Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Expanding the Phenotype and Genetic Defects Associated with the *GOSR2* Gene

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Abstract: **Background:** The homozygous missense mutation c.430G>T (p.G144W) in the *GOSR2* gene has been repeatedly shown to cause progressive myoclonus epilepsy/ataxia. Thus far, no other disease associated *GOSR2* mutation has been reported.
Methods: From epilepsy, movement disorder and genetic clinics 43 patients suffering from progressive myoclonus epilepsy/ataxia were screened for defects in *GOSR2, SCARB2* and *CSTB*.
Results: A 61-year-old female patient suffering from progressive myoclonus epilepsy was found to be compound heterozygous for the known c.430G>T and a novel c.491_493delAGA (p.K164del) *GOSR2* mutation. This is so far the oldest *GOSR2* patient and her disease course seems overall milder.
Conclusions: This finding further highlights the *GOSR2* gene as a cause of progressive myoclonus epilepsy and expands the genotype for a potentially weaker disease allele.

Progressive myoclonus epilepsies (PMEs) or ataxias are a group of neurological syndromes characterized by myoclonus, ataxia, epilepsy, and often cognitive decline, which worsen over time.[1] PMEs can clinically be subdivided depending on whether cognitive decline is a prominent feature,[1] and mode of inheritance can be a further clue toward the causative gene. Four genes are known to be associated with autosomal-recessive PME with largely preserved intellect: *CSTB* (MIM 601145)[2]; *SCARB2* (MIM 602257)[3,4]; *PRICKLE1* (MIM 608500)[5]; and *GOSR2* (MIM 604027).[6] Recently, a heterozygous de novo mutation in *KCNC1* (MIM 176258) has been shown to cause the same phenotype.[7] The most prominent PME with largely preserved cognition is Unverricht-Lundborg disease (ULD; MIM 254800) resulting from mutations in the *CSTB* gene.[2] Mutations in Golgi SNAP receptor complex member 2 (*GOSR2*) have been shown to cause an ULD-like phenotype.[6,8,9] However, this disease usually onsets earlier than ULD, around age 2, with myoclonus and ataxia. Frequently, generalized tonic-clonic seizures then develop. Owing to rapid progression of action myoclonus and ataxia, patients are often left wheelchair bound already in their first or second decade. Thus far, all 17 reported patients with *GOSR2*-mediated PME have been shown to carry the same homozygous c.430G>T (p.G144W) mutation, the result of a founder effect.[6,8,9] No other *GOSR2* mutation has thus far been shown to be associated with PME.

Methods

We assembled a cohort of 43 single patients or family probands showing a clinical presentation suggestive for progressive myoclonus epilepsy/ataxia syndrome. Patients were negative for mutations in ATN1, mitochondrial A8344G, and A3243G. The study was approved by the local ethical board, and informed consent was given by all patients. All 12 scavenger receptor class B, member 2 (*SCARB2*) exons and *GOSR2* c.430G>T were screened by Sanger sequencing.

Results

We report here on the analysis of a series of 43 PME families/patients. Twelve patients were found to have CSTB mutations. Sequencing the remaining 31 probands found no *SCARB2*

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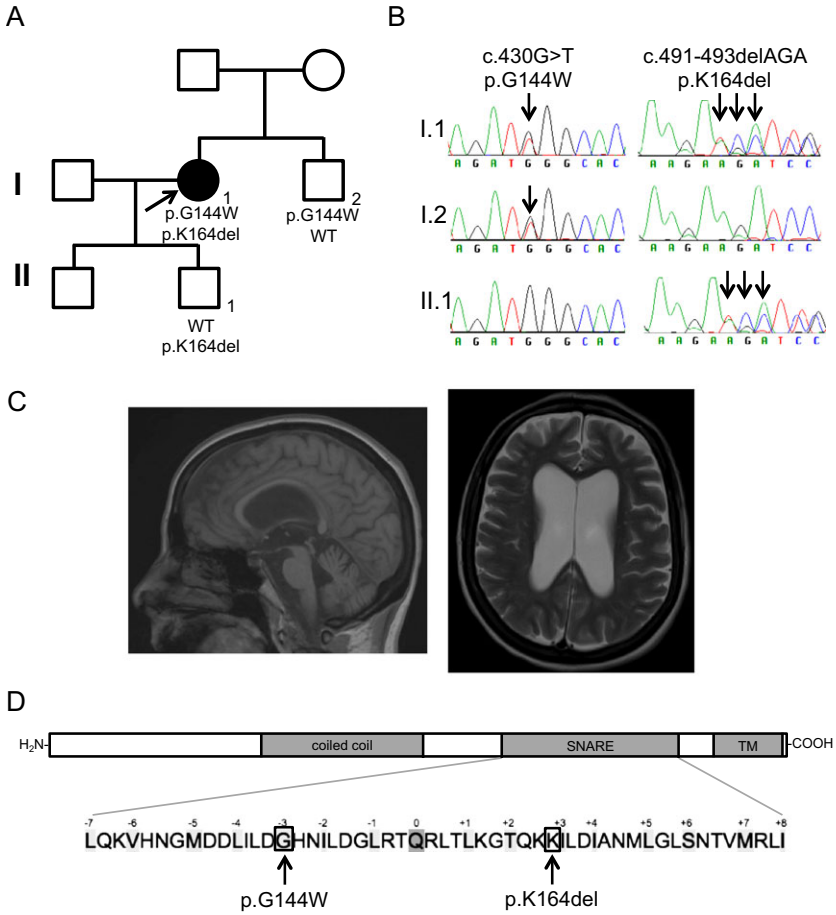

Figure 1 (**A**) Pedigree depicting the index case (arrow), her unaffected son and brother. (B) Chromatograms of the c.430G>T and c.491-493delAGA *GOSR2* mutations. (C) MRI of the *GOSR2* patient at age 59. (**D**) GOSR2 domain structure (Uniprot O14653-1) and detailed SNARE domain.[10]

mutations. However, 1 patient was found to be heterozygous for the *GOSR2* c.430G>T (p.G144W) mutation (Fig. 1A,B), and sequencing of the remaining *GOSR2* exons in this patient revealed a novel in-frame 3-base-pair deletion (c.491_493delAGA), which was not found in any of the other screened patients. This mutation causes the deletion of a lysine (p.K164del) in the functionally important, highly conserved soluble N-ethylmaleimide-sensitive factor adaptor protein receptor (SNARE) domain of the protein (Fig. 1D).[10] Genetic testing in the younger of 2 healthy sons showed that he bears the c.491_493delAGA (p.K164del) mutation in *GOSR2* in the heterozygous state (Fig. 1A,B), confirming that the patient carries the mutations on separate alleles. The patient's brother, who suffers from typical cervical dystonia, has a single heterozygous c.430G>T (p.G144W) *GOSR2* mutation (Fig. 1A,B). Interestingly, a maternal uncle was diagnosed with athetoid cerebral palsy, but he was not available for clinical or genetic assessment.

The proband of the *GOSR2* PME family is a 61-year-old British Caucasian female (see Video 1). She presented with mild gait ataxia at age 2 as well as transient episodes of motor deterioration triggered by infection and fever. Subsequently, she developed generalized action myoclonus and epilepsy at around age 14. In her twenties, she required a wheelchair to mobilize for longer distances and completely lost independent mobility in her thirties. Cognitive dysfunction was not a prominent feature, although mild cognitive decline was noted on repeated neuropsychometric testing. Brain imaging revealed generalized cerebral and cerebellar atrophy already in her thirties and was last repeated at age 59 (Fig. 1C). Electrophysiology confirmed a cortical origin of the myoclonus. Scoliosis and areflexia were also noted; however, electromyography and nerve conduction studies were unremarkable. Currently, the patient lives in a residential care facility and is dependent for all the basic activities of daily living. Seizure control has been maintained through a combination of valproate, clonazepam, primidone, and levetiracetam with a reduction in myoclonus.

Discussion

These findings expand the *GOSR2* mutation spectrum with only the second mutation type identified thus far. Interestingly, the brother who is also a mutation carrier (p.G144W/WT) has dystonia, suggesting that *GOSR2* carriers should be examined

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in the future to substantiate this finding. Clinical presentation of the proband shares some features with the previously reported *GOSR2* PME patients,[8,9] namely, early disease onset with ataxia as well as episodes of worsening associated with febrile illness, scoliosis, areflexia, and preserved cognition. However, the patient had a milder disease course than the other *GOSR2* patients reported thus far. At age 61, she is older than any other reported case, and she only became wheelchair bound in her thirties as opposed to the first/second decade of life as in most of the cases. The novel *GOSR2* deletion shortens the distance between the layer +2 and layer +3 amino acids in the GOSR2 SNARE domain (Fig. 1D).[10] This might result in SNARE domain misalignment during SNAREpin formation and, ultimately, reduced membrane fusion. Taken together, this report expands the *GOSR2* genotype and phenotype with a novel mutation and a milder disease course.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

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D.M.K.: 1B, 3B
C.B.: 1C, 3B
K.B.: 1A, 1C, 3B
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Supporting Information

A video accompanying this article is available in the supporting information here.

Video 1. Video of *GOSR2* patient at age 54 shows myoclonus at rest. Myoclonus is more pronounced in action and can be triggered by light touch. Finger-nose test is severely impaired as a result of myoclonus and ataxia.

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