

A Novel Duplication Confirms the Involvement of 5q23.2 in Autosomal Dominant Leukodystrophy

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Objective: To identify the underlying locus and disease-causing mutation for adult-onset autosomal dominant leukodystrophy (ADLD).

Design: Previously, an adult-onset ADLD locus on chromosome 5q23 was mapped between markers D5S1495 and CTT/CCT15. This region contains 13 known and putative candidate genes. A 2-point linkage analysis confirmed linkage of a large multigenerational French Canadian family to chromosome 5q23. In addition, screening of the 13 genes within the candidate interval as well as 5 neighboring genes was completed, followed by comparative genomic hybridization.

Subjects: A multigenerational French Canadian family with ADLD mimicking progressive multiple sclerosis was identified and studied. Eight affected family members were available for the study and presented with autonomic dysfunction as well as upper motorneuron signs affecting gait.

Results: The thorough candidate gene approach did not identify any mutation. Consequently, a whole-chromosome comparative genomic hybridization for chromosome 5 identified a 280-kilobase duplication within the chromosomal band 5q23.2 in 2 affected individuals. This duplication contains 3 genes: *LMNB1*, *FLJ36242*, and *MARCH3*.

Conclusion: We have identified a novel duplication on chromosomal band 5q23.2 in a French Canadian family with ADLD that supports the implication of duplicated *LMNB1* as the disease-causing mutation. However, additional functional studies of lamin B1 overexpression are necessary to elucidate the involvement of lamin B1 in myelination and in degenerative disorders such as ADLD and multiple sclerosis.

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HEREDITARY LEUKODYSTROPHIES are genetic disorders that affect mainly the cerebral white matter. The most common forms are childhood-onset diseases with a recessive inheritance pattern. Several mutant genes leading to biochemical abnormalities have been identified as the cause of these recessive leukodystrophies including arylsulfatase A, galactocerebrosidase, and very-long-chain fatty acids. More recently, the subunits of the eukaryotic initiation factor 2B, an important translation initiation factor, have been linked to vanishing white matter disease (OMIM 603896) and childhood ataxia with cerebral hypomyelination.¹

The known causes of autosomal dominant adult-onset leukodystrophy (ADLD) were reviewed by Baumann and Turpin² and many are late-onset forms of the childhood leukodystrophies. Two X-linked forms, Pelizaeus-Merzbacher disease and adrenoleukodystrophy, have also been described.^{2,3}

Autosomal dominant adult-onset leukodystrophy mimicking multiple sclerosis (MS) is an adult-onset leukodystrophy characterized by autonomic dysregulation, pyramidal signs, and cerebellar dysfunction. The main feature is symmetrical primary demyelination in the central nervous system of patients that is visible on computed tomographic scans or magnetic resonance images. This disease was first described by Eldridge et al,⁴ and several families with ADLD from different ethnic origins have since been described, namely 2 Irish American,⁵ 1 Swedish,⁶ 4 Japanese,⁷⁻¹⁰ 1 French,¹¹ and 1 Italian¹² family. These families generally presented in the same way except for the autonomic features, which were only reported for certain families with ADLD.⁶ Linkage studies initially localized the gene to chromosome 5q31.¹³ Further fine mapping in the Swedish family narrowed down the candidate region to a 1.5-megabase pair (Mb) region on chromosome 5q23 between markers D5S1495 and CT/CCT15.

During a candidate gene analysis, Padiath et al⁵ identified 3 tandem duplications in the ADLD candidate region by means of single-nucleotide polymorphism (SNP) sequence-peak comparisons. In the study, they presented 4 families including 2 Irish American families with a common ancestor and 2 Japanese families. The borders of 2 of the 3 duplications were determined; they spanned approximately 341 kilobase pairs (kb) and 169 kb, respectively. The duplicated regions consistently contained 3 genes: *LMNB1*, *FLJ36242*, and *MARCH3*.⁵

Lamin B1 (*LMNB1*) belongs to the family of lamins (*LMNA*, *LMNB1*, and *LMNB2*), which are type V intermediate filaments in the nuclear lamina.¹⁴ However, the function of *LMNB1* has not been well characterized. Mice deficient in *LMNB1* die shortly after birth and display bone and lung abnormalities.¹⁵ On a molecular level, the nuclear membrane of the deficient mouse embryonic fibroblasts showed nuclear blebs possibly due to impaired cellular differentiation. Overexpression of the fly ortholog, *lamin DM_o*, as well as a human *LMNB1* transgene in a *Drosophila melanogaster* model using different drivers showed increased lethality, most notably in the glial-specific model.⁵ Mutations have also been described in other lamins; for example, mutations in *LMNA* cause different types of muscular dystrophies, lipodystrophy, and premature aging diseases. Similar phenotypes were also found in *LMNA*-null mice. Interestingly, *LMNB1* is ubiquitously expressed throughout development, whereas *LMNA* is only expressed in differentiated cells. Mutations in *LMNB2* are associated with acquired partial lipodystrophy.¹⁶ In addition, the autosomal dominant Pelger-Huet anomaly is caused by reduced expression of the *LMNB* receptor, which affects neutrophil nuclear shape and chromatin distribution in a dose-dependent manner.¹⁷ These diseases are called *laminopathies* and are caused by mutations in the nuclear lamins.^{14,18} In this study we present a French Canadian family with ADLD, a likely laminopathy, in which an approximately 280-kb duplication on chromosome 5q23 has been identified.

METHODS

SUBJECTS

Informed written consent was obtained from subjects to participate in the study, which was approved by the local ethics review board of the Centre Hospitalier de Charlevoix, where all of the subjects were recruited. Peripheral blood samples were obtained from 21 individuals including 8 affected family members. The DNA was extracted by standard methods and lymphoblastoid cell lines were established.¹⁹ Individuals were recruited by a neurologist (J.-P.B.), and the diagnosis was based on a complete neurological examination and imaging of the brain by magnetic resonance imaging or computed tomographic scan. Five patients had complementary procedures such as electroencephalogram, electromyogram and nerve conduction studies as well as laboratory testing of blood and cerebrospinal fluid.

GENOTYPING

Polymorphic markers were amplified by polymerase chain reaction, incorporating radiolabeled sulfur 35 deoxyadenosine triphosphate into the product. The products were separated on

6% denaturing polyacrylamide gels and visualized on autoradiographic film. Key markers were initially genotyped in and around the ADLD locus, followed by more extensive fine mapping. Linkage analysis was performed using the MLINK program of the LINKMAP software package²⁰ (National Institutes of Health, Bethesda, Maryland) assuming equal recombination frequency; a disease frequency of 1/1000 persons; age liability classes of 0-46 years, 50% penetrance; older than 47 years, 90% penetrance; and a phenocopy rate of 0. Haplotype construction assuming minimal recombination was performed manually and ordered according to the goldenpath physical map (UCSC Genome Browser; <http://www.genome.ucsc.edu/>).

MUTATION DETECTION

Genomic primers were designed to amplify the 18 candidate genes (*LOX*, *ZNF474*, *SNCAIP*, *SNX24*, *SNX2*, *PRDM6*, *CCDC100*, *CSNK163*, *ZNF608*, *KIAA1281*, *GRAMD3*, *ALDH7A1*, *RNUXA*, *LMNB1*, *MARCH3*, *MEGF10*, *FLJ00410*, *PRRC1*) found within the extended candidate interval. All coding exons and at least 50 base pairs of the flanking intronic sequence were amplified. Primer sequences will be made available on request. Polymerase chain reaction products were sequenced at the Genome Quebec Centre for Innovation.

More specifically, primers for the *LMNB1* gene were designed to amplify the 11 exons, including the complete 5' and 3' untranslated regions. The samples tested included 2 affected individuals, 1 control (a spouse), and hybrid cell line DNA derived from individual R17697 (patient IV:9) (GMP genetics Inc, Waltham, Massachusetts).²¹ The hybrid cell line allowed us to analyze the affected allele of chromosome 5 in isolation.

Using comparative genomic hybridization technology performed by Nimblegen Systems, Inc (Madison, Wisconsin), 2 individuals were also tested for copy-number variants.²² The 2 samples were compared with a reference sample consisting of pooled DNA from 6 healthy individuals. The analysis of SNP peaks visible on sequence traces was also performed to confirm the extent of the duplication. A list of analyzed SNPs will be made available on request.

RESULTS

CLINICAL DATA

Figure 1 shows the multigenerational French Canadian family with ADLD with autosomal dominant segregation in 16 affected members over 3 generations. Interestingly, an affected branch of the family also carries a disease allele for the saccin-encoding gene; therefore individual IV:1 was affected with both ADLD and autosomal recessive spastic ataxia of Charlevoix-Saguenay (OMIM 270550). Autosomal recessive spastic ataxia of Charlevoix-Saguenay is a young-onset spastic ataxia with a high carrier prevalence in the Charlevoix-Saguenay-Lac-Saint-Jean region of Quebec. Eight affected individuals were followed up by the same neurologist (J.-P.B.) while the clinical details of older family members were obtained through oral personal accounts. The disease status of each affected member was confirmed by imaging. The fifth generation was not included because of age-dependent reduced penetrance.

The symptoms in this family usually presented early in their fifth decade of life and consisted of bladder and/or bowel disturbances, lower limb weakness, orthostatic hy-

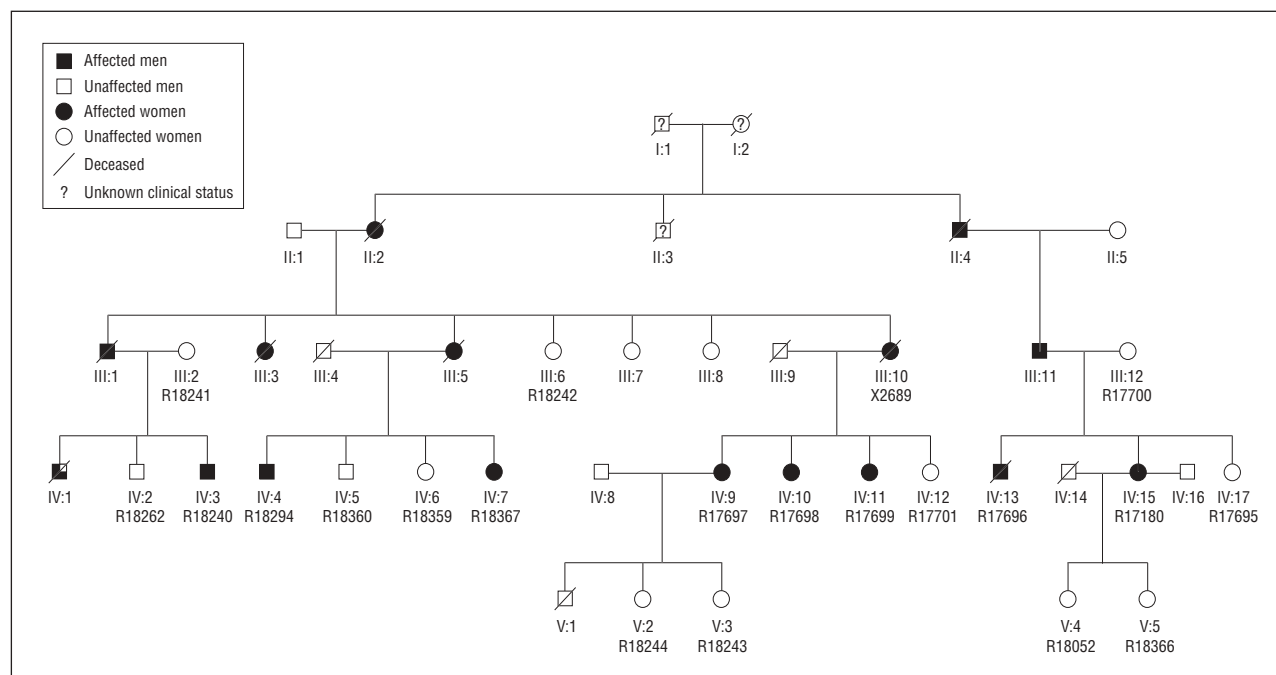


Figure 1. The family tree of adult-onset autosomal dominant leukodystrophy (ADLD)-1. Pedigree showing autosomal dominant segregation ADLD in a large French Canadian family. Individual IV:1 (black filled square with smaller white square) was also affected with autosomal recessive spastic ataxia of Charlevoix-Saguenay. Roman numerals are general patient identifiers; numbers beginning with *R* are laboratory identifiers (DNA is available for these individuals).

potension, and/or impotence. The disease progresses slowly and sometimes seems to remit (as is seen in MS). The severity of the disease also varies within the family; the most severe outcomes were observed in individuals who had the longest disease duration. The 2 affected subjects in the second generation (II:2 and II:4) were said to be “crawling on the floor” in their fifties. One individual (III:10) became bedridden (tetraplegic and anarthric) at 72 years of age, but survived until 78 years.

The signs and symptoms of the family are similar to those described by Eldridge et al,⁴ with a few exceptions. The lower limbs show marked hyperreflexia in most individuals with occasional involvement of the upper limbs. The patients display a spastic gait and have frequent falls. The Babinski sign is usually present or indifferent. There are less overt cerebellar signs with slightly affected rapid alternating movements and finger-to-nose tests. The sensory system is intact, with no hearing or visual loss noted. No dementia was reported in this family either. The nerve conduction studies were normal and the electroencephalogram did not show any epileptic discharges, but did show a diffuse slowing of electrical activity. Some autonomic features including impotence, bladder incontinence, constipation or fecal incontinence, decreased sweating, and orthostatic hypotension were eventually present in all affected individuals. One patient (IV:13) was most severely dysautonomic and had severe episodic temperature dysregulation leading to drops in temperature to as low as 32°C, which may ultimately have caused his death. Other causes of death in the family were neoplasms and infections, with an average age at death of 62 years. A brain magnetic resonance image (**Figure 2A** and **B**) of individual IV:4 is representative of those seen in other family members. The fluid-attenuated inversion recovery images show severe and confluent abnormalities of the white matter, even more

pronounced in the posterior areas, and no significant cortical atrophy or ventriculomegaly. The spinal cord (**Figure 2C**) has consistently shown severe atrophy throughout. There is no neuropathological data available. Specific laboratory tests were conducted to exclude differential diagnosis of other leukodystrophies. In particular, the laboratory tests for ARSA (metachromatic leukodystrophy), accumulation of very long-chain fatty acids (characteristic of X-linked adrenoleukodystrophy), galactosylceramide, and oligoclonal bands were negative in tested affected individuals.

LINKAGE AND HAPLOTYPE ANALYSIS

Two-point linkage analysis using an age-based liability class showed a Z_{\max} of 4.03 ($\theta=0$) for marker D5S2039. The markers D2S2055 and D2S649 showed a log of odds score of less than -2 and therefore excluded the regions outside of these markers. Fine mapping ensued and extensive genotyping of more than 35 markers in the region determined the critical segregating region between markers D5S2055 and D5S649 that spans 13 Mb or 7.74 cM. This candidate region overlapped the locus reported by Coffeen et al,¹³ and the overlap contained the aforementioned 18 candidate genes (**Table**). Meanwhile, Marklund et al⁶ reported a smaller locus flanked by markers D5S1495 and CTT/CCTT15 (1.47 Mb) that only contained 13 genes.

After an optimal marker density was achieved, a candidate gene screen followed. The 18 candidate genes were thoroughly screened and no mutation was identified. The absence of a point mutation led to the Nimblegen comparative genomic hybridization analysis, which identified a large duplication spanning approximately 280 kb (**Figure 3**). The duplicated region contains 2 complete

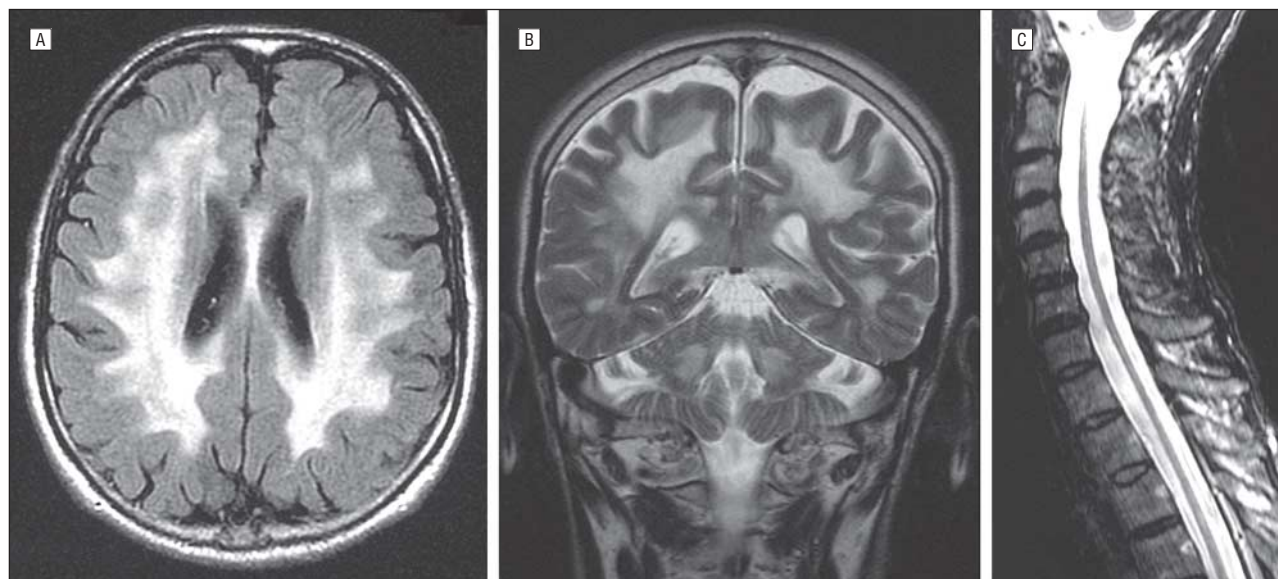


Figure 2. Imaging of 2 patients in the family. Hyperintense diffuse abnormalities are seen on fluid-attenuated inversion recovery (FLAIR) and T2 sequences of magnetic resonance imaging for all patients in this family affected with adult-onset autosomal dominant leukodystrophy. A, Axial FLAIR image of the brain of a 55-year-old man (patient IV:4) showing hyperintensities of the whole white matter, somewhat more pronounced in the posterior areas, with slight to moderate cortical atrophy but no ventriculomegaly. B, Coronal T2 image of the brain of the same subject, including the posterior fossa, demonstrating involvement of the cerebellar pedunculus (which is present in all patients). C, A 57-year-old woman (patient IV:15) with a 17-year history of severe progressive urinary retention followed by walking difficulties; sagittal T2 image shows marked atrophy of the cervical and dorsal spinal cord without abnormal intrinsic signal.

genes, *LMNB1* and *FLJ36242*, as well as the 5' end of the *MARCH3* gene. Sequencing of additional SNPs in the region as previously described by Padiath et al⁵ further confirmed the duplication. There were neither known copy-number variants nor insertions and/or deletions within and near the duplication.

COMMENT

This study identified a novel duplication on chromosome 5q23 in a large French Canadian family affected with ADLD. The finding confirms the results from Padiath et al⁵ that the cause of ADLD is a duplication containing 3 genes: *MARCH3* (partially), *FLJ36242*, and *LMNB1*. The implication of a duplication in a demyelinating, highly penetrant, Mendelian disorder demonstrates the importance of including a copy-number variant analysis in standard mutation screens. Furthermore, sequence analysis should be programmed to recognize differences in peak heights that are suggestive of a duplication or a deletion. Hybrid cells containing only the affected allele did not aid in detecting the duplication and are more useful in detecting deletions.

Of the 3 genes found within the duplication, *LMNB1* is the only complete gene known to be expressed in the brain, with particularly high expression in the cerebellum. Further analysis of the *LMNB1* gene in the patients' brain samples showed that there were higher levels of *LMNB1* mRNA and protein.⁵ Taken with the fact that duplications have been identified in 4 families with ADLD without other mutations in the candidate interval, overexpression of *LMNB1* is the most likely cause of ADLD. However, overexpression studies in a cell model and eventually in a second organism will be necessary to better understand the role of *LMNB1* in ADLD. In ad-

Table. The ADLD Candidate Region

Marker	Mb ^a	Subject	
		IV:13 ^b	IV:3 ^b
D5S659	114145374	5	1
D5S2055	115324701	4	10
D5S1468	116007287	4	4
D5S467	121434681	3	3
D5S2070	121972220	5 ^c	5 ^c
D5S818	123139024	6 ^c	6 ^c
D5S2039	123402069	2 ^c	2 ^c
DD5S804	125112813	4 ^c	4 ^c
D5S1391	127284456	2 ^c	2 ^c
D5S649	127324334	3 ^c	1 ^c
D5S2078	128191470	4 ^c	3 ^c
D5S642	128219363	8 ^c	4 ^c

Abbreviations: ADLD, adult-onset autosomal dominant leukodystrophy; Mb, megabase pairs.

^aMegabase pair according to the National Center for Biotechnology Information Build 36.1 used in the University of California Santa Cruz genome browser.

^bAlleles according to Fondation Jean Dausset-Centre d'Etude du Polymorphisme Humain.

^cRepresents the candidate region determined by Coffeen et al.¹³

dition, the question remains whether point mutations in *LMNB1* can also lead to this phenotype.

The duplication was identified by comparative genomic hybridization analysis in 2 affected individuals and verified by SNP peak analysis. Although the exact borders of the duplication were not determined because the region contained the same 3 genes as the ones identified by Padiath et al,⁵ the duplication was found to be of a different size and was estimated to span 280 kb. The fact that 3 similar duplications were found in 3 ethnic groups suggests that there might be a sequence motif predispos-

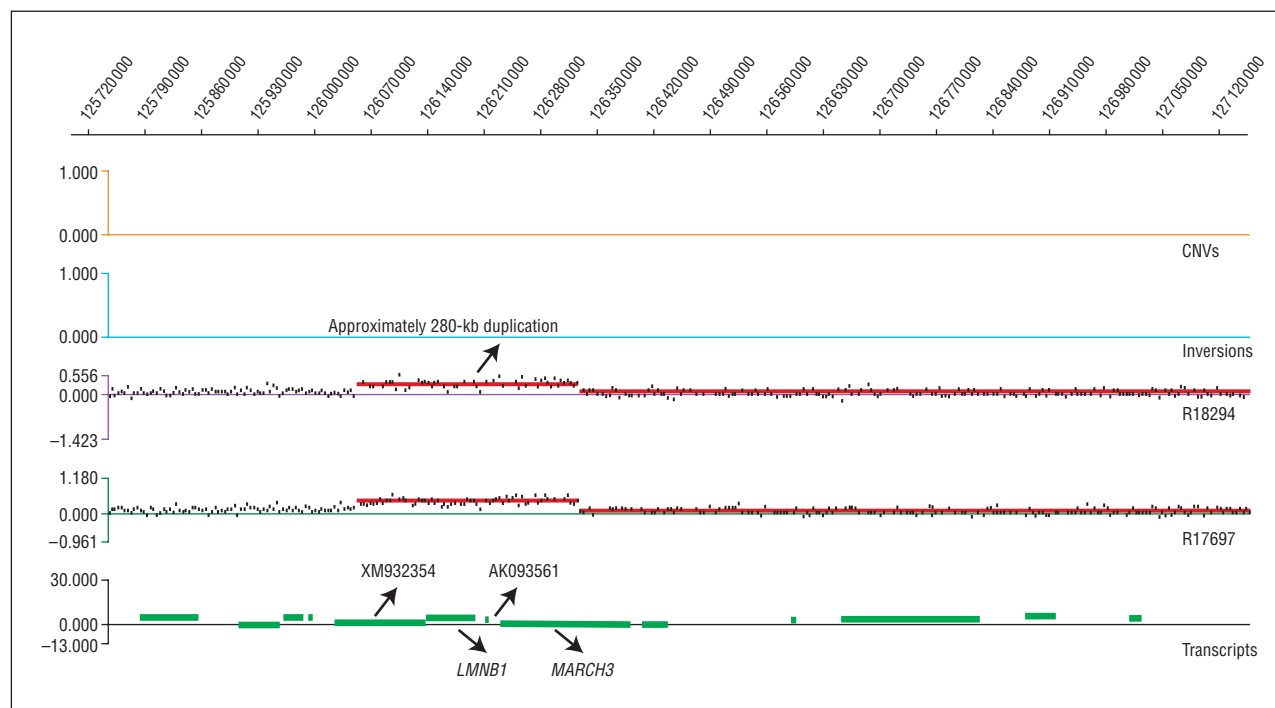


Figure 3. A schematic of the chromosome 5q duplication. The duplication as represented by the SignalMap software of Nimblegen Systems, Inc (Madison, Wisconsin). Two affected individuals show a positive signal for a duplication of approximately 280 kilobase pairs (kb) compared with 6 pooled reference DNA samples. The genes *LMNB1*, *MARCH3*, and *FLJ36242* lie in this duplication. Note that *MARCH3* overlaps the border of the duplication. The XM932354 transcript no longer exists in current databases but was included in the Nimblegen analysis. The known copy-number variants (CNVs) and insertion/deletions in the University of California Santa Cruz (UCSC) HG18 (National Center for Biotechnology Information Build 36.1) release are also depicted. Also note the absence of known variants in the duplication segment. The numbers at the top represent the physical location of the bases according to UCSC (<http://genome.ucsc.edu/>).

ing the flanking region to coupled homologous and non-homologous recombination in the flanking region. This type of recombination has previously been studied in Pelizaeus-Merzbacher disease, another demyelinating disorder, in which an excess of proteolipid protein results in defective myelin assembly in the Golgi apparatus.²³ It is not yet understood how overexpression of these 2 genes specifically lead to demyelination. In general, little is known about the function of the *LMNB1* protein; recent studies have focused on its role in attaching the nucleus to the cytoskeleton.²⁴

Autosomal dominant adult-onset leukodystrophy caused by mutations in *LMNB1* is part of a larger group of diseases called laminopathies.²⁵ Interestingly, ADLD is the only laminopathy caused by overexpression, which might explain why this disease has a demyelinating phenotype as opposed to lipodystrophies or muscular dystrophies. However, the laminopathies do share similarities in that there is high intrafamilial variability and that they are caused by mutations in proteins with a general function such as *LMNB1* and *EIF2B*, which lead to cell-specific phenotypes.¹

Clinically, the French Canadian family with ADLD does not strikingly differ from the previously reported families. The affected individuals presented with gait abnormalities and autonomic dysfunction, but did not have severe cerebellar signs or dementia. One individual, IV:13, died because of severe temperature dysregulation that was left untreated by the patient. This individual had a normal thalamus and hypothalamus as well as a normal corpus callosum on magnetic resonance images. Simi-

larly, temperature dysregulation in MS is also rare and has recently been reviewed by Benarroch²⁶ and Merkelsbach et al.²⁷ In addition, patients with ADLD in the French Canadian family reported partial remittance of the disease, which somewhat resembles MS evolution. However, no MS samples have yet been screened for potential copy-number variants in this region, though this represents an interesting future experiment.

Recent studies have marked the protein sirtuin 2 as a therapeutic avenue for demyelinating disease specific to oligodendrocytes because it was shown that the levels of sirtuin 2 transport are reduced in *PLP*-knock-out mice.^{28,29} In addition, lamins are early targets for caspase degradation.³⁰ These interesting therapeutic avenues, together with a shift in focus to overexpression of *LMNB1*, might lead the way in the development of potential therapies for myelin disorders.

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Critical revision of the manuscript for important intellectual content: Simoes-Lopes, Katz, Verlaan, Dupré, Thibault, Bouchard, and Rouleau. *Statistical analysis:* Verlaan. *Obtained funding:* Meijer and Rouleau. *Administrative, technical, and material support:* Meijer, Laurent, Katz, St-Onge, Mathurin, Bouchard, and Rouleau. *Study supervision:* Mathurin, Bouchard, and Rouleau.

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