairment, downbeat nystagmus, teenage or adult onset, cerebellar atrophy (60, 61)

SCAR11 (1 family)  SYT14  614229  Psychomotor retardation, late onset, cerebellar atrophy (62)

CAMRQ2  WDR81  610185  Occasional quadripedal gait, cognitive impairment, congenital onset, hypoplasia of cerebellum and corpus callosum (63, 64)

AOA3 (1 family)  PIK3R5  615217  Oculomotor apraxia, sensorimotor involvement, teenage onset, cerebellar atrophy (65)

SCAR13  GRM1  614831  Cognitive impairment, mild pyramidal signs, short stature, seizures, congenital onset, cerebellar atrophy (66, 67)

CAMRQ4 (1 family)  ATP8A2  615268  Cognitive impairment, occasional quadripedal gait, congenital onset, cerebellar and cerebral atrophy (68)

SCAR7 (Allelic to CLN2)  TPP1  609270  Pyramidal signs, posterior column involvement, tremor, childhood onset, atrophy of the cerebellum and pons (69, 70)

Ataxia and hypogonadotropism  RNF216  212840  Hypogonadotropic hypogonadism, dementia, occasional chorea, childhood to young adult onset, cerebellar and cerebral atrophy (71, 72)

SCAR18  GRID2  616204  Tonic upgaze, psychomotor retardation, retinal dystrophy, infantile onset, cerebellar atrophy (73, 74)

SCAR16  STUB1  615768  Pyramidal signs, neuropathy, occasional hypogonadism, variable age at onset, cerebellar atrophy (75, 76)

SCAR12  WWOX  614322  Tonic-clonic epilepsy, mental retardation, spasticity, neonatal to childhood onset, variable cerebellar or cerebral atrophy (77, 78)

ATLD2 (1 family)  PCNA  615919  Telangiectasias, sensorineural hearing loss, photosensitivity, cognitive impairment, short stature, childhood onset, cerebellar atrophy (79)

SCAR20  SNX14  616354  Mental retardation, sensorineural hearing loss, macrocephaly, dysmorphism, infantile onset, cerebellar atrophy (80, 81)

SCAR17  CWF19L1  616127  Mental retardation, congenital onset, cerebellar hypoplasia (82, 83)

ACPBD  DNAJC3  616192  Diabetes mellitus, UMN signs, demyelinating neuropathy, (84)
(1 family) sensorineural hearing loss, childhood to adult onset, generalized supra- and infratentorial atrophy ...

Allelic to SCA5 (9, 103) SPAX5 AFG3L2 614487 Ataxia, spasticity, oculomotor apraxia, myoclonic Allelic to (104, 105)

SPAX5 SPARCA1 (Tay-Sachs, Sandhoff) - Refsum disease type C Nieman Pick Abetalipoproteinemia (1 family)

ACPHD Ataxia, combined cerebellar and peripheral with hearing loss and diabetes mellitus; AOA ataxia with oculomotor apraxia; ARCA autosomal recessive cerebellar ataxia; ARSACS autosomal recessive spastic ataxia of Charlevoix-Saguenay; AT ataxia-telangiectasia; ATLD ataxia-telangiectasia-like disorder; AVED ataxia with vitamin E deficiency; CI Cayman ataxia; CAMOS cerebellar ataxia mental retardation optic atrophy and skin abnormalities; CAMRQ cerebellar ataxia mental retardation with or without quadrapedal locomotion; DCMA Dilated cardiomyopathy with ataxia; DES Desequilibrium syndrome; EAOH Early-onset ataxia with oculomotor apraxia and hypoalbuminemia FRDA Friedreich ataxia; IOSCA infantile onset spinocerebellar ataxia; LIKNS Lichtenstein-Knorr syndrome; MGCA5 3-methylglutaconic aciduria type 5; MHRAS mitochondrial recessive ataxia syndrome; MCSZ Microcephaly seizures developmental delay; MSSH Marinesco-Sjogren syndrome; MTDFS mitochondrial DNA depletion syndrome 7; PEOA3 progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant 3; PHARCS polineuropathy hearing loss ataxia retinitis pigmentosa and cataract; SANDO sensory ataxic neuropathy with dysarthria and ophthalmoplegias; SCAE spinocerebellar ataxia with epilepsy SCAN1 spinocerebellar ataxia with axonal neuropathy 1; SCAR Spino-cerebellar ataxia, autosomal recessive; ScSMe Seizures sensorineural deafness ataxia mental retardation and electrolyte imbalance; SPAX Spastic ataxia; UMN upper motor neuron.

Table 1.2 Other complex movement or multisystem recessive disorders that have prominent ataxia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>OMIM</th>
<th>Clinical features and imaging findings</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetalipoproteinemia</td>
<td>MTP</td>
<td>200100</td>
<td>Fat malabsorption symptoms, hypocholesterolemia, hypotriglyceridemia, Friedreich-like ataxia, neonatal onset, absence of cerebellar atrophy</td>
<td>Multisystem</td>
<td>(95)</td>
</tr>
<tr>
<td>Nieman Pick type C</td>
<td>NPC1</td>
<td>257220</td>
<td>Vertical supranuclear ophthalmoplegia, ataxia, splenomegaly, childhood to adult onset, variable cerebellar or cerebral atrophy</td>
<td>Multisystem</td>
<td>(96, 97)</td>
</tr>
<tr>
<td>Nieman Pick type C</td>
<td>NPC2</td>
<td>607625</td>
<td></td>
<td>Multisystem</td>
<td>(98, 99)</td>
</tr>
<tr>
<td>Refsum disease</td>
<td>PAHX</td>
<td>266500</td>
<td>Retinitis pigmentosa, polyneuropathy, ataxia, increased CSF protein, anosmia, deafness, ichthyosis, teenage onset, elevated serum phytic acid, absence of cerebellar atrophy</td>
<td>Multisystem</td>
<td></td>
</tr>
<tr>
<td>Late-onset GM2 gangliosidosis (Tay-Sachs, Sandhoff)</td>
<td>HEXA</td>
<td>272800</td>
<td>Ataxia, dystarthis, intellectual impairment, extrapyramidal signs, adult onset, cerebellar atrophy</td>
<td>Lyososomal storage disease</td>
<td>(100-102)</td>
</tr>
<tr>
<td>Late-onset GM2 gangliosidosis (Tay-Sachs, Sandhoff)</td>
<td>HEXB</td>
<td>268800</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPARCA1</td>
<td>SPTBN2</td>
<td>615386</td>
<td>Ataxia, cognitive impairment, eye-movement abnormalities, early childhood onset, cerebellar atrophy</td>
<td>Allelic to SCA5</td>
<td>(9, 103)</td>
</tr>
<tr>
<td>SPAX5</td>
<td>AFG3L2</td>
<td>614487</td>
<td>Ataxia, spasticity, oculomotor apraxia, myoclonic</td>
<td>Allelic to SCA5</td>
<td>(104, 105)</td>
</tr>
<tr>
<td>Condition</td>
<td>Gene</td>
<td>OMIM</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boucher-Neuhauser/Gordon Holmes syndrome</td>
<td>PNPLA6</td>
<td>215470</td>
<td>Epilepsy, neuropathy, dystonia, optic atrophy, childhood onset, cerebellar atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gillespie syndrome</td>
<td>ITPR1</td>
<td>206700</td>
<td>Ataxia, hypogonadotropic hypogonadism, chorioretinal dystrophy or brisk reflexes, childhood onset, atrophy of cerebellum and pons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAX2/SPG58</td>
<td>KIF1C</td>
<td>611302</td>
<td>Spastic paraparesis, cerebellar ataxia, childhood or teenage onset, white matter changes in the internal capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPG7</td>
<td>SPG7</td>
<td>607259</td>
<td>Spasticity, pyramidal signs, cerebellar signs, optic neuropathy, ptosis, teenage or adult onset, cerebellar atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPG5</td>
<td>CYP7B1</td>
<td>270800</td>
<td>Non-progressive cerebellar ataxia, iris hypoplasia, cognitive impairment, neonatal onset, progressive cerebellar atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPG11</td>
<td>KIAA1840</td>
<td>604360</td>
<td>Spasticity, ataxia, cognitive impairment, sensorimotor neuropathy, childhood or teenage onset, thin corpus callosum, signal abnormalities in cervical cord</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPG46</td>
<td>GBA2</td>
<td>614409</td>
<td>Cerebellar ataxia, spastic dysarthria, mild cognitive impairment, hearing loss, cataracts, childhood onset, cerebellar and cerebral atrophy, thin corpus callosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital disorders of glycosylation type 1A</td>
<td>PMM2</td>
<td>212065</td>
<td>Psychomotor retardation, axial hypotonia, abnormal eye movements, peripheral neuropathy, congenital onset, cerebellar hypoplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBSL</td>
<td>DARS2</td>
<td>611105</td>
<td>Cerebellar ataxia, tremor, spasticity, dorsal column dysfunction, axonal neuropathy, childhood to adult onset, signal abnormalities in cerebral white matter and specific brainstem and spinal cord tracts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial complex IV deficiency</td>
<td>COX20</td>
<td>220110</td>
<td>Cerebellar ataxia, dystonia, sensory axonal neuropathy, variable, childhood or teenage onset, cerebellar atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
<td>CP</td>
<td>604290</td>
<td>Diabetes, dementia, movement disorder, cerebellar ataxia, retinal degeneration, late onset, decreased signal intensity in thalamus, basal ganglia and dentate nucleus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurodegeneration with brain iron accumulation 2A and 2B</td>
<td>PLA2G6</td>
<td>256600</td>
<td>Cerebellar ataxia, psychomotor retardation, psychiatric features, axonal sensorimotor neuropathy, infantile or teenage onset, cerebellar atrophy and variable iron accumulation in globus pallidus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poretti-Botshauser syndrome</td>
<td>LAMA1</td>
<td>615960</td>
<td>Nonprogressive ataxia, oculomotor ataxia, psychomotor retardation, early childhood onset, cerebellar dysplasia with cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior column ataxia with retinitis pigmentosa</td>
<td>FLVCR1</td>
<td>609033</td>
<td>Posterior column degeneration and retinitis pigmentosa, childhood onset, signal abnormalities in cervical spinal cord</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HSP: hereditary spastic paraplegia; LBSL: leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; SPARCA1: spectrin-associated autosomal recessive cerebellar ataxia type 1; SPAX: spastic ataxia; SPG: spastic paraplegia.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>OMIM</th>
<th>Clinical features and imaging findings</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuronal ceroid lipofuscinoses</td>
<td>CLN5</td>
<td>256731</td>
<td>Psychomotor retardation, visual failure, seizures, childhood to teenage onset, cerebellar and cerebral atrophy</td>
<td>Ataxia is a rare feature</td>
<td>(130, 131)</td>
</tr>
<tr>
<td></td>
<td>CLN6</td>
<td>601780</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sialic acid storage diseases (ISSD and Salla disease)</td>
<td>SLC17A5</td>
<td>604369</td>
<td>Hypotonia, cerebellar ataxia and mental retardation, infantile to adult onset, cerebellar atrophy and demyelination</td>
<td>Complex syndrome</td>
<td>(132, 133)</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>AHI1, ARL13B, CC2D2A, others</td>
<td>Many</td>
<td>Ataxia, hypotonia, neonatal breathing abnormalities, mental retardation, nephromophthisis, congenital onset, agenessis of the cerebellar vermis</td>
<td>Complex neonatal polygenic syndrome</td>
<td>(134, 135)</td>
</tr>
<tr>
<td>Hartnup disorder</td>
<td>SLC6A19</td>
<td>234500</td>
<td>Transient manifestations of pellagra, cerebellar ataxia and psychosis, amino aciduria, early onset</td>
<td>Metabolic disorder</td>
<td>(136)</td>
</tr>
<tr>
<td>Childhood ataxia with central nervous system hypomyelination/vanishing white matter disease</td>
<td>elf2B</td>
<td>603896</td>
<td>Cerebellar ataxia with spasticity. Rapid deterioration following head trauma or febrile illness, infantile to adult onset, diffusely abnormal cerebral white matter</td>
<td>Leukodystrophy</td>
<td>(137, 138)</td>
</tr>
<tr>
<td>L-2-Hydroxyglutaric aciduria</td>
<td>L2HGDH</td>
<td>236792</td>
<td>Psychomotor retardation, epilepsy, macrocephaly, cerebellar ataxia, infantile onset, subcortical leukoencephalopathy and cerebellar atrophy</td>
<td>Metabolic disorder</td>
<td>(139, 140)</td>
</tr>
<tr>
<td>GOSR2-linked progressive myoclonus epilepsy</td>
<td>GOSR2</td>
<td>614018</td>
<td>Ataxia, myoclonic epilepsy, raised creatine kinase, early childhood onset, variable cerebellar and cerebral atrophy</td>
<td>Epileptic disorder</td>
<td>(141)</td>
</tr>
<tr>
<td>Tremor-ataxia with central hypomyelination</td>
<td>POLR3A</td>
<td>607694</td>
<td>Tremor, cerebellar ataxia, cognitive regression, UMN signs, childhood onset, hypomyelination of deep white matter, cerebellar atrophy, thin corpus callosum</td>
<td>Leukodystrophy</td>
<td>(142)</td>
</tr>
<tr>
<td>Recessive Behr’s syndrome</td>
<td>OPA1</td>
<td>210000</td>
<td>Optic atrophy, ataxia, peripheral neuropathy, digestive symptoms, infantile or childhood onset, cerebellar atrophy</td>
<td>Optic atrophy</td>
<td>(143, 144)</td>
</tr>
</tbody>
</table>

*ISSD infantile sialic acid storage disease*
1.9 Figures

Figure 1.1 Flow diagram

Records identified through database searching (n = 3750) → Additional records identified through reference lists, OMIM and GeneReviews (n = 49) → Records after duplicates removed (n = 2354) → Records screened (n = 2354) → Records excluded (n = 2224) → Studies included in qualitative synthesis (n = 130)
1.10 Supplementary material

Search strategy for MEDLINE/Pubmed

1. recessive[TIAB] OR sporadic[TIAB]
2. ataxi*[TIAB] OR “spinocerebellar degenerations”[MeSH Major topic] OR “cerebellar ataxia”[MeSH Major topic]
4. animals[MeSH] NOT humans[MeSH]

1 AND 2 AND 3 NOT 4
1.11 References


23


Chapter 2 Building a conceptual framework: a new classification for recessive cerebellar ataxias

Original title
The Classification of Autosomal Recessive Cerebellar Ataxias: A consensus statement from the Society for Research on the Cerebellum and Ataxias Task Force

2.1 Résumé

Introduction
Il n’y a pas de classification reconnue des ataxies cérébelleuses récessives, un groupe de maladies caractérisé par une importante hétérogénéité génétique et des phénotypes complexes. L’objectif du groupe de travail était de développer un consensus sur la classification des ataxies récessives afin de définir une approche clinique structurée au patient se présentant pour ataxie, de regrouper les ataxies selon la symptomatologie clinique et de définir ce champ de recherche en identifiant des mécanismes physiopathologiques communs aux différentes maladies.

Méthode
Le groupe de travail s’est basé sur la revue systématique de la littérature présentée précédemment pour identifier les pathologies récessives caractérisées principalement par un syndrome moteur cérébelleux et une évidence de dégénérescence cérébelleuse. Cette revue de littérature a été mise à jour pour inclure les nouveaux articles publiés après la rédaction du premier article et pour prendre en compte les critères d’inclusion redéfinis par le groupe de travail. Celui-ci regroupait 12 experts internationaux qui se sont penchés sur les orientations générales de la classification et les enjeux spécifiques soulevés en cours de la réalisation.

Résultats
Au total, 59 maladies génétiques ont été incluses dans la liste mise à jour des ataxies récessives primaires. Pour chaque ataxie, la distribution géographique est présentée en plus des caractéristiques cliniques et radiologiques discriminantes. Les ataxies récessives primaires ont été classifiées selon le tableau clinique et selon le mécanisme physiopathologique impliqué. Une approche clinique structurée au patient se présentant pour ataxie est détaillée. Nous avons également identifié 48 maladies génétiques additionnelles associées avec une présentation ataxique et qui devraient être incluses dans le diagnostic différentiel des ataxies héréditaires récessives.
2.2 Abstract

Introduction
There is currently no accepted classification of recessive cerebellar ataxias, a group of disorders characterized by important genetic heterogeneity and complex phenotypes. The objective of this task force was to build a consensus on the classification of recessive ataxias in order to develop a general approach to a patient presenting with ataxia, organize disorders according to clinical presentation, and define this field of research by identifying common pathogenic molecular mechanisms in recessive ataxias.

Methods
The work of this task force was based on the previously presented systematic scoping review of the literature that identified recessive disorders characterized primarily by cerebellar motor dysfunction and cerebellar degeneration. This review was updated to include the articles published after the previous article and to account for redefined inclusion criteria by the task force. The latter regrouped 12 international ataxia experts who decided on general orientation and specific issues.

Results
We identified 59 disorders that are classified as primary recessive ataxias. For each of these disorders, we present geographical and ethnical specificities along with distinctive clinical and imagery features. The primary recessive ataxias were organized in a clinical and a pathophysiological classification, and we present a general clinical approach to the patient presenting with ataxia. We also identified a list of 48 complex multisystem disorders that are associated with ataxia and should be included in the differential diagnosis of recessive ataxias.

Conclusion
This classification is the result of a consensus among a panel of international experts, and it promotes a unified understanding of recessive cerebellar disorders for clinicians and researchers.

2.3 Introduction
The classification of hereditary ataxias represents a significant challenge due to the large number of neurological and metabolic diseases that present with cerebellar dysfunction and the phenotypic...
heterogeneity in known genetically defined disorders. Indeed, ataxia is a presenting feature in degenerative disorders that target mainly the cerebellum, but it may be present in hereditary spastic paraplegias, inborn errors of metabolism, and various encephalopathies. Proper classification and phenotypic understanding is of primary importance in this field where the high prevalence of repeat expansion disorders, which are not adequately covered by next generation sequencing (NGS) techniques (1, 2), precludes NGS as a first diagnostic step and requires phenotypic evaluation to perform custom gene testing when applicable. Nevertheless, autosomal recessive ataxias have remained an ill-defined and disorganized group of disorders for two main reasons. First, unlike the dominant ataxias that have been organized with a numerical naming system, recessive disorders presenting with ataxia have been named in a highly heterogeneous manner according to clinical features, physicians’ surname, or regions of high prevalence. Second, several recessive multisystemic or complex metabolic disorders present with ataxia, such that it is difficult to properly circumscribe this group of disorders and classify it in a meaningful way for both clinicians and researchers. Hence, the Society for Research on the Cerebellum and Ataxias (SRCA) Task Force on the Classification of Recessive Cerebellar Ataxias was created in 2016 to regroup a panel of international ataxia experts in order to propose a classification relevant to clinical practice and researchers. As a first step, we undertook a systematic scoping review of the literature to identify all recessive disorders presenting with ataxia, select those in which cerebellar degeneration was a core feature, and propose a first classification. This systematic scoping review has been previously published (3), and served as the basis for the current work.

Recently, the Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders proposed a revised naming system based on the gene name associated with a phenotypical prefix. They presented a list of 92 gene-defined recessive disorders associated with ataxia for which this naming system would be applied and an exhaustive list of disorders that may occasionally present with ataxia (4). This represents a useful reference for interpretation of NGS results. However, in a significant number of listed disorders, the cerebellum is only one of many affected organs in multisystemic and metabolic disorders. For example, maple syrup urine disease, caused by BCKDHB mutations, and congenital disorders of glycosylation 1a, 1c, and 1q have been included. These disorders are inborn errors of metabolism characterized by developmental delay, hypotonia, and metabolic defects, and ataxia is only mild, found in a minority of patients, or present solely during episodes of metabolic decompensation. Hence, there remains a need for a classification system that focuses on disorders affecting primarily the cerebellum and
organizes clinical and paraclinical information to promote an understanding of cerebellar disorders useful not only to ataxia experts, but also to general neurologists, learners, patients, and researchers.

The objective of this task force was to build a consensus on the classification of recessive ataxias in order to develop a general approach to a patient presenting with ataxia, organize disorders according to clinical presentation, and define this field of research by identifying common pathophysiological mechanisms in recessive disorders presenting with ataxia. This aims at bringing together clinicians and researchers to promote a common understanding of recessive cerebellar disorders in order to advance research and improve patient care.

2.4 Methods

The first step was to identify all recessive disorders presenting with ataxia. Recessive cerebellar ataxias were defined as disorders with autosomal recessive inheritance characterized by a cerebellar motor syndrome of gait ataxia, dysmetria, adiadochokinesia, nystagmus, and dysarthria associated with cerebellar degeneration as demonstrated by imagery or pathology. A pathogenic mutation had to be identified in at least two independent families for a specific gene to be included. Purely malformative disorders were excluded, and disorders with complex phenotypes where ataxia is a secondary or late feature were also excluded. We conducted a systematic scoping review of the literature to identify relevant reports. The methodology and results of this systematic scoping review have been published previously (3). In the first publication, this review process had allowed the identification of 2354 records and was current as of September 2016. The literature search was updated and is current as of October 2018.

The second step was to regroup a panel of 12 international ataxia experts to create a logical classification system and build a consensus. Ataxia experts were identified from various geographical regions and areas of expertise within the field of ataxias, ensuring proper representation of regional differences in prevalence and clinical approach to ataxias. Discussions spanned over two years, included meetings at two SRCA international conferences, and concerned general orientation, clinical approach, specific disorders, classification issues, and regional specificities. The first author (MB) reviewed identified records for inclusion, extracted clinical, epidemiological, and molecular data to build the classifications and wrote the text integrating all authors’ input and comments. All authors approved the final manuscript and list of included disorders.
2.5 Results

The final list of included recessive cerebellar ataxias is presented in Table 2.1 and includes 59 primary recessive ataxias, which regroup 15 disorders that are more prevalent and widely distributed and 44 disorders that are less frequent and reported only in certain populations or few families. Because ethnic and regional specificities are an essential element to consider in the appraisal of a patient with a recessive ataxia, areas where the disorder has been reported to date are listed. Metabolic or mitochondrial disorders where ataxia is only a secondary non-specific finding in a multisystemic phenotype were excluded, as cerebellar pathology is not central in these disorders. However, clinicians must bear in mind that some of these disorders may present with a milder juvenile or adult onset phenotype where cerebellar ataxia may predominate, for example in Niemann Pick disease type C, Tay-Sachs disease, sialic acid storage disorders, congenital disorders of glycosylation, and Zellweger spectrum disorders. As some of these metabolic disorders may benefit from early treatment, clinicians must keep a high index of suspicion to test for these disorders, and they should be included in large NGS gene panels for ataxia. These and other complex disorders that may occasionally present with ataxia are presented in Table 2.2. This second list is not exhaustive and presents only the main or most frequent disorders occasionally associated with ataxia. Disorders in which the cerebellar phenotype is not clearly established have been excluded.

Table 2.1 Primary autosomal recessive ataxias

Table 2.2 Other metabolic or complex disorders that have ataxia as an associated feature

Clinical approach to a patient presenting with ataxia

1° The first step in evaluating a patient with ataxia is to perform a detailed clinical evaluation that includes a clinical history, a family history, a targeted neurological and systemic physical evaluation, and relevant paraclinical tests. The temporal course is a central element in determining the underlying etiology. Indeed, a chronic progressive evolution over months to years, without trauma or toxin exposure, is suggestive of a hereditary disorder, whereas acute or subacute onset points towards an acquired etiology. A clinical history and physical examination are essential to assess the severity of the cerebellar syndrome and the presence of associated neurological features or systemic involvement. Headache, fever, or an associated autoimmune disorder should prompt the consideration of acquired etiologies. A detailed family history should be obtained to search for relatives with similar symptomatology. Laboratory tests may be useful to rule out acquired causes or as biomarkers for certain disorders. Neuroimaging, preferably with magnetic resonance imaging,
Electromyography and nerve conduction studies can prove the presence of clinically suspected or subclinical neuropathy and provide evidence of associated myopathy.

2° Following the clinical assessment, one should verify that acquired and treatable causes for ataxia have been excluded. These include vascular disease, trauma, infection, primary or metastatic tumor, excess alcohol consumption, vitamin deficiency, Creutzfeldt-Jakob disease, and immune mediated-cerebellar ataxias such as multiple sclerosis, celiac disease, anti-GAD (glutamic acid decarboxylase) ataxia, and paraneoplastic cerebellar degenerations. Clinical evaluation should reveal previous exposure to toxins or traumatic injuries, along with specific signs and symptoms suggestive of infectious, vascular or metastatic disease. Laboratory tests are useful to identify vitamin deficiencies or autoimmune conditions. Specifically, testing for antibodies involved in paraneoplastic or autoimmune cerebellar degeneration may be particularly useful for patients with a subacute progression, older age at onset and absence of family history. The paraneoplastic antibodies most associated with cerebellar degeneration are anti-Yo, anti-Hu, anti-Tr, and anti-mGluR1 antibodies; the tumors most often involved are breast and gynaecological tumors, Hodgkin lymphoma, and small cell lung carcinoma (5). Large paraneoplastic autoantibodies panels are now available and may reduce the delay associated with serial testing.

3° Once acquired causes have been ruled out, a genetic etiology may be considered, especially in the presence of a positive family history, early onset, chronic progressive course, or with a set of clinical signs and symptoms that is reminiscent of a well-described genetic disorder. One should bear in mind that a negative family history does not rule out a genetic cause, and sporadic cases may be due to recessive or mitochondrial inheritance, de novo mutations, genetic anticipation, incomplete penetrance, variability in disease expression, paternity error, gonadic mosaicism, or incomplete phenotyping of family members. Indeed, recessive disorders may appear as sporadic in small kindred or with incomplete family history. In other cases, a complete family history should allow identification of the mode of transmission.

4° If recessive inheritance is suspected, the next step in clinical evaluation is to consider age at onset and clinical signs and symptoms to evaluate if the clinical picture is reminiscent of a well-described disorder. Presentation in infancy suggests ataxia-telangiectasia (AT) or autosomal recessive ataxia of Charlevoix Saguenay (ARSACS). Childhood or teenage onset should raise the suspicion for Friedreich ataxia (FRDA), ataxia with oculomotor apraxia 1 (AOA1) and 2 (AOA2),
and POLG-related disorders. Finally, recessive ataxia with onset in adulthood is evocative of SYNE1-related autosomal recessive cerebellar ataxia 1 (ARCA1), autosomal recessive cerebellar ataxia 3 (ARCA3) associated with ANO10 mutations and spastic paraplegia 7. However, there are large variations in the age at onset of most of the presented disorders, and FRDA is one of the best examples with some patients presenting with late-onset FRDA (>25 years of age) or very-late-onset FRDA (>40 years of age).

Clinical signs and symptoms may provide clues to identify the mutated gene. Indeed, certain discriminating clinical features or combinations of neurological symptoms may be helpful to guide the clinician towards specific genes (Figure 2.1 and Table 2.1). As one may observe in Figure 2.1, none of the recessive ataxias reported up to now presents with a pure cerebellar phenotype. Even ARCA1, which used to be the prototype of a pure cerebellar phenotype (6), has recently been reported to be associated with upper and/or lower motor neuron involvement in 58% of cases, with some rare patients presenting with a very severe early-onset neuromuscular phenotype (7). The presence of motor neuron involvement, polyneuropathy, extra-pyramidal movement disorders, eye movement abnormalities such as oculomotor apraxia, intellectual impairment, and associated multisystemic involvement may guide the clinician towards a particular diagnosis. Some clinical syndromes are particularly evocative of specific disorders. Multisystemic involvement with sensory loss, muscle weakness, cardiomyopathy, diabetes, optic atrophy and sensorineuronal hearing loss is characteristic of FRDA, which is the prototype of a disorder associated with mitochondrial dysfunction. Other associated disorders present with similar features and occasionally epilepsy, retinal involvement, or ophthalmoplegia, such as POLG-related disorders, ARCA2, ataxia with vitamin E deficiency (AVED), Marinesco-Sjogren Syndrome (MSS), and others. Extra-pyramidal involvement with oculomotor apraxia, elevated α-fetoprotein, and occasional polyneuropathy are typical findings of AT, AT-like disorder, AOA1, AOA2, AOA4 and Spinocerebellar ataxia recessive 26 (SCAR26). All these disorders are associated with genes involving DNA repair systems, which highlights how clinical symptoms may reflect the underlying genetic defect. Nevertheless, recessive ataxias are characterized by important phenotypic variability and significant clinical overlap between different pathologies, such that predicting the mutated gene according to the clinical phenotype is prone to errors even for ataxia experts (8). Some laboratory tests may serve as useful biomarkers for recessive ataxias. Altered levels of vitamin E, α-fetoprotein, albumin, coenzyme Q10, cholesterol, cholestanol, lactate, sex hormones and gonadotropins have been associated with specific disorders (see Table 2.1). Dosing of immunoglobulins, very long chain fatty acids and hexosaminidase may be relevant according to clinical suspicion.
5° Once the clinical assessment is complete, genetic testing is indicated to confirm the mutated gene or allow a more specific diagnosis if the clinical picture is nonspecific. Initial testing should include searching for the Friedreich ataxia-associated trinucleotide repeat expansion in the FXN gene considering the high prevalence of this mutation, its incomplete coverage through next-generation sequencing methods (1), and the heterogeneous clinical phenotype. Searching for a FXN repeat expansion can be done with frataxin protein analysis or gene analysis with Southern blot or PCR. Moreover, clinicians may consider testing for another specific gene through Sanger sequencing or Multiplex Ligation-dependant Probe Amplification (MLPA) if the clinical and paraclinical data is highly evocative of a particular disorder, if there is a confirmed mutation in a relative, or in isolated populations where selected disorders are highly prevalent. Finally, a panel for the dominantly inherited CAG-repeat expansion spinocerebellar ataxias may also be considered as part of the initial assessment if family history is inconclusive regarding the mode of inheritance and considering the high prevalence of these mutations and their incomplete coverage through next-generation sequencing methods (1).

6° If single gene testing does not provide a molecular diagnosis, one should consider high-throughput NGS methods either with a multigene panel, whole exome sequencing or whole genome sequencing. Several studies have demonstrated the efficacy and cost efficiency of multigene panels (9), targeted exome sequencing (8, 10), or whole exome sequencing (11, 12), with a diagnostic yield varying between 18% and 80%. Highest yield is obtained for patients with early-onset ataxia, positive family history and consanguinity among parents. NGS panels allow for better coverage of included genes and reduce the volume of genetic variants that are unrelated to the clinical phenotype, while exome sequencing may reveal mutations in genes that were not previously known to be associated with ataxia (1). Whole genome sequencing may be considered in selected cases with appropriate genetic counseling, but its diagnostic yield is uncertain (13). Once genetic testing is completed and a pathogenic mutation has been identified, it is of primary importance to provide specialized genetic counseling for the patient and his or her relatives along with symptoms management and disease treatment when available.
Pathophysiological mechanisms underlying recessive cerebellar ataxias

The importance of a proper recessive ataxia classification goes beyond the clinical diagnosis perspective. Recessive ataxias can be regrouped according to the deficient cellular and metabolic pathways involved, which provides a better understanding of cerebellar physiology and of its selective vulnerability to certain metabolic processes. This is also essential from a therapeutic perspective, as disorders that belong to the same metabolic pathway may respond to the same treatment options, which presents drug repurposing potential. Figure 2.3 presents the main pathways involved in cerebellar ataxias. Certain genes are presented more than once since some proteins are involved in several metabolic pathways or may interfere with other cellular processes as they accumulate in neurons or glial cells.

Figure 2.3 Classification of autosomal recessive ataxias according to molecular pathogenesis

Certain pathways are predominantly involved, notably mitochondrial dysfunction, which may result from increased production of reactive oxygen species and oxidative stress (ATM, FXN, TTPA), deficient Coenzyme Q10 metabolism (APTX, COQ8A), abnormal mitochondrial DNA maintenance with progressive mutagenesis (PNKP, POLG, TWNK), defective mitochondrial protein synthesis or quality control (AFG3L2, PMPCA, SPG7), altered mitochondrial dynamics (SACS, VPS13D), defective mitochondrial respiratory chain assembly (COA7, COX20), or abnormal mitochondrial RNA maturation and processing (DARS2, MTPAP). Interestingly, many of these disorders also present with a mitochondrial clinical syndrome as shown in Figure 1. Disorders of DNA repair mechanisms are also common, with double strand break repair pathway (ATM, MRE11A, SETX, TDP2) or single strand break repair complexes (APTX, PNKP, XRCC1) predominantly involved. Most of these genes are also associated with a susceptibility to ionizing radiations and predisposition for cancers, but the neurological syndrome is characterized by cerebellar involvement and extra-pyramidal movement disorders. Hence, the cerebellum seems to have a peculiar susceptibility to DNA damage, but the underlying mechanism is not understood. Finally, altered synaptic morphology or synaptic dysfunction of Purkinje cells (PC) is frequently involved in recessive ataxias, and is characterized by aberrant morphology at the PC/parallel fibers synapse (CA8, CAPN1, GRID2, ITPR1), impaired dendritic architecture (SPTBN2, SYNE1), or dysregulation of glutamate transmission (ATCAY, GRM1). Other disorders have been implicated in synaptic dysfunction through indirect evidence, for example SLC9A1, which localizes in presynaptic terminals and is involved in the modulation of synaptic activity (14). Of interest, many of these disorders are characterized by significant cognitive impairment that goes beyond what is expected in the cerebellar cognitive-affective syndrome and cause intellectual disability,
developmental delay or dementia, highlighting the importance of synaptogenesis in cognitive development.

2.6 Discussion

We present a new clinical classification of recessive ataxias in parallel with a pathophysiological classification. The objective of this classification is to provide a tool for clinicians and researchers that facilitates the understanding of this complex group of disorders and defines this field of research. This work is based on the results of our systematic scoping review of the literature (3). We updated this literature review and regrouped a panel of 12 international ataxia experts to build a consensus on the definition and classification of cerebellar ataxias. The task force vision is that a classification goes beyond the listing of disorders, and must organize diseases in a way that allows better understanding and clinical mastery of this group of disorders. Hence, we proposed a clinical classification along with a pathophysiological classification, which enabled us to observe that there is significant overlap between these two classifications, highlighting how clinical presentation is in some cases a good projection of the underlying biochemical defect. This has potential applications from bench to bedside since treatments that address a specific pathogenic pathway may have therapeutic potential in all disorders in which this pathway is affected. The clinical classification is presented along with a structured clinical approach to a patient presenting with ataxia, which is intended as a clinical tool for expert and non-expert clinicians. Despite the increasing accessibility of NGS techniques, there remains a critical place for clinical judgment in the prescription of genetic tests and interpretation of results, taking into account the technical limitations and risk of finding variants of unknown significance. Recently, Renaud and colleagues published the results of a diagnostic algorithm for recessive ataxias that integrates 124 clinical features to propose three potential diagnoses among a list of 67 recessive disorders that may present with ataxia (15). This is a very promising tool, but its pragmatic impact on molecular testing strategy, final diagnostic rate, patient management, or time-efficiency remains to be validated. In the meantime, it is essential for clinicians to be at ease with a general approach to recessive ataxias with NGS techniques often permitting molecular diagnosis when the clinical picture is non-specific.

One of the major strengths of this classification proposal is that it is based on a consensus from a panel of international ataxia experts, thereby ensuring a proper representation of regional differences in the prevalence and clinical approach to ataxias. Moreover, the literature search was based on a systematic scoping review of the literature whose methodology has been published before and which permitted an unbiased appraisal of all potentially relevant articles. Nevertheless, there are some limitations to this classification proposal that are inherent to classifying a group of
diseases that evolves very rapidly and that is highly heterogeneous. First, as new evidence emerges regarding the identification of novel ataxia-associated genes and as new phenotypes are described for previously described disorders, this classification will need to be updated. This was highlighted by the significant additions to the list of primary recessive ataxias since the original systematic review was conducted in 2016. Indeed, many new genes and new phenotypes of previously described genes have been reported in only two years, which suggests that there is a need for periodic updates to the present classification or an online resource. Moreover, several decisions were made in the elaboration of this classification regarding general orientation, purpose of a classification, inclusion of specific disorders, and classification categories. The lists presented here offer in our opinion the best compromise between synthesis and exhaustiveness for the expert and non-expert clinician.

Compared to a previously published report by the Movement Disorders Society Task Force (4), we decided to exclude disorders in which cerebellar involvement is a minor or late finding in a complex multisystem phenotype or disorders that are already classified on their own such as genes associated with Joubert syndrome. The objective was to identify the core disorders that are involved in recessive ataxias in order to define this field of research and build a classification that would be accessible for all clinicians. Indeed, with the progressive advent of affordable NGS diagnostic testing, we believe that it is most important for clinicians to be at ease with one classification and familiar with the most frequent disorders in their unique ethnical and clinical context. Disorders in which ataxia has been reported as a rare or late finding should be included in large NGS testing strategies, but in our opinion should not be categorized as primary ataxias per se. From this perspective, our classification complements the proposal by the Movement Disorders Society Task Force.

There remain some important challenges to be addressed in the field of recessive ataxias. First, the issue of a proper nomenclature system has been much debated. Recently, the Movement Disorders Society Task Force proposed a revised naming system based on an ataxia prefix associated with the gene name (4); this was part of a larger effort to revise the nomenclature of all genetic movement disorders. This system overcomes the limitations of the numbered nomenclature, notably unconfirmed genes and erroneously attributed phenotypes, but its ease of use by non-experts and patients remains uncertain. Moreover, some disorders were assigned as many as three phenotypic prefixes while some other disorders that are among the most prevalent causes of recessive ataxia, such as POLG, were not assigned an ataxia prefix. Hence, there remains a debate concerning the attribution of prefixes and the integration of this naming system with other fields in neurology and
other specialties as many genes involved in ataxia have very complex multisystem phenotypes. Finally, one of the most important challenges in this field of orphan diseases is to develop targeted treatment strategies that address the pathogenic mechanism underlying symptoms progression. To this end, we believe that identifying common pathophysiological pathways may provide an opportunity for drug repurposing or enlarge the number of patients that are admissible for drug trials in order to find treatments for these rare but debilitating diseases.

2.7 Conclusion

We present a clinical and a pathophysiological classification of autosomal recessive ataxias along with a clinical approach to a patient presenting with ataxia. This classification is the result of a consensus among a panel of international experts, and it promotes a unified understanding of recessive cerebellar disorders for clinicians and researchers.

2.8 Tables

Table 2.1 Primary recessive cerebellar ataxias

<table>
<thead>
<tr>
<th>MDS Nomenclature¹ or gene name</th>
<th>OMIM</th>
<th>Geographic specificities</th>
<th>Additional clinical clues and neuroimaging findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most prevalent ataxias</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATX-FXN FRDA</td>
<td>229300</td>
<td>Most prevalent in populations of European descent, Middle East and North Africa; absent in Far East populations</td>
<td>Bilateral Babinski sign, square-wave jerks, scoliosis, hypertrophic cardiomyopathy, sensory involvement, teenage onset, spinal cord atrophy, absence of cerebellar atrophy</td>
<td>(16, 17)</td>
</tr>
<tr>
<td>ATX-ATM AT</td>
<td>208900</td>
<td>Second most common cause of recessive ataxia worldwide, especially in regions with low inbreeding</td>
<td>Telangiectasias, oculomotor apraxia, photosensitivity, immunodeficiency, predisposition for cancer, dystonia, myoclonus, choreoathetosis, tremor, elevation of α-fetoprotein, infantile onset, cerebellar atrophy</td>
<td>(18-20)</td>
</tr>
<tr>
<td>ATX-APTX AOA1/EAOH</td>
<td>208920</td>
<td>Most prevalent in Japan; second most prevalent ataxia in Portugal</td>
<td>Oculomotor apraxia, cognitive impairment, axonal motor polyneuropathy, late onset of hypoalbuminemia, elevated α-fetoprotein and hypercholesterolemia, childhood onset, cerebellar atrophy</td>
<td>(21-23)</td>
</tr>
<tr>
<td>ATX-SETX AOA2</td>
<td>606002</td>
<td>Worldwide, second most prevalent in Eastern France</td>
<td>Axonal sensorimotor polyneuropathy, pyramidal signs, oculomotor apraxia, head tremor, chorea, dystonia, elevation of α-fetoprotein, teenage onset, cerebellar atrophy</td>
<td>(24-26)</td>
</tr>
<tr>
<td>ATX/HSP-SACS ARSACS</td>
<td>270550</td>
<td>Worldwide</td>
<td>Spastic paraparesis, retinal striation with thickened retinal nerve fibres, sensorimotor neuropathy, pes cavus, infantile or childhood onset, anterior superior cerebellar atrophy, occasional T2-weighted linear hypointensities in pons</td>
<td>(27, 28)</td>
</tr>
<tr>
<td>POLG MIRAS, SANDO, SCAE</td>
<td>607459</td>
<td>Prevalent in populations of European descent, especially Scandinavia, UK and Belgium.</td>
<td>Cerebellar and sensory ataxia, dysarthria, progressive external ophthalmoplegia, myoclonus, epilepsy, myopathy, migraine, variable age at onset, signal abnormalities in cerebellum and thalamus</td>
<td>(29, 31)</td>
</tr>
<tr>
<td>ATX-SYNE1 ARCA1</td>
<td>610743</td>
<td>Worldwide</td>
<td>Pure cerebellar ataxia with occasional upper and/or lower motor neuron involvement, cognitive impairment, late onset, cerebellar atrophy</td>
<td>(6, 7, 32)</td>
</tr>
<tr>
<td>HSP/ATX-SPG7 SPG7</td>
<td>607259</td>
<td>Described worldwide, frequent in Europe</td>
<td>Spasticity, pyramidal signs, optic neuropathy, ptosis, ophthalmoparesis, bladder dysfunction, adult onset, cerebellar atrophy</td>
<td>(33, 34)</td>
</tr>
<tr>
<td>COQ8A (ATX-HSP-SACS) ARCA2</td>
<td>612016</td>
<td>European descent, Algeria, Middle East</td>
<td>Exercise intolerance, epilepsy, myoclonus, developmental delay, intellectual disability</td>
<td>(35, 36)</td>
</tr>
<tr>
<td>Gene</td>
<td>ARCA3</td>
<td>ARCA3 Accession</td>
<td>Description</td>
<td>Prevalence</td>
</tr>
<tr>
<td>-------------</td>
<td>-------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ADCK3</td>
<td>613728</td>
<td></td>
<td>Childhood onset, cerebellar atrophy, occasional stroke-like cerebral lesions</td>
<td></td>
</tr>
<tr>
<td>ATX-ANO10</td>
<td>277460</td>
<td>Worldwide, high prevalence around Mediterranean sea</td>
<td>Dorsal column involvement, areflexia, retinitis pigmentosa, head titubation, low serum vitamin E, skeletal disfigurements, teenage onset, spinal cord atrophy, occasional cerebellar atrophy</td>
<td>Worldwide, high prevalence around Mediterranean sea</td>
</tr>
<tr>
<td>ATX-TTPA</td>
<td>213700</td>
<td>Worldwide</td>
<td>Dementia, pyramidal signs, tendon xanthomas, atherosclerosis, cataracts, diarrhea, elevated serum cholesterol, polyneuropathy, childhood to adult onset, variable cerebellar atrophy, cerebellar or cerebral white matter anomalies</td>
<td>Worldwide, high prevalence around Mediterranean sea</td>
</tr>
<tr>
<td>ATX-CYP27A1</td>
<td>248800</td>
<td>Worldwide</td>
<td>Cataracts, intellectual disability, myopathy, short stature, childhood onset, cerebellar atrophy</td>
<td>Worldwide, high prevalence around Mediterranean sea</td>
</tr>
<tr>
<td>ATX-SIL1</td>
<td>271245</td>
<td>Described worldwide, highly prevalent in Finland</td>
<td>Ataxia, sensory axonal neuropathy, hypotonia, optic atrophy, ophthalmoplegia, sensorineural deafness, areflexia, hypogonadism, liver involvement, infantile onset, atrophy of brainstem and cerebellum</td>
<td>Described worldwide, highly prevalent in Finland</td>
</tr>
</tbody>
</table>

**Rare ataxias or described only in few families**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Accession</th>
<th>Description</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATX-ABHD1</td>
<td>612674</td>
<td>Europe, USA, Middle East, Algeria</td>
<td>Demyelinating sensorimotor neuropathy, pes cavaus, cataracts, hearing loss, retinitis pigmentosa, teenage onset, cerebellar atrophy</td>
</tr>
<tr>
<td>ATX/HSP</td>
<td>614487</td>
<td>Colombia, Saudi Arabia</td>
<td>Ataxia, spasticity, oculomotor apraxia, myoclonic epilepsy, neuropathy, extrapyramidal involvement, optic atrophy, severe cases with developmental regresion, microphthalmia, hysparrythmia and intractable epilepsy, infantile to childhood onset, cerebellar atrophy</td>
</tr>
<tr>
<td>AFG3L2</td>
<td>610238</td>
<td>Grand Caiman Island, Pakistan</td>
<td>Psychomotor retardation, hypotonia, strabismus, bradykinesia, occasional dystonia, neonatal or infantile onset, cerebellar hypoplasia</td>
</tr>
<tr>
<td>ATCAY</td>
<td>613227</td>
<td>Iran, Saudi Arabia, Syria</td>
<td>Mild intellectual disability, occasional quadrapedal gait, tremor, hyperreflexia, congenital onset, cerebellar atrophy, periventricular white matter anomalies</td>
</tr>
<tr>
<td>ATX-CA8</td>
<td>616907</td>
<td>Europe, Middle East, Brazil, Japan, Punjab</td>
<td>Pyramidal signs, pes cavaus, dystarthis, ataxia, slow saccades, cognitive impairment, teenage to adult onset, vermin cerebellar atrophy</td>
</tr>
<tr>
<td>ATX-CAPN1</td>
<td>615651</td>
<td>Europe, North Africa, Turkey, Japan</td>
<td>Chorioretinopathy, optic neuropathy, learning disability, headaches, occasional mild spasticity, childhood to adult onset, T2 hypersignal in cerebellar and cerebral peduncles with internal capsule, myelin microvaculatation</td>
</tr>
<tr>
<td>ATX-CLCN2</td>
<td>220110</td>
<td>Italy, Japan</td>
<td>Sensorimotor neuropathy, hypoflexia, mild cognitive impairment, elevated serum creatine kinase, elevated lactate and pyruvate, ragged red fibers, infantile to childhood onset, cerebellar atrophy, supratentorial leucopathy, spinal cord atrophy</td>
</tr>
<tr>
<td>ATX-COX2</td>
<td></td>
<td>Turkey</td>
<td>Growth retardation, pyramidal signs, sensory neuropathy, extra-pyramidal features, elevation of blood lactate, childhood or teenage onset, cerebellar atrophy</td>
</tr>
<tr>
<td>ATX-CWF19L1</td>
<td>616127</td>
<td>Turkey, Netherlands</td>
<td>Intellectual disability, congenital to infantile onset, cerebellar atrophy</td>
</tr>
<tr>
<td>HSP/ATX</td>
<td>270800</td>
<td>Worldwide, prevalent in Europe</td>
<td>Pyramidal signs, dorsal column sensory deficits, urger incontinence or voiding, childhood or teenage onset, white matter lesions</td>
</tr>
<tr>
<td>HSP/ATX</td>
<td>611105</td>
<td>Worldwide, high carrier rate in Finland</td>
<td>Pyramidal signs, dorsal column dysfunction, axonal neuropathy, tremor, cerebral lactic acidosis, seizures, infantile to adult onset, signal abnormalities in cerebral white matter and specific brainstem and spinal cord tracts</td>
</tr>
<tr>
<td>ATX-DNAJC19</td>
<td>610198</td>
<td>Canadian Hutterite population, Finland, Turkey</td>
<td>Dilated cardiomyopathy, non-progressive cerebellar ataxia, intellectual disability, testicular dysgenesis, anemia, increased urinary 3-methylglutatonic acid, infantile onset, progressive cerebellar atrophy</td>
</tr>
<tr>
<td>HSP/ATX</td>
<td>614409</td>
<td>Tunisia, Cyprus, Italy, Norway</td>
<td>Pyramidal signs, spastic dystarthis, cognitive impairment, hearing loss, cataracts, urger</td>
</tr>
<tr>
<td>Condition</td>
<td>Gene</td>
<td>Region/Population</td>
<td>Clinical Features</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>GDAP2</td>
<td>-</td>
<td>Belgium, Dutchland, Egypt</td>
<td>Pyramidal signs, cognitive impairment, adult onset, cerebellar atrophy, thin corpus callosum</td>
</tr>
<tr>
<td>ATX/HSP-GJC2</td>
<td>HLD2 or Pelzcau-Merzbacher-like disease</td>
<td>608804 Worldwide</td>
<td>Nystagmus, hypotonia progressing to spastic tetraparesis, developmental delay, dystonia, chorea, neonatal to infantile onset, diffuse hypomyelination</td>
</tr>
<tr>
<td>MYC/ATX-GOSR2</td>
<td>Progressive myoclonic epilepsy 6</td>
<td>614018 North Sea region</td>
<td>Absence, myoclonic seizures, scoliosis, late cognitive impairment, axonal sensory neuropathy and anterior horn cell involvement, raised creatine kinase, infantile onset, occasional cerebellar atrophy</td>
</tr>
<tr>
<td>ATX-GRID2</td>
<td>SCAR18</td>
<td>Middle East, Morocco</td>
<td>Developmental delay, intellectual disability, occasional pyramidal signs, short stature, seizures, congenital onset, cerebellar atrophy; allelic with SCA4</td>
</tr>
<tr>
<td>GRM1</td>
<td>SCAR13</td>
<td>Roma ethnic group in Bulgaria</td>
<td>Developmental delay, intellectual disability, occasional pyramidal signs, short stature, seizures, congenital onset, cerebellar atrophy; allelic with SCA44</td>
</tr>
<tr>
<td>ATX-GRN</td>
<td>CLN11</td>
<td>Italy, Portugal, Brazil</td>
<td>Myoclonic epilepsy, retinopathy, dementia, adult onset, cerebellar atrophy</td>
</tr>
<tr>
<td>ATX-ITPR1</td>
<td>Gillespie syndrome</td>
<td>206700 Brazil, Europe, North Africa, Middle East, Asia, Caribbean islands</td>
<td>Autosomal recessive and dominant transmission. Non-progressive cerebellar ataxia, iris hypoplasia, hypotonia, intellectual disability, facial dysmorphism, neonatal onset, progressive cerebellar atrophy; allelic with SCA15 and SCA29</td>
</tr>
<tr>
<td>HSP/ATX-KIF1C</td>
<td>SPAX2/SPG58</td>
<td>611302 Palestine, Morocco, Turkey, Germany</td>
<td>Spastic paraparesis with pyramidal signs, tremor, childhood or teenage onset, T2 hyperintensity in internal capsules, paretical and occipital white matter, cerebellar peduncles, and pyramidal tracts</td>
</tr>
<tr>
<td>ATX-KCNJ10</td>
<td>EAST/SeSAME syndrome</td>
<td>612780 Africa, Middle East, India, Caucasian, Afro-Caribbean population</td>
<td>Epilepsy, sensorineural deafness, intellectual disability, tubulopathy and electrolyte imbalance, hypotonia progressing to spasticity, infantile onset, cerebellar hypoplasia, signal anomaly in dentate nuclei</td>
</tr>
<tr>
<td>ATX-L2HGDD</td>
<td>L-2-hydroxyglutaric aciduria</td>
<td>236792 Worldwide</td>
<td>Developmental delay, macrocephaly, hypotonia, elevated levels of L-2-hydroxyglutaric acid, infantile to adult onset, subcortical white matter, dentate nuclei and basal ganglia signal anomalies, cerebellar atrophy</td>
</tr>
<tr>
<td>ATX-MRE11A</td>
<td>ATLD</td>
<td>604391 Described in Europe, Saudi Arabia, Canada, Pakistan and Japan.</td>
<td>Oculomotor apraxia, extra-pyramidal movement disorders, occasional myoclonus, childhood onset, cerebellar atrophy</td>
</tr>
<tr>
<td>MTPAP</td>
<td>SPAX4</td>
<td>613672 Amish families</td>
<td>Pyramidal signs, optic atrophy, sensitivity to ionizing radiations, developmental delay, cognitive impairment, growth failure, infantile onset</td>
</tr>
<tr>
<td>ATX-PEX10</td>
<td>PBD 6B or ZSD</td>
<td>614871 Caucasians, Japan</td>
<td>Axonal motor or sensorimotor neuropathy, variable cognitive impairment, nystagmus, hypo or hyperreflexia, childhood to adolescent onset, cerebellar atrophy</td>
</tr>
<tr>
<td>ATX-PMPCA</td>
<td>SCAR2</td>
<td>213200 Lebanon, France, French Canadians</td>
<td>Intellectual disability, hypotonia, short stature, severe phenotype with lactic academia and ophthalmoplegia, congenital or infantile onset, cerebellar atrophy</td>
</tr>
<tr>
<td>PNKP</td>
<td>AOA4</td>
<td>616267 European descent</td>
<td>Dystonia, oculomotor apraxia, sensorimotor polyneuropathy, cognitive impairment, childhood onset, cerebellar atrophy</td>
</tr>
<tr>
<td>ATX/HSP-PNPLA6</td>
<td>BNS/GHS/DMCS</td>
<td>215470, 275400 Worldwide</td>
<td>Hypogonadotropic hypogonadism, chorioretinal dystrophy, pyramidal signs, childhood onset, atrophy of cerebellum and pons; allelic to HSP39</td>
</tr>
<tr>
<td>ATX/HSP-POLR3A</td>
<td>HLD7, 4H syndrome</td>
<td>607694 Worldwide</td>
<td>Tremor, variable cognitive impairment, spasticity, hyperreflexia, variable hypodontia and dysmorphism, hypogonadotropic hypogonadism, myopia, short stature, infantile to childhood onset, diffuse cerebral hypomyelination, cerebellar atrophy, thin corpus callosum, T2 hypointense thalalunus</td>
</tr>
<tr>
<td>ATX-POLR3B</td>
<td>HLD8</td>
<td>614381 Japan, Caucasians, Syria, African American</td>
<td>Intellectual disability, vertical gaze limitation, hypodontia, hypogonadotropic hypogonadism, myopia, mild hyperreflexia, short stature, infantile</td>
</tr>
<tr>
<td>Gene</td>
<td>Syndrome/Description</td>
<td>Location</td>
<td>Population</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>------------</td>
</tr>
<tr>
<td>ATX-RNF216</td>
<td>Mediterranean to childhood onset, diffuse cerebral hypomyelination with partly myelinated internal capsule, cerebellar atrophy, thin corpus callosum, T2 hypointense thalamus</td>
<td>Middle East, Caucasians</td>
<td>212840</td>
</tr>
<tr>
<td>SCYL1</td>
<td>44</td>
<td>European, Middle East, Cuba, Ashkenazi Jews</td>
<td>616719</td>
</tr>
<tr>
<td>ATX-SNX14</td>
<td>44</td>
<td>Portugal, Middle East, North Africa, Central Asia</td>
<td>616354</td>
</tr>
<tr>
<td>SLC9A1</td>
<td>44</td>
<td>Turkey, Han Chinese</td>
<td>616291</td>
</tr>
<tr>
<td>ATX-SPTBN2</td>
<td>44</td>
<td>Middle East, Egypt, North America</td>
<td>615386</td>
</tr>
<tr>
<td>ATX-STUB1</td>
<td>44</td>
<td>China, Middle East, Caucasians</td>
<td>615768</td>
</tr>
<tr>
<td>TDP2</td>
<td>44</td>
<td>Ireland, USA</td>
<td>616949</td>
</tr>
<tr>
<td>ATX-TPP1</td>
<td>44</td>
<td>The Netherlands, African American population</td>
<td>609270</td>
</tr>
<tr>
<td>HSP/ATX-UCHL1</td>
<td>44</td>
<td>Norway, Turkey</td>
<td>615491</td>
</tr>
<tr>
<td>ATX-VLDR</td>
<td>44</td>
<td>North American Hutterite population, Middle East, Europe</td>
<td>224050</td>
</tr>
<tr>
<td>VPS13D</td>
<td>44</td>
<td>Europe, USA, French Canadian, Egyptian, Javanese</td>
<td>607317</td>
</tr>
<tr>
<td>ATX-WDR81</td>
<td>44</td>
<td>Turkey, Yemen</td>
<td>610185</td>
</tr>
<tr>
<td>XRCC1</td>
<td>44</td>
<td>India, Pakistan</td>
<td>617633</td>
</tr>
</tbody>
</table>

In part inspired from (3).

1 MDS nomenclature: Nomenclature proposed by the Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders (4) with a phenotypical prefix followed by the gene name. ATX Ataxia; HSP Hereditary spastic paraplegia; MYC Myoclonus.

2 Acronyms: AOA ataxia with oculomotor apraxia; ARCA autosomal recessive cerebellar ataxia; ARSACS autosomal recessive spastic ataxia of Charlevoix-Saguenay; AT ataxia-telangiectasia; ATLD ataxia-telangiectasia-like disorder; AVED ataxia with vitamin E deficiency; BNS Boucher-Neuhäuser syndrome; CA Cayman ataxia; CAMRQ cerebellar ataxia mental retardation with or without quadripedal locomotion; DCMA Dilated cardiomyopathy with ataxia; DES Desequilibrium syndrome; EAOH Early-onset ataxia with oculomotor apraxia and hypoalbinemia FRDA Friedreich ataxia; GHS Gordon Holmes Syndrome; HLD hypomyelinating leukodystrophy; IOSCA infantile onset spinocerebellar ataxia; LIKNS Lichtenstein-Knorr syndrome; MGCAS 3-methylglutaconic aciduria type 5; MIRAS mitochondrial recessive ataxia syndrome; Mitochondrial complex 4 deficiency; MSS Marinesco-Sjogren syndrome; MTDP7 mitochondrial DNA depletion syndrome 7; NBI Neurodegeneration with brain iron accumulation; OMCS Oliver McFarlane Syndrome; PBD Peroxisome biogenesis disorder; PEOA3 progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal dominant 3; PHARC polynuropathy hearing loss ataxia retinitis pigmentosa and cataract; SANDO sensory ataxic neuropathy with dystarthis and ophthalmparesis; SCAE spinocerebellar ataxia with epilepsy SCAN1 spinocerebellar ataxia with axonal
Table 2.3 Other metabolic or complex recessive disorders that have ataxia as an associated feature

<table>
<thead>
<tr>
<th>MDS Nomenclature(^1) or gene name</th>
<th>Alternate nomenclature (^2)</th>
<th>OMIM</th>
<th>Additional clinical clues</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATX-AH1</td>
<td>Joubert syndrome (including COACH syndrome)</td>
<td>Many, see 213300</td>
<td>Developmental delay, ataxia, hypotonia, neonatal breathing abnormalities, intellectual disability, nephropathitis, congenital onset, agenesia of the cerebellar vermis with molar tooth sign; in COACH syndrome, associated with occular colobomas and hepatic fibrosis</td>
<td>(141, 142)</td>
</tr>
<tr>
<td>ATX-ALDH5A1</td>
<td>Succinic semialdehyde dehydrogenase deficiency</td>
<td>603147</td>
<td>Developmental delay, intellectual disability, language dysfunction, hypotonia, hyporeflexia, autistic behavior and hallucinations, infantile to childhood onset, T2 hypersignal in globi pallidi</td>
<td>(143, 144)</td>
</tr>
<tr>
<td>ATX-ALG6</td>
<td>CDG1c</td>
<td>603147</td>
<td>Developmental delay, hypotonia, seizures, protein-losing enteropathy, psychiatric manifestations, nystagmus, strabismus, failure to thrive, dysmorphic features, neonatal to infantile onset, occasional brain atrophy</td>
<td>(145, 146)</td>
</tr>
<tr>
<td>DYT/ATX-ATP7B</td>
<td>Wilson disease</td>
<td>277900</td>
<td>Tremor, dystonia, parkinsonism, choreoathetosis, liver disease, psychiatric involvement, Kayser-Fleischer rings, childhood to adult onset, T2 hypersignal in basal ganglia or brainstem</td>
<td>(147)</td>
</tr>
<tr>
<td>ATP8A2</td>
<td>CAMRQ4</td>
<td>615268</td>
<td>Global development delay, cognitive impairment, microcephaly, ataxia or quadrapedal gait, choreoathetoid movement, congenital onset, cerebellar and cerebral atrophy or delay in myelination</td>
<td>(148, 149)</td>
</tr>
<tr>
<td>HSP/ATX-B4GALNT1</td>
<td>SPG26</td>
<td>609195</td>
<td>Pyramidal signs, ataxia, spastic paraplegia, cognitive impairment, axonal peripheral neuropathy, occasional cerebellar ataxia and extrapyramidal signs, scoliosis, childhood to teenage onset, cerebral cortical atrophy, T2 white matter hypointensity</td>
<td>(150)</td>
</tr>
<tr>
<td>ATX-BTD</td>
<td>Biotinidase deficiency</td>
<td>253260</td>
<td>Seizures, hypotonia, developmental delay, optic atrophy, sensorineural hearing loss, skin rash, alopecia, hepatosplenomegaly, optic atrophy, exacerbation during infections, infantile to childhood onset, white matter anomalies including delayed demyelination</td>
<td>(151, 152)</td>
</tr>
<tr>
<td>MYC-CLN</td>
<td>CLN</td>
<td>256731</td>
<td>Myoclonic epilepsy, psychomotor retardation or regression, ataxia, visual loss, ataxia, infantile to adult onset, cerebellar and cortical atrophy</td>
<td>(153)</td>
</tr>
<tr>
<td>NBIA/DYT/PARK-CP</td>
<td>Acruloplasminemia</td>
<td>604290</td>
<td>Diabetes, dementia, parkinsonism, dystonia, cerebellar ataxia, retinal degeneration, involuntary movements, anemia, low serum and urinary copper, adult onset, decreased signal intensity in thalamus, basal ganglia and dentate nucleus</td>
<td>(154)</td>
</tr>
<tr>
<td>MYC/ATX-CSTB1</td>
<td>Unverricht and Lundborg disease/EPM1</td>
<td>254800</td>
<td>Stimulus-sensitive and action-sensitive myoclonus, tonic-clonic generalized seizures, mild cerebellar ataxia, cognitive impairment, emotional lability, childhood to adolescent onset, normal brain MRI</td>
<td>(155)</td>
</tr>
<tr>
<td>EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5</td>
<td>Vanishing white matter disease</td>
<td>603896</td>
<td>Cerebellar ataxia with spasticity, clinical deterioration following head trauma, febrile illness or surgery, infantile to adult onset, symmetric and diffusely abnormal cerebral white matter that appears isointense to cerebrospinal fluid</td>
<td>(156, 157)</td>
</tr>
<tr>
<td>MYC/ATX-EPM2A MYC/ATX-NHLRC1</td>
<td>Lafora disease</td>
<td>607566</td>
<td>Myoclonus, generalised tonic-clonic seizures, occipital seizures, headaches, behavioural deterioration, rapidly progressive dementia, cerebellar ataxia, spasticity, adolescent onset, normal initial brain MRI with progressive diffuse atrophy</td>
<td>(158, 159)</td>
</tr>
<tr>
<td>ERCC4</td>
<td>Xeroderma pigmentosum/Cockayne syndrome</td>
<td>278760</td>
<td>Photosensitivity, solar lentigines growth retardation, microcephaly, ataxia, chorea, cognitive impairment, adolescent to adult onset, cerebellar and brainstem atrophy</td>
<td>(160, 161)</td>
</tr>
<tr>
<td>HSP/ATX/NBIA-FA2H</td>
<td>SPG35/FAHN</td>
<td>612319</td>
<td>Spastic paraparesis, pyramidal signs, dystonia, ataxia, dystarthis, optic atrophy, seizures, cognitive impairment, childhood to adolescent onset, T2 subcortical and periventricular white matter hyperintensity, atrophy of cerebellum and brainstem</td>
<td>(162)</td>
</tr>
<tr>
<td>ATX/HSP-FOLR1</td>
<td>Neurodegeneration due to cerebral folate transport</td>
<td>613068</td>
<td>Developmental regression, hypotonia, myoclonic, tonic or atactic seizures, cerebellar ataxia, chorea, tremor, autism spectrum disorder, occasional pyramidal signs, infantile onset, delayed myelination in cerebral white matter, cerebellar atrophy</td>
<td>(163, 164)</td>
</tr>
<tr>
<td>Gene/Comorbidity</td>
<td>Description</td>
<td>Onset and Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSP/ATX-GAN1</td>
<td>Giant axonal neuropathy I</td>
<td>Peripheral sensorimotor neuropathy, weakness, ataxia, dysarthria, pes cavus, typical frizzy hair, infantile to teenage onset, cerebellar atrophy</td>
<td>(165, 166)</td>
<td></td>
</tr>
<tr>
<td>DYT/PARK-GLB1</td>
<td>GM1 gangliosidosis type II</td>
<td>Developmental regression in childhood with gait disorder and cognitive impairment, dystonia, hepatosplenomegaly, ataxia, skeletal dysplasia, cardiomyopathy, infantile to childhood onset, progressive diffuse atrophy</td>
<td>(167, 168)</td>
<td></td>
</tr>
<tr>
<td>ATX/HSP-HEXAB</td>
<td>Tay-Sachs disease</td>
<td>Infantile form with weakness, motor regression, cerebellar atrophy, juvenile form with ataxia, dysarthria, incoordination; adult form with ALS-like symptomatology</td>
<td>(169, 170)</td>
<td></td>
</tr>
<tr>
<td>ATX/HSP-HEXAB</td>
<td>Sandhoff disease</td>
<td>Similar to Tay-Sachs with organomegaly</td>
<td>(171)</td>
<td></td>
</tr>
<tr>
<td>HSD17B4</td>
<td>Peroxisome bi-functional protein deficiency</td>
<td>Sensorineural hearing loss, sensorineural deafness, infantile to teenage onset, hypotonia followed by spastic quadriparesis, ataxia, dysarthria, dementia, blindness. Juvenile form with ataxia, dysarthria, incoordination; adult form with ALS-like symptomatology</td>
<td>(172, 173)</td>
<td></td>
</tr>
<tr>
<td>HSP-KIAA1840</td>
<td>SPG11</td>
<td>Spasticity, ataxia, cognitive impairment, sensorimotor neuropathy, childhood or teenage onset, thin corpus callosum, signal abnormalities in cerebral cord</td>
<td>(174, 175)</td>
<td></td>
</tr>
<tr>
<td>MYC/ATX-KCTD7</td>
<td>EPM3/CLN14</td>
<td>Multifocal myoclonic seizures, status myoclonus, motor and language regression, intellectual disability, cerebellar ataxia, infantile onset, diffuse cerebral and cerebellar atrophy, T2 periventricular white matter hyperintensity</td>
<td>(176, 177)</td>
<td></td>
</tr>
<tr>
<td>ATX-MAN2B1</td>
<td>Alpha-mannosidosis</td>
<td>Dysmorphism, skeletal abnormalities, visceromegaly, sensorineural hearing loss, immunodeficiency, cognitive impairment, psychosis, ataxia, neonatal to adulthood onset, cerebellar atrophy, partially empty sella turcica, white matter abnormalities</td>
<td>(178)</td>
<td></td>
</tr>
<tr>
<td>HSP/ATX-MLC1</td>
<td>Megalencephaly, leukencephalopathy with subcortical cysts</td>
<td>Macrocyst, initial radiological-clinical discrepancy, eventual motor regression, ataxia, spasticity, epilepsy, cognitive decline, infantile onset, diffuse supratentorial white matter signal anomalies</td>
<td>(179)</td>
<td></td>
</tr>
<tr>
<td>ATX-MSTO1</td>
<td>MMYAT</td>
<td>Myalgia, proximal muscle weakness, psychiatric manifestations, developmental delay, tremor, dysmoria, pigmentary retinopathy, growth retardation, neonatal to childhood onset, cerebellar atrophy</td>
<td>(180, 181)</td>
<td></td>
</tr>
<tr>
<td>MYC/ATX-NEU1</td>
<td>Neuraminidase deficiency or sialidosis type I and II</td>
<td>Myoclonic epilepsy, visual impairment, cherry red spots, ataxia, dysarthria, severe phenotype with dysmorphic features, dysostosis multiplex, hepatosplenomegaly, developmental delay, increased urinary bound sialic acid, variable age at onset, diffuse cerebellar and cerebral atrophy</td>
<td>(183, 184)</td>
<td></td>
</tr>
<tr>
<td>NKX6-2</td>
<td>SPAX8 with hypomyelination leukodystrophy</td>
<td>Nystagmus, developmental delay, hypotonia followed by rapid progressive spasticity, weakness, dystonia, dysphagia, ataxia, visual impairment, infantile to childhood onset, brain hypomyelination, occasional cerebellar atrophy</td>
<td>(185, 186)</td>
<td></td>
</tr>
<tr>
<td>ATX-NPC1</td>
<td>Niemann-Pick type C</td>
<td>Variable supranuclear ophthalmoplegia, gelastic cataplexy, premature cognitive decline, dystonia, hepatosplenomegaly, respiratory failure, seizures, psychiatric features, neonatal to adult onset, variable cerebellar or cerebral atrophy</td>
<td>(187-189)</td>
<td></td>
</tr>
<tr>
<td>OPA1</td>
<td>Behr syndrome</td>
<td>Optic atrophy, papillary signs, sensorimotor peripheral neuropathy, cerebellar ataxia, developmental delay, gastrointestinal symptoms, infantile or childhood onset, cerebellar atrophy; alicic to dominant optic atrophy</td>
<td>(190, 191)</td>
<td></td>
</tr>
<tr>
<td>PEX2</td>
<td>PBD5B/Zellwe ger-spectrum disorder</td>
<td>Hypotonia, seizures, inability to feed, ataxia, hyporeflexia, slow saccades, sensorimotor neuropathy, childhood to adult onset, cerebellar atrophy</td>
<td>(192, 193)</td>
<td></td>
</tr>
<tr>
<td>ATX-PEX7</td>
<td>PBD9B</td>
<td>Retinitis pigmentosa, polyneuropathy, ataxia, anosmia, pes cavus, skeletal abnormalities, ichthyosis, hearing loss, cataracts, cardiomyopathy, elevated phytic acid, childhood or teenage onset, absence of cerebellar atrophy</td>
<td>(194)</td>
<td></td>
</tr>
<tr>
<td>ATX-PHYH</td>
<td>Refsum disease</td>
<td>Retinitis pigmentosa, polyneuropathy, increased cerebrospinal fluid protein, anosmia, sensorineural hearing loss, ichthyosis, ataxia, teen age onset, elevated serum phytic acid, absence of cerebellar atrophy</td>
<td>(195)</td>
<td></td>
</tr>
<tr>
<td>NBIA/DYT/PAR</td>
<td>NBIA 2A</td>
<td>Psychomotor retardation or regression, hypotonia followed by spastic quadriparesis, ataxia, strabismus, nystagmus, infantile to teenage onset,</td>
<td>(196, 197)</td>
<td></td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATX-PMM2</td>
<td>CDG 1a</td>
<td>212065</td>
<td>Intellectual disability, axial hypotonia, visceral involvement with feeding difficulties and cardiac involvement, dysmorphic features, cerebellar ataxia, strabismus, peripheral neuropathy, retinitis pigmentosa, skeletal abnormalities, infantile to adult onset, cerebellar hypoplasia or atrophy</td>
<td>(198, 199)</td>
</tr>
<tr>
<td>ATX-PTRH2</td>
<td>IMNEPD</td>
<td>616263</td>
<td>Developmental delay, intellectual disability, hypotonia, muscular weakness, demyelinating sensorimotor neuropathy, dysmorphism, ataxia, microcephaly, growth retardation, sensorineural deafness, pancreatic insufficiency, infantile onset, variable cerebellar atrophy</td>
<td>(202, 203)</td>
</tr>
<tr>
<td>SEPSECS</td>
<td>PCH 2D</td>
<td>613811</td>
<td>Developmental delay, intellectual disability, hypotonia, dystonia, microcephaly, seizure, ataxia, spasticity, chorea, congenital to infantile onset, cerebellar and cerebral atrophy, thinning of corpus callosum</td>
<td>(204, 205)</td>
</tr>
<tr>
<td>ATX-SLC17A5</td>
<td>Sialic acid storage diseases</td>
<td>604369 269920</td>
<td>Severe neonatal phenotype with ascites, failure to thrive and early death. Milder infantile phenotype with hypotonia, cerebellar ataxia and intellectual disability, infantile to adult onset, hypomyelination, cerebellar atrophy</td>
<td>(206-208)</td>
</tr>
<tr>
<td>SLC2A1</td>
<td>GLUT1 deficiency</td>
<td>606777</td>
<td>Epileptic encephalopathy, psychomotor retardation, hypotonia, dystonia, microcephaly, ataxia, spasticity, seizures, infantile onset, absence of cerebellar atrophy</td>
<td>(209, 210)</td>
</tr>
<tr>
<td>ATX-SLC52A2</td>
<td>SCAR3/ BVVLS2</td>
<td>271250 614707</td>
<td>Sensorimotor neuropathy, optic atrophy, blindness, sensorineural hearing loss, respiratory insufficiency, bulbar involvement, childhood onset, absence of cerebellar atrophy; ataxia is on a spectrum between Brown-Vialetto-Van Laere syndrome type 2 and SCAR3</td>
<td>(211-213)</td>
</tr>
<tr>
<td>SLC6A19</td>
<td>Hartnup disorder</td>
<td>234500</td>
<td>Transient manifestations of pellagra, cerebellar ataxia, psychosis, dystagmus and ophthalmoparesis, cognitive impairment, amino aciduria, early onset</td>
<td>(214)</td>
</tr>
<tr>
<td>SLC25A46</td>
<td>CMT6B</td>
<td>616505</td>
<td>Optic atrophy, blindness, severe sensorimotor neuropathy, hyporeflexia, ataxia, pes cavus, sensory loss in lower limbs, sensitive and cerebellar ataxia, dystonia, divergent strabismus, neonatal to childhood onset, cerebellar and brain atrophy, T2 hypointensity in cerebellar white matter</td>
<td>(215, 216)</td>
</tr>
<tr>
<td>ATX-SRD5A3</td>
<td>CDG 1q</td>
<td>612379</td>
<td>Hypotonia, intellectual disability, optic nerve atrophy, dystagmus, ocular colobomas, ichthyosis, palmoplantar keratoderma, mild ataxia, congenital to childhood onset, cerebellar vermian hypoplasia</td>
<td>(217, 218)</td>
</tr>
<tr>
<td>ATX-TTC19</td>
<td>MC3DN2</td>
<td>615157</td>
<td>Muscular hypotonia progressing to spasticity, developmental delay, neurological regression with loss of language and ambulation, cognitive regression, rapid evolution, axonal motor neuropathy, psychiatric features, infantile to adult onset, cerebellar and cerebral atrophy, T2 hypersignal in basal ganglia, bilateral inferior olive involvement</td>
<td>(219-221)</td>
</tr>
<tr>
<td>ATX-WDR73</td>
<td>GMS/ SCAR5</td>
<td>251300</td>
<td>Intellectual disability, nephrotic syndrome, microcephaly, hypotonia, epilepsy, optic atrophy, skin abnormalities, infantile to childhood onset, cerebellar and cerebral atrophy</td>
<td>(222, 223)</td>
</tr>
<tr>
<td>WFS1</td>
<td>Wolfram syndrome</td>
<td>222300</td>
<td>Diabetes mellitus, optic atrophy, diabetes insipidus, deafness, renal abnormalities, ataxia, intellectual disability, psychiatric features, childhood to adolescent onset, generalized brain and cerebellar atrophy</td>
<td>(224)</td>
</tr>
<tr>
<td>WWOX</td>
<td>SCAR12</td>
<td>614322</td>
<td>Tonic-clonic epilepsy, intellectual disability, spasticity, neonatal to childhood onset, variable cerebellar or cerebral atrophy, phenotypic spectrum with infantile epileptic encephalopathy associated with psychomotor retardation and growth retardation</td>
<td>(225, 226)</td>
</tr>
</tbody>
</table>

1 MDS nomenclature: Nomenclature proposed by the Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders (4) with a phenotypical prefix followed by the gene name. ATX Ataxia; DYT Dystonia; HSP Hereditary spastic paraplegia; MYC Myoclonus; NBIA Neurodegeneration with brain iron accumulation PARK Parkinsonism.

2 Acronyms: ALS Amyotrophic lateral sclerosis; BVVLS2 Brown-Vialetto-Van Laere syndrome type 2; CAMRQ cerebellar ataxia mental retardation with or without quadriplegic locomotion; CDG Congenital disorder of glycosylation; CLN Neuronal ceroid lipofuscinosis; CMT Charcot-Marie-Tooth; COACH Cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis; EPM Progressive myoclonic epilepsy; FAHN Fatty acid hydroxylase-associated neurodegeneration; GMS Galloway-Mowat syndrome; IMNEPD Infantile-onset multisystem neurologic, endocrine, and pancreatic disease; MC3DN2 Mitochondrial complex III deficiency, nuclear type 2; MMYAT Mitochondrial myopathy and ataxia; NBIA Neurodegeneration with brain iron accumulation; PBD Peroxisome biogenesis disorder; PCH Pontocerebellar hypoplasia; SCAR Spinocerebellar ataxia; autosomal recessive; SPAX Spastic ataxia; SPG Spastic paraplegia.
2.9 Figures

Figure 2.1 Clinical classification of autosomal recessive ataxias

The gene associated with each primary recessive ataxia is classified according to the most frequent clinical syndrome described for this disorder. Note that some disorders have more complex or variable phenotypes and are placed in the overlapping areas between two categories. Genes presented in larger font represent the most prevalent ataxias.
Figure 2.2 Graphical summary of the clinical approach to a patient presenting with ataxia

1° Obtain clinical history with temporal course, family history, physical examination, and paraclinical tests

2° Exclude acquired causes

3. Evaluate mode of inheritance

4° Evaluate the clinical syndrome to assess whether it corresponds to a well characterized genetic disorder

5° Test for Friedreich ataxia and other specific single gene if high clinical suspicion or confirmed mutation in a relative

6° Test for multiple genes through next generation sequencing (gene panel, WES or WGS)

WES whole exome sequencing; WGS whole genome sequencing.
A Purkinje cell is depicted along with a granule cell and parallel fibers. Subcellular organelles and structures are represented graphically. Each gene is classified at one or more subcellular localizations according to the different metabolic pathways involved.
2.10 References


Chapter 3 Contributing to the evidence: the phenotypical description of a cerebellar ataxia in the French-Canadian population

Titre original de l’article
Characterization of the phenotype with neurocognitive impairment and protein mislocalization in ELOVL4-associated Spinocerebellar ataxia 34

3.1 Résumé

Introduction
L’ataxie spinocérébelleuse 34 est une ataxie dominante causée par des mutations du gène ELOVL4 et dont l’atteinte neurologique et neurocognitive demeure partiellement caractérisée. Les études précédentes n’ont pas démontré d’anomalies biochimiques supportant le rôle pathogénique de la protéine ELOVL4 dans le développement de la maladie. L’objectif principal de cette étude était de caractériser le profil d’atteinte neurologique et neurocognitive chez les patients symptomatiques porteurs de la mutation c.504 G>C dans ELOVL4. L’objectif secondaire était de démontrer la présence d’anomalies dans la localisation et la distribution subcellulaire de la protéine ELOVL4 dans la peau de patients atteints de la maladie.

Méthode

Résultats
Les patients avaient un syndrome cérébelleux tardif et lentement progressif (âge moyen du début des symptômes, 47 ans; étendue, 32 à 60 ans) caractérisé par une ataxie tronculaire et appendiculaire, une dysarthrie, des saccades hypométriques et des poursuites saccadiques. Aucun patient ne présentait d’atteinte suggestive d’érythrokératoderme variable, ce qui avait été rapporté dans les études précédentes. L’imagerie par résonance magnétique a révélé une atrophie cérébelleuse associée à une atrophie protubérantielle (4 patients sur 6), et un hypersignal cruciforme...
de la protubérance (2 patients sur 6). La tomographie par émission de positrons au Fluorodéoxyglucose a mis en évidence un hypométabolisme cérébelleux diffus chez les cinq patients testés et un hypométabolisme pariétal léger chez trois patients. Des déficits cognitifs significatifs ont été notés dans la sphère exécutive, ainsi que des déficits apparents dans les sphères visuospatiale et attentionnelle. Trois patients présentaient une atteinte psychiatrique caractérisée par la désinhibition, l’euphorie, l’impulsivité et l’anxiété. L’analyse des fibroblastes dermiques a démontré que la protéine ELOVL4 est délocalisée et forme des agrégats pathologiques dans la peau des patients atteints, ce qui supporte un effet dominant négatif de la mutation sur la localisation de la protéine.

**Conclusions**

Les résultats présentés supportent le rôle pathogénique des mutations de *ELOVL4* dans l’atteinte cérébelleuse et dressent un portrait détaillé du phénotype de l’ataxie spinocérébelleuse 34 avec une atteinte neurocognitive et neurocomportementale typique du syndrome cognitif et affectif du cervelet. Les cliniciens devraient considérer le diagnostic d’ataxie spinocérébelleuse 34 même en l’absence d’érythrokératodermie variable et devraient rechercher systématiquement la présence d’atteinte cognitive et psychiatrique.

**3.2 Abstract**

**Introduction**

*ELOVL4*-associated Spinocerebellar ataxia 34 (SCA34) is a recently described dominant ataxia with poorly defined neurologic and neurocognitive features. Previous studies have failed to demonstrate biochemical anomalies supporting the pathogenic role of ELOVL4 in the disorder. The primary objective of this study was to characterize the neurological and neurocognitive profile of patients with the c.504 G>C mutation in *ELOVL4*. The secondary objective was to demonstrate the presence of ELOVL4 cellular abnormalities in the skin of patients.

**Methods**

We investigated a large multi-generational French-Canadian kindred presenting with a late-onset pure cerebellar ataxia. The design is a genetic case series with case-control analysis of cognitive and behavioral impairments. Immunohistochemistry of dermal fibroblasts from the skin of an affected patient was performed to evaluate the presence of ELOVL4 protein cellular localization and distribution anomalies in this disorder.
Results
Nine affected and 10 unaffected family members agreed to participate in the study. Five age- and education-matched controls were recruited to analyze results of neuropsychological evaluations. Patients had a late-onset slowly progressive cerebellar syndrome (mean age at onset, 47 years; range, 32 to 60 years) characterized by truncal and limb ataxia, dysarthria, hypometric saccades, and saccadic pursuits. No patient had past or current signs of erythrokeratodermia variabilis, which had been reported in previous studies. Magnetic resonance imaging revealed cerebellar atrophy, associated with pontine atrophy (4 of 6 patients), and cruciform hypersignal in the pons (2 of 6 patients). Fluorodeoxyglucose Positron Emission Tomography showed diffuse cerebellar hypometabolism in all five tested patients with subtle parietal hypometabolism in three patients. Significant cognitive deficits were found in executive functioning, along with apparent visuospatial and attention deficits. Three patients had associated psychiatric features with disinhibition, euphoria, impulsiveness, and anxiety. Immunohistochemistry of dermal fibroblasts showed mislocalization of the ELOVL4 protein, which appeared punctate and aggregated, supporting a dominant negative effect of the mutation on protein localization.

Conclusions
Our findings support the pathogenicity of ELOVL4 mutations in cerebellar dysfunction and provide a detailed characterization of the SCA34 phenotype, with neurocognitive and neurobehavioral changes typical of the cerebellar cognitive-affective syndrome. Clinicians should consider SCA34 even in the absence of erythrokeratodermia variabilis and should systematically assess for cognitive and psychiatric manifestations.

3.3 Introduction
The dominantly inherited spinocerebellar ataxias are a heterogeneous group of disorders characterized by cerebellar and pontine dysfunction. Although a growing number of genes harboring pathogenic mutations have recently been associated with hereditary ataxias, approximately half of patients remain without a specific molecular diagnosis (1), highlighting the need for better clinical characterization of patients in order to guide clinical and molecular investigations, as well as management.

Spinocerebellar ataxia 34 (SCA34) was recently described by Cadieux-Dion and colleagues (2) in a French-Canadian family that had previously been characterized with dominant ataxia and skin lesions typical of erythrokeratodermia variabilis (EKV) (3). The first mutation described was the non-synonymous c.504 G>C substitution in ELOVL4, which encodes the elongation of very long...
chain fatty acids protein 4 (ELOVL4). Since then, three other reports have described dominant ataxia cases attributed to different ELOVL4 mutations. Ozaki et al. reported two Japanese families presenting with a cerebellar disorder associated with multisystem atrophy-like features on magnetic resonance imaging (MRI), but lacking cutaneous manifestations (4), while Bourassa et al. and Bourque et al. both reported single Brazilian and English Canadian patients with neurocutaneous involvement (5, 6). Besides the motor and cutaneous phenotype, little is known on the impact of ELOVL4 mutations on other neurological functions, including cognition.

Cognitive and affective dysfunction in relation with cerebellar disease has first been described by Schmahmann (7), who regrouped the associated symptoms in the cerebellar cognitive-affective syndrome (CCAS). Recent functional imaging studies have shown that the cerebellum is divided into functionally distinct areas: the sensorimotor region in the anterior lobe and lobule VIII, the cognitive region in the posterior lobes, and the affective region in the posterior vermis (8-10). The CCAS is characterized by impairment in executive functioning, visuospatial organization, and language, along with psychiatric features (7, 11). It is expected to result from disruption of cerebro-cerebellar loops, particularly cerebellar projections to association cortices in the dorsolateral prefrontal and parietal lobes as well as to the limbic regions (9, 10, 12). Previous studies have shown significant neurocognitive and neurobehavioral involvement in selected degenerative hereditary ataxias (13-15), but previous reports of SCA34 patients either reported apparent normal cognition (2) or did not report on neurocognitive involvement (4-6). Hence, the presence of cognitive dysfunction in SCA34 patients had never been formally tested before.

To date, biological validation of biochemical anomalies in ELOVL4-linked SCA34 remains elusive. ELOVL4 is a member of the elongase family of proteins that is involved in the elongation of very long chain fatty acids (VLCFA) with carbon chains of 24 atoms or longer. Previous reports have demonstrated that serum levels and ratios of VLCFA (C22 to C26), corresponding to the ELOVL4 substrates and products, remained within normal limits in patients affected by SCA34 (2, 4). Slightly elevated blood linoleic acid (C18) levels were reported in two individuals, but the signification of this remained uncertain (2). The ELOVL4 protein catalyzes the rate-limiting reaction in the production of two products that have relative tissue-specificity: very long chain saturated fatty acids (VLC-SFA), which are involved in skin barrier formation and sphingolipid production, and very long chain poly-unsaturated fatty acids (VLC-PUFA), which are essential for photoreceptor cells of the macula and also for production of sphingolipids (16). The structure of ELOVL4 is composed of seven helicoidal transmembrane (TM) domains (4), a conserved dilysine endoplasmic reticulum signal, and a histidine dideoxy binding motif (HXXHH) that has enzymatic
activity in fatty acid condensation. Little is known on the function of ELOVL4 protein in the brain. However, mouse studies have shown that the protein is widely expressed with a regional and cell type-specific distribution (17). In the cerebellum, the protein is located in all parts of the cerebellar cortex and in the deep cerebellar nuclei, and it is mainly expressed in neurons and oligodendrocytes, which is compatible with the role of VLC-SFA in myelin production. Skin appears to be a relevant tissue to investigate the biochemical anomalies associated with ELOVL4 mutations considering that the brain and skin are the two human organs with the highest concentrations of sphingolipids, some of which are dependent on the presence of ELOVL4 for synthesis (18).

Our primary objective was to characterize the neurological and neurocognitive phenotype of patients bearing the ELOVL4 c.504 G>C mutation from a large five-generation French-Canadian family in order to better define disease manifestations. The secondary objective was to demonstrate that skin fibroblasts of patients with the mutated ELOVL4 allele had subcellular localization or distribution anomalies supporting ELOVL4 dysfunction as the cause of SCA34.

3.4 Methods
Clinical and cognitive assessment
We investigated a large five-generation French-Canadian kindred presenting with a late-onset pure cerebellar ataxia with pontocerebellar atrophy on MRI. A total of 19 individuals, 9 affected and 10 unaffected, provided written informed consent to participate in the study. We collected genomic DNA and conducted clinical interviews and neurological evaluations for all participants. All participants were evaluated in December 2013, and six affected patients had regular clinical follow-up until July 2018 when they were evaluated by an ophthalmologist to search for retinal abnormalities and had a formal SARA score rating. MRI was performed in six affected individuals, and three underwent nerve conduction studies. All patients were specifically questioned regarding the presence of cutaneous involvement, and one self-reporting patient had a thorough evaluation by a dermatologist.

Five patients and as many cognitively healthy controls underwent formal neurocognitive and neuropsychiatric assessment at the CHU de Québec Memory Clinic (www.cliniquedememoire.ca). Controls were family caregivers and were age- and education-matched to participants. The Mini-Mental State Examination (MMSE) was performed with each participant. Data derived from the Montreal Cognitive Assessment (MoCA) (19) and additional local cognitive measures was summarized according to composite scores for the main cognitive domains: attention (digit span, numeric substitution), executive functions (abstract thinking, lexical verbal fluency, Go/No-Go,
Luria, Trail Making B, Rey complex figure test [RCFT] copy), visuospatial skills (block copy, clock drawing), memory (5-word list free and cued recall), and language (Alzheimer's disease assessment scale-cognitive subscale – naming, comprehension, and sentence repetition tasks). Key neuropsychiatric symptoms were assessed clinically. Patients’ scores were compared to controls’ using the paired sample t-test. The youngest patient (V-1) underwent a detailed neuropsychological assessment (California Verbal Learning Test-II, Delis-Kaplan Executive Function System, DO-80, Taylor complex figure, Minnesota Multiphasic Personality Inventory, Ruff 2&7, Tower of London test and WAIS-IV). Functional imaging with [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) was performed in the five patients who underwent cognitive evaluation.

This project was approved by the research ethics committee of the CHU de Québec (PEJ-299, 2012-1311). The participants received no financial compensation.

Whole exome sequencing and genetic analysis
In order to identify the genetic mutation underlying ataxia in this family, whole-exome sequencing was carried out on five affected members. Genomic DNA was extracted from peripheral blood leucocytes following the manufacturer’s protocol (Puregene; Gentra Systems, Inc). WES was carried out on five affected members of the family. Exome capture was carried out using SeqCap EZ Exome Library v3 kit (Nimblegen, Roche) with 1µg of genomic DNA. Exon-enriched DNA libraries from these five individuals were sequenced on the Illumina HiSeq2000 with a paired-end 100 bp length configuration. Reads were mapped against the Human Reference Genome hg19 using the Burrows-Wheeler Aligner (BWA) (v0.7.5). Single nucleotide variations and copy number variations, including insertions/deletions (indels) were called using The Genome Analysis Toolkit (GATK) (v2.6) (20) and annotated using ANNOVAR13 (21). The exomes were analyzed using step-by-step filtering strategies. Basic filters were used to remove low quality variants: minimum position coverage >6, minimum reads supporting the variant >3, minimum mutation frequency >0.15. Genetic variants were then filtered to retain only variants respecting the following criteria: 1) shared by all 5 affected family members sequenced by WES, 2) non-synonymous single nucleotide variants, splicing site variants or coding indels, 3) with a minor allele frequency (MAF) < 0.1% in Exome Aggregation Consortium (ExAC), and 4) not present in 186 controls from our in-house dataset. In order to validate our results and examine segregation of the identified ELOVL4 DNA variations with the disease in the family, we used specific PCR primer pairs (forward: CATTGCTTTCCACTGAACACA; reverse CATGCCTTGTACATTTTTGTGC) to amplify DNA from 18 family members and sequenced them by Sanger sequencing (Applied Biosystem’s 3730xl
DNA Analyzer technology). One additional family member was tested with commercially available Sanger sequencing of ELOVL4 from Prevention Genetics™.

Fibroblast cells isolation and culture
A skin biopsy was performed on the patient who reported cutaneous involvement. The fibroblast cells were isolated from skin biopsies and kept in liquid nitrogen until used as previously described (22). Briefly, fibroblasts were cultivated in DMEM with 10% Fetal Bovin Serum (FBS) (Seradigm) with 100 IU/mL penicillin G (Sigma-Aldrich) and 25 µg/mL gentamicin (Gemini Bio-product) in 8% CO₂ at 37 °C. They were cultured in flasks until confluency (100%) prior to be split and seeded in 6-well plate containing sterile glass coverslips.

Immunofluorescence analyses
Fibroblasts cells, grown on glass coverslips, were fixed in 4% (w/v) paraformaldehyde in phosphate-buffered saline for 20 minutes and blocked for 1 hour in 5%(w/v) goat serum 0.1% Triton X-100 in phosphate-buffered saline at room temperature. Immunofluorescence was performed using antibodies recognizing ELOVL4 (rabbit polyclonal, Abcam ab224608) and calnexin (mouse monoclonal, Invitrogen MA3-027), and used at 1:200 diluted in blocking solution overnight at 4 °C. Fluorescent signal distribution was visualized by epifluorescence microscopy after incubation with secondary antibodies, anti-mouse or anti-rabbit IgG conjugated to Alexa Fluor 488 (green) or 594 (red) (Invitrogen mouse 488 #A11001 and rabbit 594 #A21207) diluted 1:500 for 2 hours at room temperature and mounted in Prolong (Fluoromont G with Dapi Invitrogen #00-4959-52).

3.5 Results
Genetic results
A total of 19 individuals (9 affected and 10 unaffected) underwent a complete neurological evaluation and genetic testing (Table 3.1). Routine biochemical investigations were normal and initial genetic screening had excluded SCA1, 2, 3, 6, 7, 8, 17, and Fragile X syndrome for this family. WES in five affected individuals revealed 426,715 DNA variations. Only one variant, a heterozygous missense mutation in the ELOVL fatty acid elongase 4 gene (ELOVL4), (NM_022726.3 c.504G>C, p.L168F), fulfilled the filtering criteria. This variant had already been reported to cause SCA34 (2), and the L168F amino acid substitution was located at a highly conserved residue in the third transmembrane domain of the protein. This mutation was predicted to be possibly damaging with a score of 0.867 according to the PolyPhen-2 website (http://genetics.bwh.harvard.edu/pph2/)(23). This mutation was confirmed in four additional
affected family members, but was absent in the 10 unaffected relatives. Hence, perfect segregation of the identified c.504 G>C mutation with the disease status in the family was observed (Figure 3.1).

Table 3.1 Detailed neurological findings in affected individuals with ELOVL4 mutation

Figure 3.1 Pedigree of a French-Canadian Family with the c.504 G>C mutation in ELOVL4

Clinical assessment

The disorder was characterized by a late-onset cerebellar syndrome (mean age at onset 47 years; range 32 to 60 years) with slow progression. Patients generally required a walker in their 70s and became wheelchair-bound in their 80s. Truncal and gait ataxia, along with dysmetria and dysarthria, were remarkable in all patients (Table 3.1). The median SARA score was 16 (range 8 to 21.5), and scores increased with advancing age. Hypometric saccades and saccadic pursuits were remarkable upon examination. Most patients denied current or previous dermatologic involvement, but one patient (IV-18) reported erythematous dry skin lesions on the lower limbs during winter beginning in her fifth decade (Figure 3.2). Nummular dermatitis was diagnosed, but there was no typical EKV lesion. Two other patients reported occasional dry skin on the lower limbs in winter, but none had erythematous lesions, and there were no active lesions at the time of evaluation. Moreover, three patients reported a history of severe gingivitis that occurred in the second decade and caused a generalized edentation that required dentures. One patient (V-1) had bilateral pale pisciform perimacular retinal lesions upon ophthalmologic examination. She had no complains of visual loss, and was examined by a retinal disease specialist who concluded that there was no evidence of Stargardt disease or retinitis pigmentosa. All other evaluated patients had a normal ophthalmologic exam. Three patients had mild sensory deficits upon evaluation, two of whom also had decreased deep tendon reflexes (DTR). Polyneuropathy was confirmed in two out of three tested patients (Table 3.1).

Figure 3.2 Dermatologic lesion in a SCA34 patient

MRI was performed in six patients and revealed mild (1/6) to severe (5/6) vermian and hemispheric cerebellar atrophy in all patients along with pontine atrophy in four (Figure 3.3). Cruciform hypersignal in the pons, also called the hot cross bun sign, was present in two patients (III-27 and IV-3). Other findings were reported only in selected patients, notably mild diffuse cerebral cortical (2/6) or sub-cortical (2/6) atrophy and leukoencephalopathy (2/6). FDG-PET revealed diffuse cerebellar hypometabolism in all five patients. Three patients also had a very subtle bilateral (2/5)
or right (1/5) parietal hypometabolism (Figure 3.3). One other patient had heterogeneous cerebral hypometabolism with preserved basal ganglia, brainstem, and mesiotemporal regions, which was possibly secondary to diffuse vascular involvement. In this patient, MRI had shown subcortical atrophy, but no evidence of previous stroke.

Figure 3.3 Neuroimaging findings in patients with the c.504 G>C mutation in ELOVL4

Cognitive assessment

Five patients were evaluated at the Clinique Interdisciplinaire de Mémoire du CHU de Québec. Their performance was compared to five age- and education-matched controls (mean education for patients=12.4±1.51 years vs 13.4±2.07 for controls). The cognitive involvement was homogeneous within affected patients with significant deficits in executive functioning and apparent impairment in visuospatial skills and attention that did not reach statistical significance (Table 3.2). Working memory, psychomotor speed, set shifting, inhibition, and planning skills were particularly affected as revealed by failure to perform backward digit span, decreased lexical verbal fluency, and impaired trail making, Luria sequence, Go/No-go, and RCFT (Figure 3.4). Visuoconstructive skills and attention were also impaired in all patients, but this did not reach statistical significance. Patients did not present deficits in memory and language. Detailed neuropsychological testing in the youngest patient (V-1) revealed a mild impairment in selective attention and working memory. Psychiatric features were remarkable in three patients, two of whom exhibited frank disinhibition and euphoria, while impulsiveness and anxiety were noted in a third patient. Detailed descriptions of cognitive evaluations are available in the Supplementary Material.

Table 3.2 Results of the clinical evaluation in SCA34 patients and controls

Figure 3.4 Impaired copy of the RCFT in three patients with the c.504 G>C mutation in ELOVL4

Aberrant ELOVL4 localization in patient fibroblasts

Immunofluorescence analysis of fibroblasts from a healthy control showed homogeneous staining of ELOVL4 seemingly colocalizing with the endoplasmic reticulum marker Calnexin at the perinuclear space (Figure 3.5A). However, mislocalization of the ELOVL4 protein beyond the perinuclear region, as well as abnormal punctates and aggregates can be observed in patient-derived fibroblasts carrying the c.504G>C mutation (Figure 3.5B).

Figure 3.5 Immunofluorescence staining of dermal fibroblasts from a SCA34 patient compared with fibroblasts from a healthy control
3.6 Discussion

We report a large family with a c.504 G>C mutation in ELOVL4 associated with cerebellar ataxia and cognitive impairment with prominent executive dysfunction. Our findings provide additional support to the putative role of ELOVL4 mutation in cerebellar function. Moreover, we provide the first evidence of ELOVL4 cellular abnormalities in SCA34 by demonstrating mislocalization and abnormal aggregation of the protein in a patient’s dermal fibroblasts.

In our cohort, all patients presented with a prominent cerebellar syndrome of late onset and slow progression. So far, ELOVL4-linked SCA34 has only been reported in patients of Canadian, Japanese, and Brazilian origins, and clinical features vary significantly amongst described patients (Table 3.3). Notably, decreased DTR and peripheral neuropathy were both observed in two patients from the present study, while 4 out of 8 of patients tested by Cadieux-Dion et al. had a mild peripheral neuropathy (2). However, patients from Ozaki et al. rather presented with increased DTR and positive Babinski signs, upper motor neuron findings that may be associated with the multiple system atrophy-like findings on imagery (4). Interestingly, two patients from the present study also presented with a hot cross bun sign, but DTR and plantar reflexes were normal. Hence, it appears that the cerebellar syndrome may be associated with peripheral polyneuropathy or pyramidal signs in patients with SCA34.

Table 3.3 Clinical and paraclinical characteristics of patients with mutations in ELOVL4 in present and previous studies

For the first time, we report SCA34 patients with deficits in executive functioning that were statistically different from age- and education-matched controls, along with apparent visuospatial and attention deficits. This was associated with psychiatric features in three patients. These findings appear typical of the CCAS (7, 11), and provide additional evidence of neurocognitive and neurobehavioral impairment in hereditary degenerative ataxias. Functional imaging showed cerebellar hypometabolism, which was associated with mild parietal hypometabolism in three patients. This could be attributable to a diaschisis phenomenon, wherein severe damage to the cerebellar hemispheres could result in reduced cerebral metabolic activity through deactivation of the cerebello-thalamic-cortical projections (24). Indeed, the parietal lobe has important afferent and efferent connections with the cerebellum. These appear to be involved in the pathophysiology of parietal ataxia, or crossed cerebellar diaschisis, a phenomenon in which patients with a primary parietal lesion develop secondary contralateral cerebellar dysfunction (25). The parietal hypometabolism observed here could reflect the opposite phenomenon, i.e., parietal dysfunction...
secondary to a primary cerebellar lesion. A previous report of parietal hypometabolism in a pure recessive cerebellar ataxia phenotype caused by SYNE1 recessive mutations supports this hypothesis (13). This phenomenon may contribute to the visuospatial and attention deficits observed in our patients and may be amenable to potential treatments targeting diaschisis (24).

As opposed to previously reported patients with the same mutation (2), our patients did not report any history of skin lesions associated with EKV. Absence of EKV may reflect either the role of a second modifier gene involved in cutaneous disease or a milder disease severity that would have gone unnoticed. The late-onset skin dryness and nummular dermatitis reported by a few patients, along with the early gingivitis episodes in three patients, may either represent milder mucocutaneous involvement or coincidental findings. Absence of EKV in ELOVL4-linked families has previously been reported in patients of Japanese origin (4).

Of particular interest, immunofluorescence analyses using dermal fibroblasts from an affected patient revealed mislocalization and aggregation of the ELOVL4 protein. Previous studies had failed to demonstrate significant serum lipid anomalies in SCA34 patients and none had evaluated alterations in human tissue (2, 4). The mislocalization and aggregation of the ELOVL4 protein observed in the patient’s fibroblast cells appear similar to those found in previous studies of Stargardt-like macular dystrophy type 3 (STGD3), which is associated with ELOVL4 dominant mutations (26-28). More specifically, Logan et al. demonstrated that ELOVL4 mutations associated with STGD3 cause mislocalization of the protein beyond the endoplasmic reticulum in a punctate and aggregated appearance very similar to what we observed (26). In this study, the mutant protein was shown to interact with wild type ELOVL4 to alter the localization of the protein and to exert a dominant negative effect on enzymatic activity that worsened if the protein was redirected to the endoplasmic reticulum (26). Therefore, it is likely that the c.504 G>C ELOVL4 mutation may also exert its pathogenic effect through a dominant negative mechanism that involves interaction with wild type ELOVL4, mislocalization, and possibly reduction in the production of VLCFA.

As expected in the evaluation of a rare disease, this study is limited by the small number of patients that originated from a single family, such that the clinical features described here may not reflect the range of clinical involvement in patients with different mutations or from different families. This was highlighted by the comparison between the findings from the actual and previous studies (Table 3.3), which showed the broad range of clinical findings in SCA34 patients. Nevertheless, it is likely that the neurocognitive impairment described here transcends single mutations and could be found in all patients with a cerebellar motor syndrome, since the cognitive deficits are also a
direct consequence of prominent cerebellar degeneration. Similarly, the skin biopsy findings would have to be confirmed in tissue specimens from additional patients, including some with different mutations, to confirm that the dominant negative effect on protein localization observed here is a ubiquitous mechanism in this disorder.

3.7 Conclusion

Our findings support the role of ELOVL4 in cerebellar function and present a more precise and exhaustive characterization of the SCA34 phenotype. Clinicians should consider the diagnosis of SCA34 even in the absence of EKV and systematically assess cognitive and psychiatric features with specific emphasis on executive, visuospatial and attention deficits. Analysis of dermal fibroblasts from a SCA34 patient supports a dominant-negative effect on ELOVL4 localization. More research is needed to understand the specific role of ELOVL4 and VLCFA in the cerebellum in order to better understand the specific pathological mechanisms of selective cerebellar dysfunction in SCA34.
3.8 Tables

Table 3.1 Detailed neurological findings in affected individuals with \textit{ELOVL4} mutations

<table>
<thead>
<tr>
<th>ID</th>
<th>Reported age at onset</th>
<th>Age at last evaluation</th>
<th>Dysarthria</th>
<th>SARA score</th>
<th>Nystagmus</th>
<th>Hypometric saccades &amp; saccadic pursuit</th>
<th>Tremor</th>
<th>Strength</th>
<th>Sensibilities</th>
<th>EMG/NCS</th>
<th>Evolution</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-3</td>
<td>60</td>
<td>82</td>
<td>+++</td>
<td>++</td>
<td>16.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>LOT</td>
<td>Slow*(s)</td>
<td>dDTR, EPR</td>
</tr>
<tr>
<td>III-7</td>
<td>50</td>
<td>86</td>
<td>+++</td>
<td>++</td>
<td>20.5</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N</td>
<td>LOVPT</td>
<td>SMPN</td>
<td>Slow*</td>
</tr>
<tr>
<td>III-20</td>
<td>50</td>
<td>83</td>
<td>+++</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Slow**</td>
</tr>
<tr>
<td>III-24</td>
<td>N/A</td>
<td>93</td>
<td>+++</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>SCI</td>
<td></td>
</tr>
<tr>
<td>III-27</td>
<td>45</td>
<td>79</td>
<td>+</td>
<td>++</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>MPN</td>
<td>Slow*</td>
</tr>
<tr>
<td>IV-3</td>
<td>40</td>
<td>74</td>
<td>++</td>
<td>++</td>
<td>21.5</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>Slow*</td>
<td></td>
</tr>
<tr>
<td>IV-6</td>
<td>50</td>
<td>72</td>
<td>+</td>
<td>+</td>
<td>16</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>Slow</td>
<td>UI</td>
</tr>
<tr>
<td>IV-18</td>
<td>50</td>
<td>66</td>
<td>++</td>
<td>++</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>LOV</td>
<td>Slow</td>
<td>UI, ND, dDTR</td>
</tr>
<tr>
<td>V-1</td>
<td>32</td>
<td>44</td>
<td>+</td>
<td>+</td>
<td>8</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Slow</td>
</tr>
</tbody>
</table>

+: present/mild; ++ moderate; +++ severe; *uses a walker; ** uses a wheelchair; dDTR decreased deep tendon reflexes; EPR extra-pyramidal rigidity; N normal; N/A not available; ND nummular dermatitis; LO(V)(P)(T) loss of vibration, proprioception, temperature; SCI severe cognitive impairment with decreased cooperation; (S)MPN (sensitivo)motor polyneuropathy; UI urinary incontinence

Table 3.2 Results of the clinical evaluation in SCA34 patients and controls

<table>
<thead>
<tr>
<th>Clinical domains</th>
<th>Patients (n=5)</th>
<th>Controls(^a) (n=5)</th>
<th>\textit{p value}(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive – Mean±sd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>5.6±1.5</td>
<td>6.8±0.4</td>
<td>0.138</td>
</tr>
<tr>
<td>Executive</td>
<td>2.4±2.1</td>
<td>5.8±0.4</td>
<td>0.042</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>9.2±1.1</td>
<td>10.6±0.5</td>
<td>0.053</td>
</tr>
<tr>
<td>Memory</td>
<td>4.2±0.4</td>
<td>4.2±0.4</td>
<td>N/A</td>
</tr>
<tr>
<td>Language</td>
<td>3±0</td>
<td>3±0</td>
<td>N/A</td>
</tr>
<tr>
<td>Psychiatric – No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>2 (40)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Euphoria</td>
<td>2 (40)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>3 (60)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (20)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Panic</td>
<td>1 (20)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Controls are age- and education-matched to patients.

\(^b\)\textit{P} values are calculated with the paired sample t-test.
Table 3.3 Clinical and paraclinical characteristics of patients with mutations in *ELOVL4* in present and previous studies

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients, n</td>
<td>9</td>
<td>19</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>French-Canadian</td>
<td>French-Canadian</td>
<td>Japanese</td>
<td>Brazil</td>
<td>English Canadian</td>
</tr>
<tr>
<td>Mean age at onset, y</td>
<td>47</td>
<td>51</td>
<td>33.9</td>
<td>Mid 20s</td>
<td>15</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Gait and limb ataxia with dysarthria (9/9)</td>
<td>Gait ataxia (12/19) limb ataxia (9/19) and dysarthria (6/19)</td>
<td>Gait and limb ataxia with dysarthria (9/9)</td>
<td>Gait and limb ataxia with dysarthria (1/1)</td>
<td>Gait ataxia (1/1), absence of limb ataxia or dysarthria</td>
</tr>
<tr>
<td>Oculomotor abnormalities</td>
<td>Nystagmus (7/8) hypometric saccades and saccadic pursuit (8/8)</td>
<td>Nystagmus (7/19) slow pursuit (5/19), slow saccades (3/19)</td>
<td>Nystagmus (7/9) supranuclear gaze palsy (3/9), altered smooth pursuit (5/9)</td>
<td>Bilateral ophthalmoplegia, diplopia, horizontal gaze-evoked nystagmus (1/1)</td>
<td>Square wave jerks, periodic alternating skew deviation, saccadic pursuit (1/1)</td>
</tr>
<tr>
<td>Motor neuron involvement</td>
<td>Decreased DTR (2/9)</td>
<td>Decreased DTR (7/19)</td>
<td>Increased DTR or Babinski (8/9)</td>
<td>None</td>
<td>Decreased DTR (1/1)</td>
</tr>
<tr>
<td>Dermatologic involvement</td>
<td>Nummular dermatitis (1/9) Absence of EKV (9/9)</td>
<td>Active or past EKV (14/19)</td>
<td>None</td>
<td>Past EKV</td>
<td>Active EK</td>
</tr>
<tr>
<td>Cognitive involvement</td>
<td>Alterations in executive, visuospatial attention (5/5), psychiatric features (3/5)</td>
<td>Cognition appeared normal</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Mild to severe cerebellar (5/5) and pontine (3/5) atrophy. Hot cross bun sign (2/5)</td>
<td>Cerebellar (6/9), pontine (5/9) and/or cerebral (4/9) atrophy, normal MRI (3/9)</td>
<td>Cerebellar and pontine atrophy (8/8), hot cross bun sign (4/6) or pontine linear hyperintensity (2/6)</td>
<td>Cerebellar and pontine atrophy (1/1)</td>
<td>Mild cerebellar and pontine atrophy (1/1)</td>
</tr>
<tr>
<td>Electrophysiological anomalies</td>
<td>Peripheral neuropathy (2/3), normal (1/3)</td>
<td>Mild peripheral axonal neuropathy (4/8)</td>
<td>None</td>
<td>Not reported</td>
<td>Normal (1/1)</td>
</tr>
</tbody>
</table>

DTR deep tendon reflexes; EKV erythrokeratodermia (variabilis); MRI Magnetic resonance imaging; VLCFA very long chain fatty acids; VLC-SFA very long chain saturated fatty acids
3.9 Figures

Figure 3.1 Pedigree of a French-Canadian Family with the c.504 G>C mutation in ELOVL4

Symbols with a + sign in the right corner indicate that the patient is bearing the identified L168F mutation in the ELOVL4 gene, the genotype is indicated below the symbol. Symbols with a – sign indicate the absence of a mutated allele in ELOVL4.

Figure 3.2 Dermatologic lesion in a SCA34 patient

Evaluation by a dermatologist revealed nummular dermatitis, but no sign of erythrokeratoderma variabilis.
Figure 3.3 Neuroimaging findings in patients with the c.504 G>C mutation in *ELOVL4*

(A) Sagittal MRI of a 68-year-old male (IV-3) showing severe cerebellar atrophy with pontine atrophy. (B) Axial MRI from the same patient showing T2 cruciform hypersignal in the pons (indicated by red arrow). (C) FDG-PET of a 70-year-old female (IV-6) showing severe cerebellar hypometabolism and minimal biparietal hypometabolism.
Figure 3.4 Impaired copy of the RCFT in three patients with the c.504 G>C mutation in *ELOVL4*

A. RCFT model. B. 64-year-old female with 12 years of education (IV-18). C. 72-year-old male with 11 years of education (IV-3) shows significant juxtaposition of details. D. 80-year-old male with 21 years of education (III-3) with a severe dysexecutive syndrome.
Figure 3.5 Immunofluorescence staining of dermal fibroblasts from a SCA34 patient compared with fibroblasts from a healthy control.

(A) ELOVL4 staining in healthy control’s fibroblasts showed homogeneous staining that appears to colocalize with the endoplasmic reticulum marker Calnexin at the perinuclear space. The nucleus marker Dapi is shown in blue. The magnification is 40x. (B) ELOVL4 staining in patient’s fibroblasts showed mislocalization of the protein beyond the perinuclear region with a punctate and aggregated appearance.
3.10 Supplementary Material

Detailed cognitive evaluations of SCA34 patients

Case III-3
This patient first came to our attention at 80 years of age. He had achieved theology studies and worked as a pastor. He was independent for activities of daily living but lived in a supervised religious housing community. Upon examination, the patient showed euphoria. He insisted on meeting the secretary who scheduled his medical appointment. There were no language deficits. He scored 27/30 on the MMSE, losing one point on calculation and two points on memory recall. He scored 24/30 on the MoCA, losing 3 points for the trail making, cube copy, and clock drawing. He also lost 3 points on memory recall, which improved with cueing. He failed on the Luria test, alternating graphic sequence and Go/No-Go task. The RCFT was significantly impaired, and he proceeded by juxtaposition of details. On praxis assessment tasks, the patient presented body-part-as-object gesture.

Case IV-3
This patient was first evaluated at 72 years of age; he was a male with a grade 11 education. He used to be an iron worker. He was mildly impaired on instrumental activities of daily living and lost his driver’s licence following a road test examination. He scored 25/30 on the MMSE, losing 4 points on calculation and one point on memory recall, which improved with cueing. On follow-up, his MMSE dropped to 21. MoCA score was 22/30, he failed the trail making and cube copy. Clock drawing was mildly impaired. Working memory was altered, he failed backward digit span and months backward. Lexical verbal fluency was significantly decreased. Abstract thinking was slightly diminished. He correctly performed the Luria but failed the Go/No-Go task. The RCFT was impaired, and he proceeded by juxtaposition of details. Language was preserved. There was no apraxia.

Case IV-6
This patient was first evaluated at 70 years of age; she was a female with a grade 12 education. She worked as a secretary. She complained about attention deficits from an early age. She had trouble finding her way while driving over five years ago, but did not report other functional impairment. Her MMSE score was 23/30. She lost her points on calculation, pentagons drawing and memory recall, which improved with cueing. She scored 24/30 on the MoCA. She failed the cube copy and her lexical verbal fluency was impaired. She failed the Go/No-Go and Luria tests. She missed 4 of
16 words on naming task. Copying of the RCFT was performed with mild errors. She did well on praxis assessment.

Case IV-18
This was a 64-year-old female with a grade 12 education. She worked as a transcriptionist but had been dismissed because of reduced performance. When questioned, she claimed that she had character incompatibility with her manager. On examination, she showed euphoric affects and lack of insight. She was talkative and disinhibited; she made inappropriate comments about physical appearance of physicians. She scored 27/30 on MMSE, losing one point on calculation and two points on memory recall. She scored 24/30 on the MoCA, she failed the trail making and cube copy. Her lexical verbal fluency was altered. She was unable to perform the Go/No-Go and Luria test. The RCFT was significantly impaired. Praxis assessment tasks were performed correctly.

Case V-1
This was a 42-year-old female with 14 years of education. She had had a diagnosis of attention deficit-hyperactivity disorder at the age of 30, which was treated with methylphenidate, and has also been diagnosed with panic disorder. She scored 28/30 on the MMSE, losing two points on memory recall, which were recovered by cueing. Her MoCA score was 29/30, she missed one point on the lexical verbal fluency. She showed impaired working memory and selective attention on detailed neuropsychological assessment. The RCFT was drawn perfectly. Subtle impulsiveness was noted.

3.11 References
Conclusion

In this master thesis, I presented three articles that expand our knowledge and understanding of hereditary cerebellar ataxias to address the issue of underdiagnosis in affected patients. The first two chapters had a common objective: to identify and classify recessive cerebellar ataxias in order for expert and non-expert physicians to better navigate this group of disorders, recognize clinical presentations, and understand underlying pathophysiology. This was a two-step process. The first chapter was a systematic scoping review of the literature that allowed the identification of 45 gene-defined disorders in which ataxia and cerebellar degeneration were central features through the retrieval of 2354 references and revision of 130 full-text articles. Thirty additional disorders were identified which presented with prominent or occasional ataxia but belonged to other disease categories or had a complex multisystem phenotype. We also included a tentative proposal of categorisation and a clinical algorithm for clinicians. The explicit objective was for this review of the evidence to serve as a basis for the work of a dedicated task force on the classification of recessive cerebellar ataxias.

From thereon, we gathered a group of 12 international ataxia experts and launched a reflection process that spanned over two years, including two in-person meetings at the Society for Research on the Cerebellum and Ataxias Symposia in 2017 and 2018. The Task Force members contributed with personal clinical and research experience, along with individual perspective to elaborate a classification that would represent a consensus from experts in this field. The second chapter presented this new conceptual framework for recessive ataxias with a clinical classification and a pathophysiological classification, which were accompanied by a stepwise approach to the diagnosis of a patient presenting with ataxia. In this final iteration, 59 gene-defined disorders were included in the list of primary recessive ataxias along with 48 complex multisystem disorders that should be included in the differential diagnosis of hereditary ataxia. This expanded number of included disorders reflected the update of the systematic review between 2016 and 2018, during which time new mutated genes and new phenotypes for previously known genes were associated with ataxia. It also reflected modified inclusion criteria following discussions within the task force, notably the decision that genes already classified in other disease categories could be included in the primary recessive ataxias if ataxia was a core element. On the opposite, certain disorders were excluded from the list following the decision that only disorders described in at least two distinct families could be included. This consensus paper aimed at providing a unique classification for recessive ataxias that expert and non-expert physicians could refer to for clinical and research purposes.
The methodology used had advantages for the elaboration of a classification. First, it was based on a systematic scoping review, which increased the likelihood of including disorders described only in specific populations and allowed an unbiased consideration of all disorders. Second, the final classification presented in chapter two was based on a consensus of international experts in the field, which ensured adequate representation of ethnical and geographical specificities in the prevalence, clinical presentation, and diagnosis of ataxia patients. It also increased the likelihood that other ataxia experts and physicians in general would adopt this classification system. Third, we developed both a clinical and a pathophysiological classification to bring together the clinical and molecular perspectives, which appeared to shed light upon one another. Indeed, we observed that the two classification systems presented significant overlap and that underlying disease mechanism was often reflected in the associated symptomatology. Finally, we worked on developing visually appealing graphic classification summaries that represent user-friendly pocket tools that are complemented by detailed tables for reference purposes. This represents a further step to promote use of this classification system by physicians in everyday practice, which is essential for the classification to serve its purpose.

There are nevertheless some limitations to this work. First, nosology and classifications are dynamic processes. As articles are published that present new genes involved in recessive ataxias or new phenotypes for previously known genes, this list of included disorders and classification will probably evolve. This was demonstrated by the modifications in the list of included disorders between the systematic review publication and the consensus proposal. Indeed, several new genes were associated with cerebellar ataxias in the two-year period before the systematic review update, notably *GDAP2* (26), *VPS13D* (27), *XRCC1* (28), and predominant ataxic phenotypes were newly described in genes previously associated with other disease categories, such as *CYP7B1* (29), *GRN* (30), *PNPLA6* (31). Therefore, this classification will have to be regularly updated to stay up to date and relevant to clinical practice. Another limitation was that the inclusion criteria of the systematic review included the element of ataxia as a central element in the clinical picture, which relies on a partly subjective appraisal of the importance of the cerebellar phenotype in the global clinical picture. This criterion is also dependent on the number and quality of described cases. For example, some articles focusing on biochemical anomalies or genetic findings only mentioned gait abnormalities, falls or ataxia in general without providing sufficient details to infer if it was due to cerebellar or sensory dysfunction (for example, (32, 33)). Hence, it remains possible that other experts could have a different opinion regarding the inclusion of certain disorders. This was minimized by the consensual development of the list of included disorders that ensured that all task
force members approved the final selection of disorders. The other methodological limitation was associated with the extent of the literature review required to cover this very large field. As a result, the search strategy was built to have a reasonable balance between sensitivity and specificity, but we could not aim for perfect sensitivity, as it would have been unrealistic to evaluate all identified articles. Therefore, it occurred that some relevant articles were not retrieved by the initial search strategy, but in these cases, we did identify subsequent related research articles or editorial comments. From there on, the revision of references allowed to identify other relevant articles concerning the same gene, such that it seems unlikely that major articles were omitted.

Previous articles had included classification proposals for recessive ataxias. Anheim et al. (22) reviewed the most frequent cerebellar ataxias in a narrative review and separated them according to the presence and type of associated neuropathy. However, they did not include the less frequent ataxias and those described only in specific geographical areas. They also included some complex multisystemic disorders in which ataxia appears as a late or minor finding, such as congenital disorder of glycosylation 1a, which is characterised by intellectual disability, hypotonia, and visceral involvement with congenital onset. In our opinion and according to task force members, these disorders do not belong to the same diagnostic category, and should rather be approached as inborn errors of metabolism. Several book chapters have also been written on recessive cerebellar ataxias, which are essential to bring awareness to this group of disorders for clinicians (23, 34). However, they were based on narrative reviews of the literature, discussing again mainly the most prevalent ataxias. Moreover, all represented the opinion of a single or small number of authors on this matter, which did not ensure a proper representation of geographical and ethnical specificities.

The most comprehensive review besides the work presented here was conducted by the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders. They undertook a global effort to revise the nomenclature system of all genetic movement disorders in order to overcome the limitations associated with the numbering systems, and proposed a phenotype prefix associated with the gene name (35). Following the publication of our systematic review, this group published a nomenclature and classification proposal for recessive ataxias in 2018. They presented a very exhaustive list of 92 disorders to which they attributed an ataxia prefix, along with 89 disorders with predominantly non-ataxia phenotypes that should be included in the differential diagnosis. This highly exhaustive list is a useful reference, but unfortunately the authors included many disorders in which the ataxia phenotype is very secondary to the global multisystem involvement, such as congenital disorders of glycosylation or myoclonic epilepsies. Moreover, they included genes associated with Joubert
syndrome, which is usually classified on its own since it is associated with mutations in 35 separate genes and has very typical neurological and renal anomalies. This exhaustiveness and the absence of organization of the included disorders reduced it to a heavy-going list of disorders that does not serve the purposes of a classification. Therefore, it constitutes a complementary reference to the classification proposed here, but can hardly be considered a classification system per se.

The third chapter of this master thesis addressed the issue of proper phenotypic characterization of hereditary ataxias, which is the basis for recognition of atypical phenotypes and classifications. We studied a large five-generation family affected with Spinoencephalobential ataxia 34 (SCA34) caused by a pathogenic mutation in \textit{ELOVL4}. This disorder had previously only been reported in three families from Quebec and Japan, and two individuals of Brazilian and English Canadian origin (36-39). The family studied herein presented some distinctive features, notably the absence of erythrokeratodermia variabilis, which had been reported in previous articles, the presence of neuropathy, and multiple system atrophy-like findings on imagery in some individuals. We also proceeded to in-depth characterization of the neurocognitive and neurobehavioral involvement in affected patients, which had been overlooked in previous studies. This showed significant executive dysfunction in affected patients along with apparent visuospatial, attention, and psychiatric involvement, which are typical findings of the cerebellar cognitive-affective syndrome (CCAS). This was the first evidence of neurocognitive impairment in this disorder, and it provided additional validation to the applicability of the universal cerebellar transform theory to hereditary ataxias. Indeed, this theory suggests that the unifying role of the cerebellum in motor, cognitive and emotional processes is to dampen variations around a homeostatic state in order to smoothen the resulting behaviour, which underlies the motor ataxia and dysmetria of thought symptomatology in cerebellar lesions (40). Before the present study, CCAS findings had mostly been reported in a few prevalent hereditary ataxias, notably SCA3 (41, 42), FRDA (43), SCA1 and SCA2 (44), which are disorders with considerable supratentorial involvement that may confound the association between cerebellar dysfunction and the cognitive deficits. Only one previous study had thoroughly evaluated cognitive impairment in patients with a pure cerebellar phenotype caused by a \textit{SYNE1} mutation, and this study had shown deficits in attention, verbal working memory, and visuospatial skills, but absence of psychiatric involvement as measured by standardized anxiety and depression questionnaires (45). These results are in line with those obtained here, and demonstrate that attention, executive function, and visuospatial skills appear to be most affected in degenerative hereditary ataxias that target mainly the cerebellum. The absence of psychiatric involvement in patients reported by Laforce et al. (45) may be due to a different evaluation method. Indeed, the
most prevalent psychiatric features reported in our patients were disinhibition and euphoria, which are likely to be overlooked by patients in self-reported questionnaires testing for anxiety and depression. Future studies should consider combining self-reported symptoms with evaluator’s assessment or proxy questionnaires to overcome this limitation.

As part of this study, we also presented immunofluorescence results of dermal fibroblasts showing the first conclusive evidence of ELOVL4 mislocalization and abnormal aggregation in this disorder. We demonstrated a dominant-negative effect on protein localization, which was an important step in the understanding of ELOVL4 pathology. These findings were similar to those obtained in patients with ELOVL4-associated Stargardt-like macular dystrophy type 3, in which researchers additionally demonstrated a dominant negative effect on enzymatic activity (46). This appears as a possible pathogenic mechanism in SCA34; an alternative hypothesis would be that protein mislocalization and aggregation causes cellular stress and exerts a toxic effect on essential cell functions. Hence, future studies should aim at evaluating the downstream mechanism through which protein mislocalization causes prominent cerebellar degeneration and which cerebellar cell types are predominantly affected.

This clinical genetic case series enabled to better define the phenotype of a little-known disorder, with in-depth characterization of the clinical involvement in a large family including specialised neurological, ophthalmologic, dermatologic, and cognitive evaluations along with functional imagery. It brought to light some atypical features and advanced our clinical and pathophysiological understanding of the impact of ELOVL4 mutations. As discussed previously, it is mainly limited by the small sample size and the fact that all patients harboured the same mutation and originated from the same family. Moreover, certain specific tests were only performed in a small number of patients, including the skin biopsy, nerve conduction studies, and ophthalmologic evaluation. This was due to the complexity of these tests and limited availability of patients to participate in all the steps of the evaluation since many participants traveled from distant cities. Hence, some of the conclusions are based on a small number of observations, and it is possible that the proportion of patients with certain specific findings may vary as more patients are described. Nevertheless, these are expected limitations in the evaluation of a very rare disease, and this study still constitutes a significant step in the understanding of this disorder.

There remain important challenges to be addressed to improve diagnostic yield in the field of hereditary ataxias. There is an enduring need for more clinical and pathophysiological studies of patients with rare disorders to obtain a clear spectrum of the typical and atypical phenotypes. As
regards to the classification and organization of disorders, there may be a place for algorithms and artificial intelligence to assist clinicians in the diagnosis of difficult patients. Recently, Renaud et al. developed a diagnostic algorithm for recessive ataxias that ranked the correct molecular diagnosis within a top 3 likely diagnoses with >90% sensitivity for 84% of genetic entities and >90% specificity for 91% of genetic entities, outperforming a panel of ataxia experts (47). This performance was limited by significant overlap (74% of the validation cohort) in the patients included in the derivation and validation cohorts, which probably overestimated the algorithm accuracy. Moreover, this algorithm probably requires significant time to perform with 124 necessary clinical and paraclinical features, and it has not demonstrated pragmatic impact on management or final diagnostic yield. Nevertheless, it is possible that diagnostic algorithms and eventually artificial intelligence may become useful assistants to suggest possible diagnoses to guide clinicians in the ordering and interpretation of genetic tests. However, these diagnostic aids will still rely on the clinician’s assessment of the presence of neurologic and systemic signs that patients often cannot report themselves.

The other major advance that will likely contribute to improving diagnostic yields is the increased accessibility and technological improvements of next-generation sequencing techniques. Indeed, some of the major limitations of these tests are the difficulty to identify repeat expansion mutations and the incomplete coverage of certain parts of the genome (48). Novel techniques have been developed to increase detection of repeat expansion mutations (49), which should facilitate prescription of genetic testing in the future. It will still remain essential for clinicians to have a good knowledge and understanding of this group of disorders to interpret the results of such tests, which often identify variants of unknown significance that have to be correlated to the clinical and paraclinical data for adequate interpretation and counseling.

Ultimately, it appears essential to ensure better diffusion of knowledge to expert and non-expert clinicians because the basis of a diagnostic process is to raise the possibility of a specific disease category. To that end, options include web-based references that can be regularly updated, graphic classification systems or pocket summaries that can be kept at hand for everyday practice. Despite technologic advances, it remains the mainstay of physicians to evaluate a patient and navigate through the range of potential diagnoses in order to obtain a definitive diagnosis. For this task, clinicians are guided by the available evidence in the literature, which must be accurate and exhaustive regarding each specific diagnosis, but also classified and organized to promote understanding and usefulness.
Bibliographie