

Letters

RESEARCH LETTER

A New *ELOVL4* Mutation in a Case of Spinocerebellar Ataxia With Erythrokeratodermia

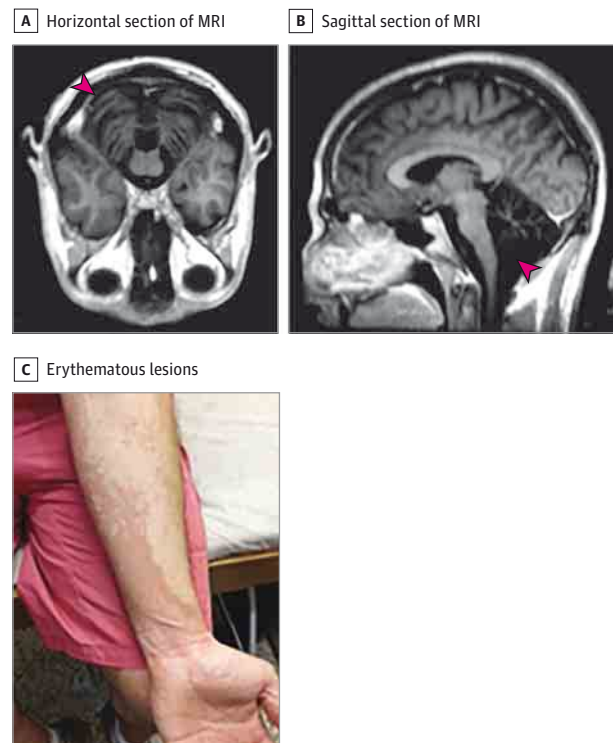
Spinocerebellar ataxia with erythrokeratodermia (SCA34; OMIM 133190) is an autosomal dominant complex form of ataxia. This condition was first described in 1972 with the report of a French-Canadian family with multiple affected individuals.¹ Four decades later, a segregating locus was identified through linkage analysis of 32 individuals from this family. Subsequent whole-exome sequencing of 3 individuals revealed a mutation in the elongation of very long-chain fatty acids-like 4 gene (*ELOVL4*) (NM_022726.3 c.504G>C); this mutation produced a defective protein (p.Leu168Phe).² We report here the identification of a different *ELOVL4* mutation in a single case who had signs consistent with SCA34. To our knowledge, our findings are the first to confirm *ELOVL4* as the cause of SCA34.

Report of a Case | A man in his 30s developed a progressive gait disorder in his mid-20s. Brain magnetic resonance imaging showed cerebellar and pontine atrophy (Figure 1, A and B). Neurological examination (H.A.G.T.) demonstrated dysarthria; diplopia; and horizontal gaze-evoked nystagmus, bilaterally, with mild bilateral ophthalmoplegia; mild dysmetria in the upper limbs; and gait ataxia, with great difficulty in the tandem gait. The patient had normal reflexes, normal position, and vibration sense, as well as normal pain and light touch sensation. His father had a mild gait disorder. The patient also had erythematous skin lesions on his forearms and legs during adolescence (Figure 1C). A dermatological evaluation (S.S.) suggested the diagnosis of erythrokeratodermia. The clinical diagnosis of Giroux-Barbeau syndrome was made.

Sanger sequencing was used to screen the proband for the presence of mutation in the *ELOVL4* gene. The analysis of all 6 exons, as well as the exon-intron boundaries, identified a heterozygote substitution (NM_022726.3 c.539A>C; Figure 2) that leads to a missense mutation (p.Gln180Pro). This variation was absent from dbSNP (<http://www.ncbi.nlm.nih.gov/SNP/>) and the Exome Variant Server (<http://evs.gs.washington.edu/EVS/>). It is predicted to be damaging by PolyPhen-2 (<http://genetics.bwh.harvard.edu/pph2/>) and Mutation Taster (<http://www.mutationtaster.org/>).

Discussion | The *ELOVL4* gene encodes a protein responsible for the elongation of very long-chain fatty acids. It contains 5 transmembrane domains, a histidine cluster dideoxy binding motif, and an endoplasmic reticulum retention signal.³ Interestingly, the mutation identified here (p.Gln180Pro) is found in the same transmembrane domain as the previously reported SCA34 mutation. Other diseases have been associated with

Figure 1. Images Supporting the Clinical Diagnosis of Spinocerebellar Ataxia With Erythrokeratodermia

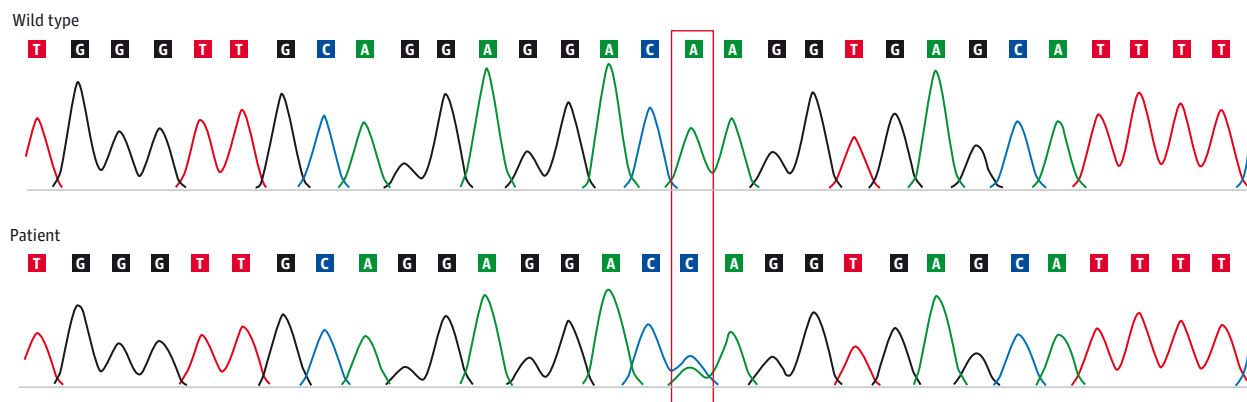


A, Horizontal section of the patient's brain magnetic resonance image (MRI) showing cerebellar atrophy (arrowhead). B, Sagittal section of the patient's brain MRI showing cerebellar and pontine atrophy (arrowhead). C, Erythematous skin lesions on the patient's arm.

ELOVL4 mutations; however, the mutations underlying these conditions affect different domains of the protein. For Stargardt-like macular dystrophy, the mutations are clustered in exon 6 and they disrupt the endoplasmic reticulum retention signal.⁴ In the complex syndrome of ichthyosis, spastic quadriplegia, and mental retardation, which might be considered to be a more severe form of SCA34, the homozygous mutations are in exon 5, which encodes the fourth transmembrane domain.⁵ Our report supports the notion that SCA34 causative mutations cluster in exon 4 of *ELOVL4* where they disrupt the third transmembrane domain. Moreover, the finding of an *ELOVL4* mutation in a patient with an SCA34 phenotype suggests that alterations in this gene lead to the same condition in separate populations.

To our knowledge, this is only the second report of *ELOVL4* mutations in SCA34, and it is the only gene thus far reported to lead to this phenotype. A member of the same gene family, *ELOVL5*, was reported to cause SCA38,⁶ adding

Figure 2. Chromatogram of the Mutation Identified



Chromatogram obtained from Sanger sequencing of exon 4 of the elongation of very long-chain fatty acids-like 4 gene and analyzed by Mutation Surveyor version 4.0 (SoftGenetics).

another lipid metabolism gene to the list of genes causing spinocerebellar ataxia.

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Author Contributions: Dr Rouleau had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Bourassa, Serafini, Teive, Dion.

Drafting of the manuscript: Bourassa, Serafini, Dion.

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Study supervision: Raskin, Teive, Dion, Rouleau.

Conflict of Interest Disclosures: Dr Rouleau holds a Canada Research Chair in Genetics of the Nervous System and the Wilder Penfield Chair in Neurosciences. No other disclosures were reported.

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OBSERVATION

Successful Antiviral Treatment of Giant Cell Arteritis and Takayasu Arteritis

A patient who satisfies American College of Rheumatology criteria for both giant-cell arteritis (GCA) and Takayasu arteritis had a dramatic favorable response to antiviral treatment. The virological and pathological findings followed by successful antiviral treatment support earlier notions that GCA and Takayasu arteritis may represent a spectrum of the same disease produced by varicella-zoster virus (VZV).

Report of a Case | A woman in her 70s developed severe right-sided temporal pain and jaw claudication. Two months later, she developed bilateral arm pain, which was worse on the left; chest pain on exertion; and shortness of breath. No arm pulses were detected and blood pressure was unobtainable by auscultation or Doppler. Angiography findings revealed bilateral subclavian artery stenosis and left axillary artery occlusion without intracranial vasculopathy. Her erythrocyte sedimentation rate was normal and C-reactive protein level was 1.6 mg/0.1 L (normal <1.0 mg/0.1 L; to convert to nanomoles per liter, multiply by 9.524). Results from a temporal artery (TA) biopsy were initially negative for GCA. Despite treatment with oral prednisone, 30 mg twice daily, she experienced progressive arm pain, intractable fatigue, anorexia, and weight loss.