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Tremor–ataxia with central hypomyelination (TACH) leukodystrophy maps to chromosome 10q22.3–10q23.31

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Abstract

Leukodystrophies are a heterogeneous group of disorders associated with abnormal central nervous system white matter. The clinical features invariably include upper motor neuron signs and developmental regression with or without other neurological manifestations. The objective of this study was to characterize clinically and genetically a new form of childhood-onset leukodystrophy with ataxia and tremor. We recruited seven French-Canadian cases belonging to five families affected by an unknown form of childhood-onset leukodystrophy. Genome-wide scans (GWS) were performed using the Illumina Hap310 or Hap610 Bead Chip to identify regions of shared homozygosity that were further studied for linkage with STS markers. All cases presented between the ages of 1 and 5 years with spasticity along with other upper motor neuron signs, prominent postural tremor, and cerebellar signs. Though motor regression is a constant feature, cognitive functions are relatively preserved, even late in the course of the disease. The higher frequency of founder diseases in the French-Canadian population and the segregation in pedigrees are suggestive of a recessive mode of inheritance. By homozygosity mapping, we established linkage to a 12.6-Mb SNP-haplotyped region on chromosome 10q22.3–10q23.31 (maximum LOD score: 5.47). We describe an autosomal recessive childhood-onset leukodystrophy with ataxia and tremor mapping to a 12.6 Mb interval on chromosome 10q22.3–10q23.31. Identification of the mutated gene will allow precise diagnosis and genetic counseling and shed light on how its perturbed function leads to white matter abnormalities.

Keywords

Leukodystrophy; White matter disease; Hypomyelination; Ataxia; Tremor; Linkage

Introduction

Leukodystrophies are a heterogeneous group of neurodegenerative disorders affecting preferentially the central nervous system white matter. These disorders lead to progressive spasticity and other upper motor neuron signs, as well as developmental and/or cognitive regression [1]. In some instances, patients may have cerebellar ataxia, peripheral nerve

involvement, psychiatric symptoms, and movement disorders [1]. A number of leukodystrophies have identified genetic causes with autosomal recessive, autosomal dominant, and X-linked inheritance [1-11]. The French-Canadian population is known for its numerous regional founder effects for recessive diseases [12]. The apparent geographical clustering of recessive French-Canadian cases of an undiagnosed leukodystrophy with ataxic features led to a search for a potential new chromosomal locus by homozygosity mapping. We report the clinical features of a new form of childhood-onset leukodystrophy and its mapping to chromosome 10q22.3–10q23.31.

Subjects and methods

Clinical evaluation and DNA isolation

We have identified a cohort of six living and one deceased cases, from five different French-Canadian families (Fig. 1), presenting in early childhood with progressive motor deterioration, spasticity, tremor, and gait ataxia. All living cases underwent a detailed neurological examination by experienced neurologists. A detailed chart review was performed for all cases, including case 6. This patient died at age 21; her parents refused the autopsy. Neuroimaging was reviewed for all cases by A.V., although for cases 3 and 6, a restricted number of images were available. This project was approved by the institutional Ethics Committee of the *Centre de Recherche du CHUM (CRCHUM)*. Informed consent was obtained from all participants or parents. Genomic DNA was extracted from peripheral blood lymphocytes using a standard method or from saliva using the Oragene DNA extraction kit (DNA Genotek, Ottawa, Canada).

Genome scan and linkage analysis

Genome-wide scans using the Illumina Hap310 or Hap610 Bead chip (310 or 610 K SNPs, respectively) were conducted at the McGill University and Genome Quebec Innovation Centre (Montreal, Canada) on all living cases and at least one non-affected family member per family. Multipoint linkage analysis was performed using GENE-HUNTER v.2.1 and Simwalk2 v.2.91 [13]. The files used for Simwalk2 were produced with Mega2 v.4.3 [14]. Marker order and genetic distances were based on the deCODE genetic map and UCSC physical map (<http://genome.ucsc.edu>, March 2006 assembly). For the linkage analyses, allele frequencies were calculated from 162 control chromosomes of non-affected French-Canadian from the Quebec province. The leukodystrophy phenotype was analyzed as an autosomal recessive trait with 100% penetrance, with an estimate disease gene frequency of 0.001 and no phenocopy.

Exclusion of candidate genes

We sequenced the coding sequence, 5' and 3' UTR of the following ten genes in the 12.6-Mb candidate interval: *PPIF* (peptidylprolyl isomerase F precursor), *ANXA11* (annexin A11), *ATAD1* (ATPase family, AAA domain containing 1), *SFTPD* (pulmonary surfactant-associated protein D), *CH25H* (cholesterol 25-hydroxylase), *EIF5A1* (eukaryotic translation initiation factor 5A-like), *SFTPA1* (surfactant protein A1 precursor), *SFTPA2* (surfactant protein A2 precursor), *LRR21* (leucine-rich repeat containing protein 21 precursor), and *NRG3* (neuregulin 3). Candidate genes were selected for sequencing based

on their expression profile (www.cgl.ucsf.edu/cgi-bin/genentech/genehub-gepis/), gene ontology (<http://genome.ucsc.edu/>), and using the SUSPECTS program (<http://www.genetics.med.ed.ac.uk/suspects/>). PCR primers (supplementary Table 1) were designed using ExonPrimer (<http://genome.ucsc.edu>) or Primer3 (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi). PCR reactions and sequencing reactions were conducted at the McGill University and Genome Quebec Innovation Centre (Montreal, Canada). Sequences were analyzed using SeqMan 4.03 (DNASTar, Madison, WI, USA), Chromas 1.62 (Technelysium, Helensvale, Australia), and Mutation Surveyor v.3.1 (SoftGenetics, State College, PA, USA).

Results

Clinical features

We recruited a cohort of 14 French-Canadian cases of leukodystrophy of unknown cause. Seven cases belonging to five families were considered to be likely affected by the same form of leukodystrophy based on their clinical and radiological characteristics. The sex ratio was six boys for one girl (Fig. 1). In family 4, the presence of a deceased distant affected female cousin (case 6) of two brothers (cases 4 and 5) favors a recessive rather than an X-linked mode of inheritance. Further support for a recessive mode of transmission comes from the observation that, in families 4 and 5, the parents are known to be distantly related and both originate from the contiguous Bellechasse and Beauce regions where another recessive founder effect has been described for a recessive ataxia (Fig. 1) [15]. The mother of case 2 also originates from the Beauce region. This micro-regional cluster further raised the possibility of a recessive founder mutation shared by these three families. Families 1 and 3 originate from the Gaspésie region also known for its regional founder effects [16,17]. The clinical features of the seven cases are summarized in Table 1. The average age of onset is 2.5 years (1–5 years), although age of onset was variable even within a single family (family 4). All cases presented with motor regression, ataxia, and tremor (Table 1). Gait was clearly modified by a combination of pyramidal spasticity and cerebellar ataxia. The gait ataxia is associated with a prominent tremor of the upper extremities, which is present both with posture holding and action, dysarthria, and abnormal ocular saccades and/or pursuits with or without gaze-evoked nystagmus. As the disease progresses, the patients' motor difficulties worsened and lead to the use of a wheelchair between ages 4 and 12 years (average 7.3 years). The exception is case 5, with a later disease onset at age 5, who is still ambulant and walking without any aid at age 12. Additional features include a history of deterioration with infections or stress (3/7, 43%), bulbar symptoms such as dysphagia (4/7, 57%), and drooling (5/7, 71%), optic atrophy (4/7, 57%), and partial complex seizures (2/7, 29%). Cognitive decline is mild and occurs later in the course, but was clearly observed in 6/7 cases. Of interest, two out of seven cases have some degree of hypodontia; case 4 is missing four teeth (teeth #12–22–31–41) and case 5 is missing one (tooth #22). One case (#7) has documented hypogonadotropic hypogonadism but no hypodontia.

All cases in the cohort have had extensive workups in different institutions. The following leukodystrophies were excluded in all living patients: metachromatic leukodystrophy, Krabbe, Canavan, and adrenoleukodystrophy. Nerve conduction studies and

electromyograms were performed in all seven patients and did not reveal any abnormalities. Sural nerve biopsies on cases 6 and 7 were normal, including electronic microscopy for case 7. Mutation screening was performed on the following genes in at least one individual: *GJA12* (case 3), *EIF2B1–EIF2B2–EIF2B3–EIF2B4–EIF2B5* (cases 3 and 4), *PLP1* (case 7), *NPC1* and *NPC2* (cases 3 and 7), and *GFAP* (cases 3 and 4). Though the tremor–ataxia with central hypomyelination (TACH) locus lies 5.1 Mb telomeric to the *PSAP* gene, we decided to exclude it by sequencing. This gene encodes the four saposins: A, B, C, and D. Mutations of the *PSAP* gene can lead to deficiency in all saposins (combined saposin deficiency), in saposin A, B, C, or D, leading, respectively, to atypical Krabbe, metachromatic leukodystrophy variant, atypical Gaucher, and Tay-Sachs variant [18–22]. No mutation in this gene was found in case 4 and the urine sulfatides were normal in cases 3 and 4, excluding this gene as responsible for TACH. FISH study for *PLP1* duplication was performed in two cases (cases 3 and 4). Sialic acid was measured in four cases (cases 1, 4, 5, and 6). These extensive investigations failed to uncover the cause for the leukodystrophy in all seven participants. The only frequent abnormality shared by six of the seven participants was the presence of high total cholesterol on the lipid profile, from a mild augmentation to an elevation significant enough to require treatment with HMG-CoA reductase inhibitor in case 7.

Available neuroimaging was reviewed for all seven cases, although only a small number of sequences were available for cases 3 and 6. The most typical MRI findings of the least (case 5) and most clinically affected (case 7) patients are illustrated in Fig. 3. All cases have a hypomyelinating leukoencephalopathy [23], with hyper or isointense appearing white matter on T1 and concomitant hyperintense white matter structures on T2. White matter abnormalities are diffuse in nature but with relative sparing of arcuate fibers and optic radiations in the less affected cases, involving the periventricular and deep white matter preferentially. The patients were also found to have increased cerebrospinal fluid spaces within the posterior fossa, as well as thinning of the corpus callosum. In the most severely clinically affected patients, there is minimal rarefaction of the deep white matter near the frontal and occipital ventricular horns on FLAIR imaging, as well as cerebellar atrophy.

Mapping of the locus and sequencing of candidate genes

DNA samples from the six living cases, at least one unaffected parent, and in cases 4, 5, and 7, siblings, were sent to McGill University and Genome Quebec Innovation Centre (Montreal, Canada) for a genome-wide scan (GWS) using the Illumina Hap310 or Hap610 Bead chip (310 or 610 K SNPs). The affected children of families 4 and 5 were found to be homozygotes for 12.6 Mb (3,000 SNPs) on chromosome 10q22.3–q23.31. Further genotyping with microsatellite (STS) markers was performed in this region. The three cases (4, 5, and 7) were found to be homozygous for all markers in this region. A multipoint cumulative LOD score of 5.47 was obtained for STS markers D10S201, D10S1777, D10S1696, and using Simwalk2 v.2.91 and Gene Hunter v.2.1 for families 4 and 5 (Fig. 2). Cases 1, 2, and 3 from families 1, 2, and 3 were found to be compound heterozygotes for the shared haplotype of families 4 and 5. This finding suggests that at least one other mutation is present in our group of patients. These results are compatible with the geographical origins of these three families (1, 2, and 3), the parents being unrelated and from different regions in

Quebec. This 12.6-Mb (rs7069982–rs2071510) locus on 10q22.3–q23.31 has not been previously associated with a leukodystrophy.

Sixty-one genes lie in the 12.6-Mb candidate interval. Investigation of changes in gene copy number using the SNP genotype generated during the GWS was performed using copy number variation (CNV) analysis with BeadStudio v3.1 (Applied Biosystems, Foster City, CA, USA) and using a propriety program of six algorithms for high-throughput detection of CNV. No putative pathogenic CNV were detected in the candidate interval. Sequencing analysis of all coding and surrounding intronic sequences, 5' and 3' UTRs were performed for the following ten candidate genes lying in the 12.6-Mb region: *PPIF*, *ANXA11*, *ATAD1*, *SFTPD*, *CH25H*, *EIF5AL1*, *SFTPA1*, *SFTPA2*, *LRRC21*, and *NRG3*. The genes were selected because their expression profiles were similar to known causal leukodystrophy genes and/or because of their presumed interaction(s) with these genes (<http://www.genetics.med.ed.ac.uk/suspects/>). The *EIF5AL1* gene was selected as one of our prime candidates because it is part of the elongation factor family of genes as the following mutated genes in CACH: *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5* [1]. *PPIF* and *SFTPD* are respectively predicted to have a similar expression profile and to have a shared function with genes belonging to the elongation factors family. The genes *SFTPD*, *SFTPA1*, *SFTPA2*, and *ANXA11* are predicted to share different functions with the *PSAP* gene (prosaposin isoform A preproprotein), a gene known to cause rare forms of Krabbe and metachromatic leukodystrophies [5]. The *SFTPD* gene is also presumed to share some of the lysosomal functions of the *ARSA* (arylsulfatase A) gene. The *CH25H* gene was chosen based on its role in cholesterol metabolism, considering that six of the seven cases have elevated total cholesterol. Finally, the *LRRC21* and *NRG3* genes were selected because of their expression profiles in the brain. No mutations were uncovered in any of these genes.

Conclusion

We describe a new form of recessive childhood-onset leukodystrophy, TACH, and map its locus to chromosome 10q22.3–10q23.31. This leukodystrophy presents around the same ages as the typical forms of metachromatic leukodystrophy and CACH (18 to 24 months and 12 months to 5 years of age, respectively) [1]. The clinical features are somewhat similar to other forms of leukodystrophies presenting in early childhood, with progressive motor deterioration, spasticity, and other upper motor neuron signs. The more typical clinical characteristics of these cases are the presence of prominent ataxia and of an important postural and action tremor. To underline this clinical observation, we chose to call it TACH. We believe that this disease is better characterized as a leukodystrophy than an ataxia because of the universal white matter abnormalities on MRI studies (Fig. 3) and because the clinical presentation is more complex, involving several other neurological systems. Its clinical presentation resembles CACH in several ways, with ataxia being an important clinical finding [1]; however, MRI features are distinct from this disorder [24]. The MRI findings of TACH are more consistent with the group of disorders characterized by hypomyelination, including those caused by *GJA12/GJC2* mutations or Pelizaeus-Merzbacher-like disease [11], HCC, or hypomyelination with congenital cataracts [25], and 4H or hypomyelination with hypodontia and hypogonadotropic hypogonadism, among others. Pelizaeus-Merzbacher-like disease was ruled out by sequencing the *GJA12* gene.

HCC was eliminated as a possible diagnosis in our cases because of inconsistent clinical features and different loci. The fact that the oldest case is treated for hypogonadotropic hypogonadism and that two participants are known for hypodontia raised the possibility that these patients may have a variant of 4H syndrome: hypomyelination, hypogonadotropic hypogonadism, and hypodontia [26-28]. The 4H syndrome was first described in 2005 [29] in four unrelated girls with progressive ataxia, hypomyelination, and delayed dentition. Since the first description, a few more patients have been reported [27-30]. It is thought to be inherited in an autosomal recessive fashion, but the chromosomal locus is still unknown. Though there appears to be some clinical overlap between 4H and TACH, none of our cases have the full set of features. Only two out seven have missing teeth, and a single patient has hypogonadotropic hypogonadism. The two sural nerve biopsies on cases 6 and 7 were interpreted as normal. The nerve biopsy of case 7 was studied by electron microscopy and no abnormality supportive of a 4H diagnosis was uncovered. Nerve biopsies of patients with the 4H syndrome were reported to demonstrate clefts lined with granular debris, expanded abaxonal space, outpocketing with vacuolar disruption, and loss of normal myelin periodicity [27]. The identification of the 4H locus or the gene for TACH will establish if the two disorders are allelic. To identify the mutated gene responsible for TACH, further genomic analyses will be required to further fine map the candidate region by recruiting additional families from Quebec and other countries. The identification of the TACH gene will contribute to our understanding of the mechanisms leading to inherited white matter diseases. It will also allow clinicians to offer definite diagnoses for one form of the growing number of leukodystrophies and genetic counseling to their families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
Pedigrees of the five French-Canadian families with tremor-ataxia with central hypomyelination (TACH), including consanguineous families 4 and 5. Affected cases are *shaded black* and participants for which a genome scan was performed are marked with an *asterisk*

Fig. 2.
Multipoint LOD scores generated by the analysis of family 4 and family 5 for 20 markers on chromosome 10q21.2–10q23.2 markers

Fig. 3.

MRI features in tremor-ataxia with central hypomyelination (TACH). Characteristic MRI images in two subjects: cases 5 (a) and 7 (b) (the least and most affected patients, at ages 11 and 21 years, respectively). The MRI show diffuse hypomyelination with diffusely increased T2 signal, isointense or hyperintense T1 signal, with relative sparing of arcuate fibers and optic radiations. Thinning of the corpus callosum is a constant feature. In the most clinically affected patients, such as in case 7, there is some periventricular deep white matter rarefaction on FLAIR images, as well as atrophy of the cerebellum

Table 1

Clinical features

Patient #	Family #	Gender	Developmental delay	Age of onset (y)	Age in 2010	Ataxia	Dysmetria	Spasticity	Hyperreflexia	Babinski	Dysarthria	Dysphagia
1	1	M	+	1	6	+	+	+	+	+	+	
2	2	M		2.5	14	+	+	+	+	+	+	+
3	3	M	+	2	10	+	+	+	+	+	+	
4	4	M	+	1	15	+	+	+	+	+	+	+
5	4	M	+	5	13	+	+	+	+		+	
6	4	F		3	N/A	+	+	+	+	+	+	+
7	5	M		3	28	+	+	+	+	+	+	+
			Mean	2.5								

Patient #	Drooling	Tremor	Gaze-evoked nystagmus	Optic atrophy	Bladder dysfunction	Seizures	Wheelchair	Age—wheelchair (y)	Neuropathy	Cognitive regression	Hypodontia	Hypogonadotropic hypogonadism	Age of death
1	+	+	+	N/A	+		+	4					
2	+	+	+	+	+	+	+	7	N/A	+			
3		+	+		+		+	5		+			
4	+	+	+	+	+	+	+	8		+	+		
5		+								+	+		
6	+	+		+	+		+	8		+			21
7	+	+	+	+	+		+	12		+		+	
			Mean					7.3					

Clinical characteristics of the seven affected cases. Note that cases 4, 5, and 6 are from the same family