CLINICAL/SCIENTIFIC NOTES OPEN ACCESS

Novel *ELOVL4* mutation associated with erythrokeratodermia and spinocerebellar ataxia (SCA 34)

Pierre R. Bourque, MD, Jodi Warman-Chardon, MD, Daniel A. Lelli, MD, Lauren LaBerge, MD, Carly Kirshen, MD, Scott H. Bradshaw, MD, Taila Hartley, MSc, and Kym M. Boycott, PhD, MD

Correspondence
Dr. Bourque
pbourque@toh.ca

Neurol Genet 2018;4:e263. doi:10.1212/NXG.0000000000000263

Erythrokeratodermia (EK) is a rare skin disorder, likely genetic and usually present from infancy.[1] There is patchy symmetrical involvement over the body surface, manifested in progressive figurate plaques of hyperkeratosis and more transient areas of erythema. There is significant overlap in the clinical and genetic features of the "variabilis" and "progressiva" forms of EK. Restricted cutaneous syndromes of EK have been described associated with mutations in the connexin (*GJB3, GJB4*, and *GJA1*) and loricrin (*LOR*) genes. The majority of patients with EK, however, have no pathogenic mutations in the *GJB* genes or *LOR*.

Three different mutations in the *ELOVL4* gene have so far been described in patients presenting with a combination of EK and spinocerebellar ataxia (SCA34).[2–4] We describe here a novel variant in *ELOVL4* associated with this syndrome. This case draws attention to the importance of assessing subtle chronic neurologic dysfunction in patients presenting with EK and, conversely, being aware of the occurrence of characteristic cutaneous lesions in this newly described syndrome of spinocerebellar ataxia.

Case description and genetic results

A 60-year-old woman was referred for assessment of visual blurring and diplopia. Her cutaneous disorder manifested around age 4 years, with widespread variable itchy areas of erythema and progressive localized skin thickening. She had no success with topical Tazorac and compounded creams. Oral acitretin (25 mg) was helpful but discontinued because of alopecia. Although her visual symptoms had only gradually appeared at age 50 years, she reported noticing ataxia of gait as far back as teenage years. Her parents who were deceased at age 73 years and age 84 years had reported no symptoms of rash or ataxia. Her 5 siblings, similarly, were asymptomatic from the dermatologic and neurologic standpoint. Two children were biologically unrelated (adopted).

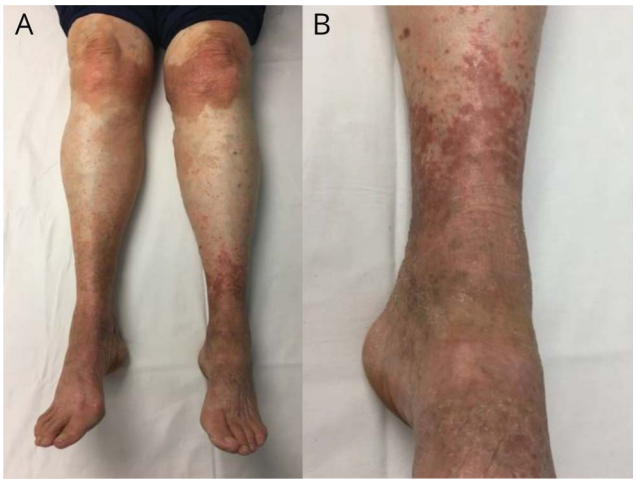
On examination, there were widespread demarcated brown erythematous keratotic plaques typical of EK over her wrists, hands, inner thighs, knees, and ankles (figure, A and B). Neuro-ophthalmic deficits included square wave jerks, saccadic pursuit, and alternating skew deviation with superimposed periodic alternating skew deviation in primary position (period 2.5 minutes). Myotatic reflexes were diffusely reduced (1+) and absent at the ankles. There was moderate rombergism and marked tandem gait ataxia, but no appendicular dysmetria. A skin biopsy showed irregular acanthosis, papillomatosis, and hyperkeratosis, in keeping with EK.

From the Department of Medicine (Neurology) (P.R.B., J.W-C., D.A.L.), University of Ottawa; Ottawa Hospital Research Institute (P.R.B., J.W-C.); Department of Medicine (Dermatology) (L.L., C.K.), University of Ottawa; Department of Anatomical Pathology (S.H.B.), University of Ottawa; and Department of Genetics (J.W-C., T.H., K.M.B.), Children's Hospital of Eastern Ontario, Ottawa, Canada.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

The Article Processing Charge was funded by the authors.

Figure Erythrokeratodermia (lower limbs)



Photographs of symmetrical brownish-red hyperkeratosis, most prominent over the knees, lower anterior legs and dorsal foot region. There were similar symmetrical lesions over the inner thigh and more subtle involvement of the dorsal forearm and wrist region.

MRI of the brain showed only subtle flattening of the ventral pons and mild global cerebellar atrophy. Nerve conduction studies and needle EMG studies were normal.

The clinical presentation suggested the possibility of SCA34. *ELOVL4* gene sequencing (Prevention Genetics, Marshfield, WI) identified a variant (c.698C>T; p.Thr233Met), which has not been reported in the literature or public databases. The amino acid substitution programs CADD (27.9), PolyPhen-2 (1.0), and MutationTaster (1.0) predict the variant to be damaging, and the Sorting Intolerant From Tolerant (SIFT) program predicts it to be tolerated (table). It was not possible to test parents, but 2 clinically unaffected siblings were tested and did not carry this variant. The patient was started on baclofen, starting at 5 mg tid and titrating up to 15 mg tid over 1 month. She reported significant improvement in the perception of oscillopsia and the duration and frequency of bouts of diplopia. She also elected to try application of beeswax cream (reported to contain 30-32 carbon very long chain fatty acids) on her legs for 2 months, which was of no benefit.

Discussion

This case broadens the genetic mutation profile of EK by reporting a patient with a fourth variant in the *ELOVL4* gene associated with SCA34 (table). The *ELOVL4* gene catalyzes the rate-limiting reaction in elongation of fatty acids with a chain length greater than C26. It is ubiquitously expressed, but particularly enriched in the retina. It is critical in the development of the outer layer of the epidermis, the stratum corneum.[5] Rare diseases associated with dysregulation of *ELOVL4* in addition to SCA34 include 2 autosomal recessive conditions: hereditary macular degeneration (Stargardt disease) and a syndrome of ichthyosis, spastic quadriplegia, and mental retardation.[6]

The clinical presentation of our patient is quite similar to what was reported in a large French Canadian family with 32 affected members.[2] In this large SCA34 family, cutaneous involvement began in infancy, with a preponderance of hyperkeratosis over erythema. Gait ataxia was noted to start

Table Clinical and MRI features of patients with *ELOVL4* mutations associated with clinical features of SCA34

	Present case	Ozaki et al.[4]	Bourassa et al.[3]	Cadieux-Dion et al.[2]
Mutation	*ELOVL4*; c.698C>T, p.Thr233Met; heterozygous	*ELOVL4*; c.736T>G, p.W246G; heterozygous	*ELOVL4*; c.539A>C, p.Gln180Pro; heterozygous	*ELOVL4*; c.504 G>C, p.L168F; heterozygous
Ethnicity	English Canadian	Japanese	South American	French Canadian
Number affected	1 clinically affected mutation carrier	9 clinically affected from 2 separated families	1 clinically affected mutation carrier	19 mutation carriers, 4 clinically unaffected
Age or mean age, onset of gait ataxia, y	15	34	Mid 20s	51
Type of ataxia	Gait (no dysarthria or limb dysmetria)	Gait, speech, and limb	Speech, gait > limbs	Gait (12/19), limb (9/19), and speech (6/19)
Progression of ataxia	Independent ambulation without aid at age 60 y	Slow, ambulatory aid after age 60 y	Only 10-y follow-up	Slow: use of cane after 10 y, use of walker by age 70 y
Oculomotor signs	Saccadic pursuit, square wave jerks, and periodic alternating skew deviation	Horizontal nystagmus (78%), supranuclear palsy (33%), and impaired smooth pursuit (56%)	Horizontal nystagmus and mild bilateral ophthalmoparesis	Horizontal nystagmus in 7/19 and slow ocular pursuit in 5/19
Myotatic reflexes	Hyporeflexia	Hyperreflexia and Babinski signs in 89%	Normal	Hyporeflexia in 7/19
Erythrokeratodermia	Infantile onset and persistent, though showing cyclical exacerbations.	None	EK of forearms and legs	EK of infantile onset but mostly resolving after age 25 y, noted in 14/19

Continued

Table Clinical and MRI features of patients with *ELOVL4* mutations associated with clinical features of SCA34 *(continued)*

	Present case	Ozaki et al.[4]	Bourassa et al.[3]	Cadieux-Dion et al.[2]
Brain MRI	Mild cerebellar and pontine basal atrophy	Pontine and cerebellar atrophy in 100%, hot cross bun sing in 67%	Moderate cerebellar and pontine atrophy	Cerebellar and pontine atrophy in 6/9 carriers tested
Support for pathogenicity	Two asymptomatic siblings did not carry the mutation. Variant not previously reported in public databases (gnomAD, EVS, and 1000Genomes). CADD (27.9), PolyPhen-2 (1.0), and MutationTaster (1.0) predict damaging. SIFT predicts tolerated.	Segregation with affected members of 2 different families. A third family has been reported in ClinVar (RCV000522609.1). Variant continues to be absent from public databases (gnomAD, EVS, and 1000Genomes). CADD (23.5), PolyPhen-2 (0.99), and MutationTaster (1) predict damaging. SIFT predicts tolerated.	Variant continues to be absent from public databases (gnomAD, EVS, and 1000Genomes). CADD (26.5), PolyPhen-2 (0.99), and MutationTaster (1) predict damaging. SIFT predicts tolerated. No segregation data.	Segregation with disease haplotype in 19 individuals. Variant continues to be absent from public databases (gnomAD, EVS, and 1000Genomes). CADD (24), PolyPhen-2 (0.99), and MutationTaster (0.87) predict damaging. SIFT predicts tolerated.
ACMG variant classification	VUS (PM2+PP3+PP4)	Likely pathogenic (PS1+PM2+PP1+PP3+PP4)	VUS (PM2+PP3+PP4)	VUS (PM2+PP1+PP3+PP4)

Abbreviations: ACMG = American College of Medical Genetics and Genomics; EK = erythrokeratodermia; EVS = Exome Variant Server database; SIFT = Sorting Intolerant From Tolerant program; VUS = Variant of Unknown Significance.

usually around age 50 years. Our patient may be unique in reporting prominent oculomotor symptoms. A periodic alternating skew deviation was significantly improved when treated with baclofen.

The possibility of SCA34 should be considered in patients with EK, and clinicians should be aware that cerebellar manifestations are relatively late and variable, whereas cutaneous involvement has an onset early in childhood. SCA34 should thus be considered in the differential diagnosis of genetic neurocutaneous disorders. Oculomotor manifestations should be specifically assessed because they may be improved with treatment.

Author contributions

P.R. Bourque: analysis and interpretation and production and revision of the manuscript. J. Warman Chardon: analysis and interpretation and critical revision of the manuscript. D.A. Lelli: acquisition and interpretation of neuro-ophthalmology data and critical revision of the manuscript. L. LaBerge: acquisition and revision of dermatology data and critical revision of the manuscript. C. Kirshen: acquisition and revision of clinical dermatology data and critical revision of the manuscript. S.H. Bradshaw: acquisition and interpretation of dermatopathology data and critical revision of the manuscript. T. Hartley: preparation of the table and assessment of genetic classification. K.M. Boycott: study supervision, critical revision of the manuscript, and overview of genetic data acquisition and interpretation.

Study funding

No targeted funding reported.

Disclosure

All authors have no financial disclosures relevant to this research and publication. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NG.

Received February 21, 2018. Accepted in final form May 7, 2018.

References

1. Ishida-Yamamoto A. Erythrokeratodermia variabilis et progressiva. J Dermatol 2016; 43:280–285.
2. Cadieux-Dion M, Turcotte-Gauthier M, Noreau A, et al. Expanding the clinical phenotype associated with ELOVL4 mutation: study of a large French-Canadian family with autosomal dominant spinocerebellar ataxia and erythrokeratodermia. JAMA Neurol 2014;71:470–475.
3. Bourassa C, Raskin S, Serafini S, Teive HA, Dion PA, Rouleau GA. A new ELOVL4 mutation in a case of spinocerebellar ataxia with erythrokeratodermia. JAMA Neurol 2015;72:942–943.
4. Ozaki K, Doi H, Misui J, et al. A novel mutation in *ELOVL4* leading to spinocerebellar ataxia (SCA) with the hot cross bun sign but lacking erythrokeratodermia: a broadened spectrum of SCA34. JAMA Neurol 2015;72:797–805.
5. Cameron DJ, Tong Z, Yang Z, et al. Essential role of ELOVL4 in very long chain fatty acid synthesis, skin permeability barrier function, and neonatal survival. Int J Biol Sci 2007;3:111–119.
6. Aldahmesh MA, Mohamed JY, Alkuraya HS, et al. Recessive mutations in ELOVL4 cause ichthyosis, intellectual disability, and spastic quadriplegia. Am J Hum Genet 2011;89:745–750.