OBSERVATION

Mutation of *SCARB2* in a Patient With Progressive Myoclonus Epilepsy and Demyelinating Peripheral Neuropathy

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Objective: To report the detection of mutations in the *SCARB2* gene in a previously described patient with progressive myoclonus epilepsy (PME) and demyelinating peripheral neuropathy.

Design: Case report.

Setting: Epilepsy Genetics Research Laboratory and Epilepsy Service in a tertiary care center.

Patient: A 27-year old male patient with PME with preserved intellect and peripheral neuropathy.

Results: We have solved a previously reported case of PME, preserved intellect, and demyelinating peripheral neuropathy. The patient is a compound heterozygote for 2 mutations in the *SCARB2* gene, which has recently been found to be a cause of PME.

Conclusions: Demyelinating neuropathy is a clinical clue to the presence of *SCARB2* mutations in PME.

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MOLECULAR GENETICS HAS revolutionized the challenging problem of diagnosing specific forms of the progressive myoclonus epilepsies (PME). Broadly, PME can be divided up into syndromes in which dementia is prominent (eg, Lafora disease and the neuronal ceroid lipofuscinoses) vs conditions in which cognition is largely preserved (eg, Unverricht-Lundborg disease and myoclonus epilepsy and ragged red fibers).[1,2] A rarer cause in the latter category is the action myoclonus renal failure syndrome (AMRF),[3] which has recently been shown to be due to mutations in the lysosomal membrane protein *SCARB2*.[4,5]

A case report recently published in the *Archives* described a patient with PME, preserved intellect, and a nonprogressive generalized demyelinating neuropathy.[6] The case was extensively investigated and no cause was found, so a novel syndrome was proposed. A diagnosis of AMRF was considered but the absence of renal impairment precluded the diagnosis clinically and the molecular cause was not known at the time of publication. Subsequently, we described cases of PME without renal impairment due to *SCARB2* mutations, with subjects being followed up for as long as 15 years without the development of overt renal disease.[7] Cases of PME due to mutations in *SCARB2* show recessive inheritance, with patients being either homozygous for the same gene mutation or compound heterozygous for 2 different mutations. Features of the aforementioned case, particularly teenage onset, clinical course, and ancestry from French Canada, where AMRF was first described,[8] suggested that he may have *SCARB2* mutations and he was therefore restudied.

REPORT OF A CASE

The 27-year-old man had PME beginning at 16 years if age, as previously described.[6] He was severely disabled with action myoclonus, requiring a wheelchair at 20 years of age. Since then, his condition has continued to deteriorate, with worsening intractable myoclonus, dysarthria, and dysphagia, difficulties managing his secretions, and full dependence in his everyday activities. Cognitive function, however, has remained intact. Generalized seizures have steadily increased in frequency despite treatment with multiple antiepileptic and antimyoclonic medications, including high doses of piracetam as well as a trial of the low glycemic index diet. His peripheral neuropathy has remained stable by electrodiagnostic criteria, with reduced compound motor and sensory action potential amplitudes, marked prolongation of f-wave latencies, and slowing of conduction velocities to the 30 to 40–m/s range.

Analysis of the *SCARB2* gene by direct sequencing, as previously described[7] re-

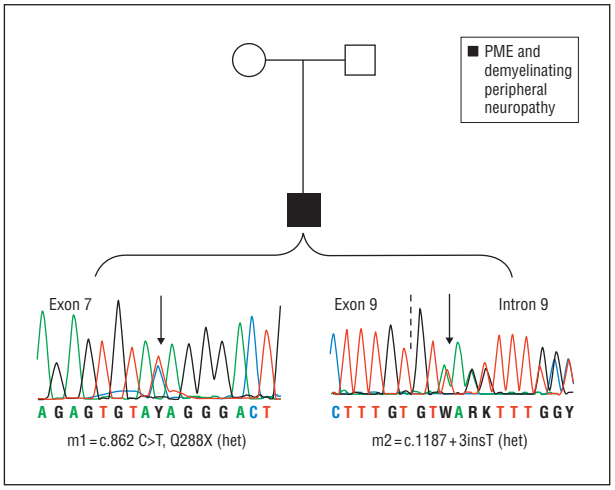

Figure. Sequencing traces showing the two heterozygous (het) *SCARB2* mutations, denoted m1 and m2. The base position of the mutation is indicated by an arrow. PME indicates progressive myoclonus epilepsy.

vealed that the patient is a compound heterozygote with 2 different mutations: a nonsense mutation, Q288X, and a splice site mutation, c11187 + 3insT (**Figure**). In view of this finding, we reevaluated his renal function. His serum creatinine level has been in the reference range and stable throughout his illness. A 24-hour urine collection contained a total protein level of 0.21 g/24 h (reference range, 0.04-0.23 g/24 h). Because a mouse model lacking *Scarb2* (*Limp2*) has deafness,[9,10] we performed an audiogram, which showed a small dip at 3-kHz frequencies in the right ear within normal limits; repeated brainstem auditory evoked responses were normal.

COMMENT

This case reemphasizes that *SCARB2* mutations can cause PME without renal failure. In the initial descriptions of ARMF, it was known that the disorder could begin with either renal or neurological involvement, often separated by a number of years.[3,8] Unfortunately, the neurological disorder is relentlessly progressive, with most patients dying of the complications of uncontrolled myoclonus in their third or fourth decade of life. We have followed up some patients for 15 years, from the onset of PME to death, and renal impairment had not developed.[7] This case appears to be a further example of either absent or severely delayed development of renal features, suggesting that there are differential pathophysiological mechanisms for the kidney and brain manifestations. Both heterozygous mutations in this case have been seen previously as homozygous mutations in cases of classic AMRF[4] (unpublished data), so the specific *SCARB2* mutations do not seem to determine the pattern of organ involvement.

A demyelinating hypertrophic peripheral neuropathy is a striking feature in the mouse with *Scarb2* (*Limp2*) deficiency.[9] Clinical peripheral neuropathy is not a feature of human patients with AMRF; however, electrophysiological evidence of neuropathy has occasionally been noted, but not extensively studied.[3,11] The data previously published on this case demonstrates the longitudinal stability of electrophysiological abnormalities, consistent with a demyelinating neuropathy.[6] Thus electrophysiological evidence of a demyelinating neuropathy can be a clinical clue to the presence of a *SCARB2* mutation, whose identification is very important in terms of prognosis and genetic counseling.

SCARB2 encodes a lysosomal membrane protein that is a member of the CD36 family of scavenger receptors.[12] The protein is widely expressed in human tissues and is thought to function in endosomal/lysosomal mediated protein degradation and recycling.[13,14] Patients presenting with progressive myoclonus epilepsy who also have evidence of a peripheral neuropathy should be investigated for mutations in *SCARB2*.

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