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## Familial West syndrome and dystonia caused by an *Aristaless* related homeobox gene mutation

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Boys with unexplained West syndrome should be examined for a mutation in the *Aristaless* related homeobox gene, especially, when the family history is positive for mental retardation and epilepsy.

X-linked West syndrome is very rare. We report on two brothers with West syndrome and dystonia with polyalanine expansion of the *Aristaless* related homeobox gene (*ARX*).

The index patient (Fig. 1a; III-2) was the second child of non-consanguineous parents, born in 2001 at term, after an uneventful pregnancy and delivery (birth weight 3659 g, 75th percentile; length 51 cm, 75th percentile; head circumference 35 cm, 50th percentile). At the age of 3 months he developed infantile spasms and a hypsarrhythmic EEG pattern. He promptly responded to vigabatrin therapy. At 5 months a generalised dystonia, i.e. increased muscle tone with dystonic posturing of limbs, was evident. At the age of 3 years, he is able to walk a few steps with help and grasping objects is very difficult. He has no expressive speech.

The elder brother of the index patient (Fig. 1a; III-1) was born in 1996 by caesarean section because of neonatal macrosomia (birth weight 4200 g, 90th percentile; length 53 cm, 90th percentile; head circumference 38 cm, >90th percentile). At the age of 3 months he showed dystonic movements and marked truncal hypotonia. One month later he developed infantile spasms and a

hypsarrhythmic EEG pattern. He did not respond to vigabatrin, but to ACTH. At the age of 8 years he is wheel-chair bound, not talking, grasping objects is not possible.

In both children metabolic tests and neuroimaging (MRI) were normal. Actually, both brothers suffer from a severe dystonia, mental impairment and rare generalised tonic-clonic seizures (the older brother), treated with valproic acid.

The family history was remarkable. In the maternal uncle (Fig. 1a; II-3, now 37 years old), spastic tetraplegia, mental retardation and epilepsy have been present since early infancy. In retrospect, the epilepsy syndrome could not be classified. MRI was not performed in this uncle, the mother or the grandmother.

From the pedigree and the clinical findings we suspected a mutation in the *ARX* gene. Following informed consent, a sequence analysis of the coding region and flanking intronic sequences of the *ARX* gene was performed. The male proband (index patient; Fig. 1a; III-2) as well as his brother and uncle were found to be hemizygous for a 21 bp GCG repeat expansion in exon 2 of the *ARX* gene c.333\_334ins(GCG)<sub>7</sub>, which expands the first of four alanine tracts from normally 16 to 23 alanine residues (Fig. 1b,c). Both the mother (Fig. 11; II-2) and the maternal grandmother (Fig. 1a; I-2) were identified as heterozygous mutation carriers using an optimised fluorescence-based PCR assay.

Mutations in the *ARX* gene have been found in a broad spectrum of disorders including X-linked infantile spasms (ISSX)/West syndrome, mental retardation [2], ataxia and dystonia (Partington syndrome), syndromic and non-syndromic forms of mental retardation, myoclonic epilepsy and X-linked lissencephaly with abnormal genitalia (XLAG) [5, 6, 8]. The mutation found in our Swiss family, which is not related to previously reported families, has been described before in boys with infantile spasms and normal MRI, severe mental and motor retardation [7]. In addition to Partington syndrome, dystonia was described in a few unpublished Australian and Norwegian cases [6], but

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