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Case report

Expansion of the ARX spectrum

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Abstract

We present four patients with ARX mutations and widely variant clinical presentations. Case 1, a female with a known ARX mutation has refractory infantile spasms and severe mental retardation. Case 2, a male presented with a neurodegenerative disorder and has a known ARX mutation likely de novo as mother is not a carrier. Cases 3 and 4, two siblings with a novel variant in ARX, which is not clearly pathogenic, have developmental delay. One of the siblings had a diagnosis of autistic spectrum disorder, failure to thrive with severe feeding difficulties, intracranial hemorrhage, and seizures. There are very few affected females with ARX related infantile spasms. These cases expand the known phenotype of this emerging condition.

Keywords: Mental retardation; Seizure disorder; X-linked mental retardation; De novo mutation; Seizures

1. Introduction

ARX, also called Aristaless-related homeobox gene, is a developmental gene located at Xp22 associated with infantile spasms and a spectrum of developmental issues including: mental retardation, temperature instability in the neonatal period, poor weight gain, ambiguous genitalia, agenesis of the corpus callosum, dystonic hand movements, dysarthria, awkward gait [1], and autism [2]. Mutations in ARX have been associated with both syndromic and non-syndromic forms of X-linked mental retardation (XLMR). ARX associated syndromic forms of XLMR include Partington syndrome, X-linked infantile spasms syndrome (ISSX), X-linked lissencephaly with abnormal genitalia (XLAG), X-linked myoclonic epilepsy with spasticity and intellectual disability (XMESID) [3], and West syndrome [1]. There is a diverse clinical spectrum associated with ARX mutations which ranges from severe XLAG, which may result in death within the first month of life, to patients with mild to moderate mental retardation (Table 1) [1,2]. ARX is also emerging as an important gene in non-syndromic XLMR [3].

The ARX gene is ~12.5 kb with five coding exons; it is an important transcription factor in the forebrain, pancreas, and testes [4]. Currently, there are at least 59 known disease-causing mutations described in this gene [4]. Known mutations include duplications, deletions, splice site mutations, missense mutations, and nonsense mutations [4]. Currently, the most prevalent ARX mutation is a 24 bp duplication (428–451 dup) in exon 2 [4]. Mutations in ARX are an important area of study, which may help us to better understand the etiology, inheritance, and clinical manifestations of XLMR.

2. Case 1

The patient was the product of a twin pregnancy conceived through the use of in vitro fertilization with a donor egg and father's sperm. In utero, she reportedly had less fetal movement than her co-twin. Birth weight was 1760 g compared to her co-twin's birth weight of 2554 g. Developmental dif-

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Table 1
Established clinical spectrum of ARX

	Phenotype	Genotype
Hydranencephaly with abnormal/ambiguous genitalia	• Most severe phenotype • Seizures in the neonatal period, developmental delay, failure to thrive, small penis, death in infancy • Lissencephaly, agenesis of corpus callosum • Females may be affected	Premature termination in the first four exons of ARX gene
X-linked lissencephaly with ambiguous genitalia (X-LAG)	• Seizures in the neonatal period, developmental delay, failure to thrive, small penis, death in infancy • Lissencephaly, agenesis of corpus callosum • Females may be affected	Premature termination in the first four exons of ARX gene
Proud syndrome (agenesis of the corpus collosum with abnormal genitalia)	• Myoclonic seizures in first year, mental retardation, nystagmus, progressive spastic quadriplegia, genito-urinary abnormalities • Dysmorphic features including coarse facial features, tapering fingers and overlapping toes, scoliosis • Agenesis of corpus callosum	Missense mutations
West syndrome	• Infantile spasms, hypsarrthymia • Mental retardation • Hypoplasia of corpus callosum and or cerebellar atrophy	Insertions in ARX gene
X-linked myoclonic epilepsy with generalized spasticity and developmental delay	• Myoclonic epilepsy, severe developmental delay, and spasticity • Mildly affected females have been reported	Missense mutations
Partington syndrome	• Movement disturbance including abnormal gait, dysarthria, and dystonia • No females reported	dup (24 bp)
Non-syndromic X-linked mental retardation	• Mental retardation with no congenital malformations or metabolic conditions	dup (24 bp) Missense mutations

Adapted from [1,2].

ferences between the patient and her co-twin were present during the first several months of life. Patient 1 made less eye contact and was less active than her sister. Seizures were initially observed at 4 months of age with subtle jerks, but then developed into head jolts, body flinches, and vocalizations and were subsequently characterized as infantile spasms with atonic, myoclonic seizures in the setting of epileptic encephalopathy. Seizure control was difficult to achieve and involved multiple anti-convulsants including: Vigabatrin, Klonopin, Topamax, and Gabitril. Finally, she responded to a 3-month trial of ACTH at high doses. After the ACTH she fed poorly and had gastroenteritis with reflux. Past surgical history has included a corpus colectomy which was done for intractable seizures and a G-tube placement.

Developmental milestones were delayed. She learned to sit independently and crawl at 15 months. At $2\frac{1}{2}$ years, she had poor visual tracking, could verbalize only three single words, and had taken up to six steps.

She had three MRIs of the brain that noted mild cortical volume loss attributed to ACTH. At age $2\frac{1}{2}$ years, physical examination yielded a head circumference between the 10th% and 25th%, height was at the 5th%, and weight was at the 65th%. She had brief visual tracking, significant drooling, and mild hypotonia. Additionally, she had hydronephrosis, torticollis, and plagiocephaly. Small bilateral epicanthal folds were noted as were mildly low set ears with slightly over folded superior helices.

3. Case 2

The patient was the first of three siblings. He was the product of an uncomplicated pregnancy and delivery at term. At the age of $4\frac{1}{2}$ months he was diagnosed with infantile spasms and was treated with ACTH without response. A vagal nerve stimulator was implanted at 1 year of age. By the time he reached 7 years of age, his seizure activity continued at approximately 20–50 seizures/day lasting approximately 4–20 min each with stiffening and had a history of head drops. He had an abnormal PET scan indicating sight asymmetry in cerebral metabolism and video electroencephalogram monitoring revealed continuous seizure activity. Medications have included Dilantin, Lamictal, Tegretol, Gabitril, ACTH, and Keppra. Seizures persisted and the patient underwent a complete corpus colostomy for seizure control. His early motor and cognitive milestones were age appropriate until approx-