Chorea-Acanthocytosis Genotype in the Original Critchley Kentucky Neuroacanthocytosis Kindred

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Objective: To determine the molecular nature of the neurological disease in the seminal family reported by Critchley et al in the 1960s, characterized by a hyperkinetic movement disorder and the appearance of acanthocytosis on peripheral blood smear. The eponym Levine-Critchley syndrome, subsequently termed neuroacanthocytosis, has been applied to symptomatically similar, but genetically distinct, disorders, resulting in clinical and diagnostic confusion.

Design: DNA analysis.

Setting: Molecular biology research laboratories.

Participants: First- and second-degree relatives of the original Critchley et al proband from Kentucky.

Main Outcome Measures: Mutations in the VPS13A gene.

Results: A mutation was identified in the VPS13A gene, responsible for autosomal recessive chorea-acanthocytosis. Haplotype reconstruction suggested that this mutation was homozygous in the proband.

Conclusion: These findings strongly support the diagnosis of chorea-acanthocytosis as the disorder described in the original report.

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Neuroacanthocytosis (NA) is an umbrella term for a genetically and phenotypically heterogeneous group of neurological conditions that occur together with spiny red blood cells known as acanthocytes. Some of the earliest cases of NA reported in the Western literature were given the eponym Levine-Critchley syndrome in recognition of the work of Irvine Levine, MD, and Edmund Critchley, DM(Oxon), FRCP. In the 1960s, these authors independently reported a neurological condition characterized by acanthocytes and normolipoproteinemia in patients from 3 different families from New England,1 Kentucky,2 and the United Kingdom.3

Advances in molecular medicine have led to the recognition of several different disorders covered by the term neuroacanthocytosis4,5 and have made contemporary use of this ambiguous term obsolete, apart from as a descriptor for a group of hyperkinetic disorders in which acanthocytosis may be seen. The main NA syndromes are defined by at least 4 genetically distinct conditions: autosomal recessive chorea-acanthocytosis (ChAc),6,7 X-linked McLeod syndrome,8 autosomal recessive pantothenate kinase–associated neurodegeneration,9 and autosomal dominant Huntington disease–like 2.10 Chorea-acanthocytosis and McLeod syndrome are considered the “core” NA syndromes, as acanthocytosis is a frequent finding in both disorders, while it is only occasionally seen in Huntington disease–like 210 and pantothenate kinase–associated neurodegeneration.9

From the literature, all of the Critchley et al cases2,3 appear to have a phenotype identical to that seen in patients in whom a molecular diagnosis of ChAc has been confirmed4,5,11 but the same does not apply to the New England family described by Levine,1 and no assumption can be made in this regard without genetic testing.

A nephew of the proband from the original Critchley et al Kentucky pedigree contacted one of us (R.H.W.) via the Internet, expressing an interest on behalf of the family in participating in any further research on the disorder affecting his uncle. Samples were obtained from several surviving family members allowing us to determine the molecular nature of the neurological disease in this seminal NA family.
To determine whether the original condition reported for this family was indeed ChAc, we screened the causative gene, VPS13A, for mutations.11 The study was approved by the relevant institutional review boards. Consent was obtained and DNA was isolated from blood (Nucleon BACC2 kit; Tepnel Life Sciences, Manchester, England) or saliva (Oragene OG-500; DNA Genotek, Kanata, Ontario, Canada) samples from the appropriate family members. For the initial mutation screening, all translated exons plus flanking regions were amplified by polymerase chain reaction and sequenced using standard protocols. For genotyping, 10 polymorphic microsatellite markers on chromosome 9 flanking the VPS13A gene and single-nucleotide polymorphism rs10869920 (c.9077-133, intron 67) were analyzed (eTable 1, http://www.archneurol.com) as well as for “proband 23”10 and her father. 

**METHODS**

Part A of the Figure shows the updated pedigree of the Kentucky family reported by Critchley et al.2 The proband’s only surviving sibling (I-8 in the Figure), now aged 78 years, has features consistent with Parkinson disease. No family members were affected outside the proband’s generation. If the underlying disease in this family is autosomal recessive ChAc, any direct descendant (II-6, II-29, II-30, II-31, and II-32) of an affected individual would be a heterozygous carrier of a VPS13A mutant allele. Blood samples were collected from family members II-29, II-30, II-31 (presumably heterozygous), II-7 (probably heterozygous), and I-8 (50% probability of being heterozygous). After DNA amplification and sequencing, a nonsense mutation in exon 56 of the VPS13A gene (c.7867C>T; p.R2623X) was found in family member II-7. We then checked for this mutation in the other 4 available samples and found this mutation in all individuals (Figure, B). This mutation has previously been described in a patient with ChAc (“proband 23”), reported as compound heterozygous.11

A second change was also detected in all 5 analyzed samples in the amplified flanking region of exon 68 (c.9077-262C>T, in intron 67). This change does not appear as a single-nucleotide polymorphism in any database and we could not detect it in 180 control chromosomes. However, its location in an intronic position far away from the splicing consensus sequences suggests that it probably does not have any pathogenic effect.

To have a clearer genetic picture for this family, additional (saliva) samples from other available potentially informative members were collected (Figure, A) to perform genotyping. These samples were examined for the 2 changes mentioned earlier. Blood samples were obtained from both parents of proband 23. This family trio was analyzed as described earlier and additionally for the 2 mutations previously reported (c.7867C>T and c.1208_1211del),13 which we found were from paternal
Identification of a disease-associated nonsense mutation in the VPS13A gene strongly supports the diagnosis of autosomal recessive ChAc in this family. This diagnosis is also entirely concordant with the clinical phenotype as initially reported and confirmed in the medical records from the evaluation of the proband at the University of Kentucky in the 1960s confirmed the presence of marked dystonia, hypokinesia, ataxia, and severe tongue biting. Basal ganglia atrophy was found on pneumoencephalogram, and acanthocytosis was found on peripheral blood smear.

COMMENT

VPS13A

Haplotype combinations 1-2, 1-3, and 2-3 detected/ deduced in the proband's siblings I-8, I-1, and I-7, and I-6 in the proband's half-sibling I-12, indicate the presence of only 3 different haplotypes (1, 2, and 3) in the proband's parents (0-1 and 0-2) and that haplotype 1 was present in the proband's father (0-2) (eTable 3 and eFigure). Therefore, the only possible haplotype combinations for 0-1/0-2 are (1) 1-2/1-3 or (2) 1-3/1-2, which imply that the proband (1-10) and his affected siblings (1-2, 1-4, 1-5, and 1-9) were homozygous for the c.7867C>T mutation (for haplotype 1, assuming no recombination). Strictly speaking, 2 more haplotype combinations could be possible: (3) 2-3/1-2 and (4) 2-3/1-3. However, they can be dismissed on the basis that a second unidentified mutation would then need to be associated with haplotype 3 (3) or 2 (4) and, therefore, individuals I-1 (3) or I-8 (4) would have been affected. Moreover, none of these 2 haplotypes were found in 3 direct descendants of the affected family member I-9.

To our knowledge, there are no reports of neurological disease in confirmed VPS13A heterozygotes; thus, we suspect that Parkinson disease in sibling I-8 is coincidental. The presence of acanthocytosis in confirmed or deduced heterozygotes I-1, I-6, and II-7 in the original report is intriguing. Heterozygotes have not been routinely examined using a standard protocol for the presence of hematological abnormalities, and indeed, the detection of acanthocytes is often problematic even in affected subjects; thus, the effect of a single mutation on erythrocyte membranes remains an unanswered question.

Genetic and phenotypic heterogeneity in the early cases of NA has resulted in clinical and diagnostic confusion, which has been resolved in part by the use of molecular methods. Molecular confirmation of the diagnosis in one of the original families supports the concept that the term Levine-Critchley syndrome described, at least in part, what is now recognized as ChAc. The disorder in Dr Levine’s family appears to have been inherited in an autosomal dominant manner, which would exclude the diagnosis of ChAc. However, this assumption must be qualified by noting that individuals termed affected possessed a variety of neurological signs with variable presence of acanthocytosis. Genetic studies of this family (reported as the “Goode family of New England”) would complete the molecular identification of the eponymous disorder.
taining medical records. We acknowledge the role of the late David Clark, MD, University of Kentucky, in originally recognizing the disorder and providing the impetus for reporting it.

REFERENCES