To the Editor

TACH Leukodystrophy: Locus Refinement to Chromosome 10q22.3-23.1

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]. We recently described a new form of childhood-onset leukodystrophy TACH (Tremor-ataxia with central hypomyelination) and mapped its locus to chromosome 10q22.3-10q23.31[2].

Since the initial description of the disorder, we have recruited a new consanguineous French-Canadian family with TACH. A detailed chart review and neurological examination were performed by an experienced neurologist. This project was approved by the institutional Ethics Committee of the Centre de Recherche du CHUM (CRCHUM). Informed consent was obtained from all participants. 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).

The patient presented at the age of six years with school difficulties. A neuropsychological evaluation revealed that she had mild mental retardation. It is only at the age of approximately twelve years that she developed a spastic and ataxic gait. Her gait difficulties progressed over time and at the age of eighteen, she required the use of a walker. She also developed a kinetic and postural tremor of the upper extremities, as seen in the previously described TACH patients. Other remarkable clinical findings are dysarthria, abnormal saccades and pursuits and hypogonadotropic hypogonadism, without hypodontia.

Genome wide scan using the Illumina Hap610 Bead chip were conducted at the McGill University and Genome Quebec Innovation Centre (Montreal, Canada) on the affected individual, unaffected siblings and parents. The affected individual was found to be homozygote for a 12.99Mb region (rs1867567 to rs7912360, 1800 SNPs) on chromosome 10 and was sharing the haplotypes of the two consanguineous families previously published[2]. This interval was overlapping the previously reported interval, reducing it from 12.6Mb to 4.3Mb on chromosome 10q22.3-23.1 (maximum LOD score 6.2, Figure), from rs2116829 to rs10882244 (626 SNPs)[3].

We sequenced the coding sequence, the exon-intron boundaries, 5' and 3' UTR of the following nine genes in the 4.3Mb candidate interval and did not uncover any mutation: *PPIF* (peptidylprolyl isomerase F precursor), *ANXA11* (annexin A11), *SFTPD* (pulmonary surfactant-associated protein D), *EIF5AL1* (eukaryotic translation initiation factor 5A-like), *SFTPA1* (surfactant protein A1 precursor), *SFTPA2* (surfactant protein A2 precursor), *RPS24* (ribosomal protein S24 isoform c), *TSPAN14* (tetraspanin 14 isoform 1), *ZMIZ1* (retinoic acid induced 17). Amongst these genes, two are duplicated, *SFTPA1* and *SFTPA2*. It is then difficult to exclude them with certainty. 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 (www.genetics.med.ed.ac.uk/suspects/). Sequencing was performed with the same protocol as described previously[2].

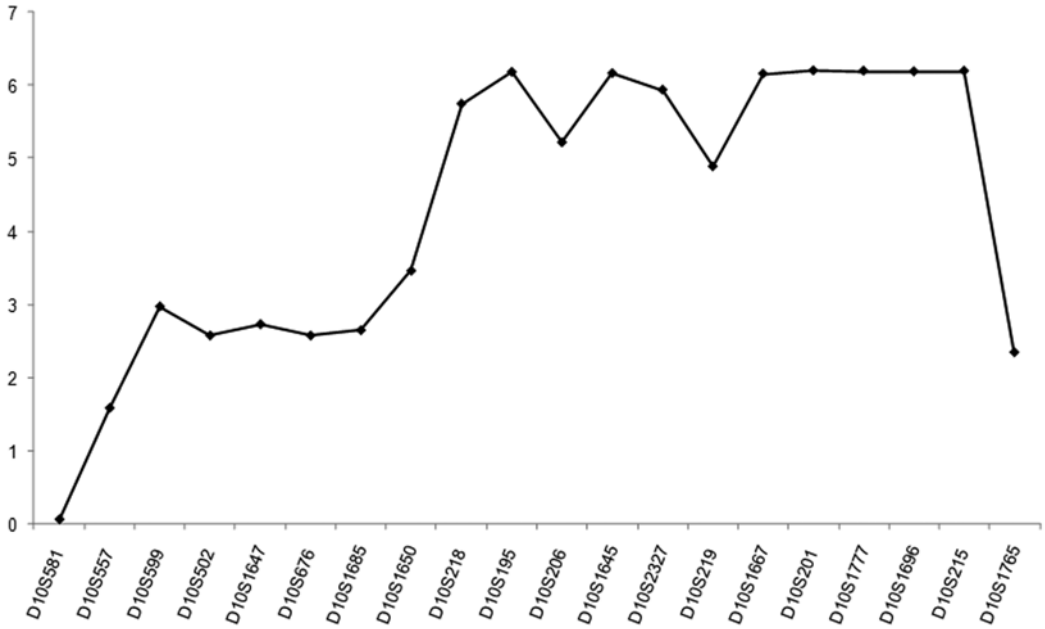

Figure: *Multipoint LOD score on chromosome 10 for three consanguineous families using Simwalk2 (v2.91). Maximum cummulative LOD score of 6.2 defining a 4.3Mb region.*

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We refined the candidate locus for TACH from 12.6 Mb to 4.3 Mb, sequenced nine candidate genes and did not uncover any mutation. Recently, the locus for the leukodystrophy with oligodontia was published on chromosome 10q22[4]. We hypothesized that TACH, leukodystrophy with oligodontia and possibly 4H syndrome (Hypomyelination, Hypodontia, Hypogonadotropic Hypogonadism)[5] are allelic conditions since they have overlapping clinical features. The identification of the TACH gene will determine if these three conditions are indeed allelic. It will also allow clinicians to offer definite diagnosis and genetic counseling to their families for one form of the growing number of leukodystrophies. Finally, it will contribute to our understanding of the mechanisms leading to inherited white matter diseases.

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