Letter to the Editor

Novel SLC9A6 mutations in two families with Christianson syndrome

To the Editor:

Mutations in SLC9A6 are associated with Christianson syndrome, a syndromic form of X-linked intellectual disability characterized by severe intellectual disability, acquired microcephaly, seizures and ataxia (1, 2). Only nine mutations and two genomic aberrations involving SLC9A6 have been reported to date (1–7). Here, we report on two German families with novel SLC9A6 mutations.

The index patient (IV:3, Fig. 1a–c) of family 1 was born with normal birth measurements. He suffered from feeding difficulties in the first weeks of life and had seizures starting from 10 months. At the age of 18 months, he had microcephaly [OFC, occipitofrontal circumference 44 cm (<3rd centile), height 82 cm (25th centile), weight 10 kg (10th centile)] and could neither walk nor talk. His sister (IV:1) had slightly delayed language acquisition and a head circumference in the range of the 3rd–10th centiles. Two maternal uncles (III:3 and III:4) suffered from severe intellectual disability, secondary microcephaly, epilepsy and scoliosis (Fig. 1d,e). X-inactivation analysis in the mother (III:2) revealed a random distribution of both alleles (54:46). The grandmother of the index patient (II:2) was healthy until the age of 55 years when she developed neurological symptoms including muscular rigidity, slowness of movements and depression. Brain magnetic resonance imaging revealed no abnormalities apart from slight general brain atrophy, and a tentative diagnosis of Parkinson’s disease was made. Her mother (I:2) was said to have parkinsonism in her seventies and died at the age of 82 years. Molecular genetic analysis of SLC9A6 (transcript ENST00000370698) revealed an insertion of one nucleotide (T) in exon 12 of SLC9A6: c.1464_1465insT (p.Thr489TyrfsX23) in the

Fig. 1. a–e: Pedigree of family 1. Family members that have been tested for the SLC9A6 mutation are marked with a bar. A plus sign marks the female family members with late-onset neurological problems (a). The index patient (IV:3) at age 18 months (b, c). Note low-set ears. Patient III:3 (d) and III:4 (e) at the age of 39 and 35 years, respectively. Note long facies in both patients. f–h: The index patient of family 2 at age 2 years (f) and 7 years (g, h). Note low-set ears, strabismus, insecure posture and absence of major dysmorphic signs.
three male patients (IV:3, III:3 and III:4) and the mother (III:2) of family 1. The siblings of the index patient and the grandmother (II:2) were not tested.

The index patient of family 2 (Fig. 1f–h) had seizures starting at the age of 16 months and strabismus. Psychomotor development was severely retarded. At the age of 7 years, he had microcephaly [OFC 46 cm (<3rd centile)]. There were no other affected family members. Specifically, the mother of this patient had neither clinical abnormalities nor skewed X-inactivation (58:42). A mutation of the first intronic nucleotide at the boundary of exon 4 to intron 4 (c.584+1G>T) of SLC9A6 was detected in the index patient and his mother.

The clinical features of the male patients reported here are in accordance with previous reports [for a review, see (2)]. Female carriers of SLC9A6 mutations have been reported to have either no clinical problems or mild cognitive deficits (1, 2). The grandmother in family 1 (II:2; Fig. 1a), who was an obligate carrier of the SLC9A6 mutation, had developed neurological problems in her fifties which can be classified as parkinsonism, and signs of parkinsonism were also present in her mother. In view of the high incidence of Parkinson’s disease in the general population, the association with an SLC9A6 mutation might be a coincidental finding. On the other hand, neuronal and glial deposition of microtubule-binding protein tau was shown in cortical and sub-cortical regions of the brains of two adult male patients with SLC9A6 mutations (3). Tau deposition is the hallmark of a group of neurodegenerative disorders such as Alzheimer’s disease, Pick’s disease and frontotemporal dementia which are caused by MAPT mutations (OMIM 157140). These observations may suggest a predisposition to tau-associated late-onset neurodegenerative disorders in female carriers of SLC9A6 mutations.

In conclusion, the two families reported here broaden the spectrum of SLC9A6 mutations. They provide further evidence for the clinical uniformity of male patients with Christianson syndrome and indicate a link to late-onset neurodegenerative disorders.

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References


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