Brain cysts associated with mutation in the Aristaless related homeobox gene, ARX

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The novel Aristaless related homeobox gene, ARX, is widely expressed in the brain and is thought to play a key role in the regulation of brain development. Neurological phenotypes caused by ARX mutations have recently started to unfold. We describe a 72 year old man with X-linked mental retardation due to a 24 bp duplication mutation in exon 2 of the ARX gene. Cerebral MRI showed bilateral cystic-like cavities in both the cerebral and cerebellar hemispheres. No retraction or expansion in neighbouring parenchyma was observed, there was no history of acute neurological impairment, and no risk factors for cerebrovascular disease were found. The lesions appeared to be congenital and represented benign developmental cysts, possibly caused by the ARX mutation.

Congenital brain anomalies are not infrequently observed among mentally retarded individuals. In one population based study, structural brain anomalies were detected on neuroimaging in approximately 13% of individuals with prenatal aetiology behind mental retardation. If the aetiology is genetic, it is likely that the brain anomalies are associated with the same underlying genetic mechanisms. We describe a man who was an affected member of a family with X-linked mental retardation. Linkage analysis mapped the disease gene to the distal part of the short arm on chromosome X. The disease gene was subsequently identified to be the Aristaless related homeobox gene, ARX, localised in Xp22.1. The ARX gene belongs to the paired class of homeobox genes. These genes are transcription factors important in the regulation of brain development. Neurological features observed in the family in addition to mental retardation included infantile spasms, epilepsy, spasticity, and cerebellar ataxia. All affected individuals were investigated with neuroimaging studies. Bilateral cerebral and cerebellar cavities resembling benign congenital cysts were demonstrated in one patient.

CASE REPORT
The patient was a 72 year old man (fig 1) who lives in a home for the mentally handicapped. Little is known about his developmental milestones, although he has always been retarded and did not walk independently before the age of 5 years. He has only been hospitalised due to cholecystitis and pancreatitis. There have been no episodes of acute neurological impairment or seizures. Due to behavioural abnormalities, he was treated with pimozide 15 mg daily. Chorea-like movements in his arms and neck were subsequently recorded. The medication was discontinued without any effect on the involuntary movements.

On examination he had a broad based spastic ataxic gait with symmetric and generalised hyperreflexia, without planter inversion. Skilled movements of the hands were impaired. Dystonia involving both hands and facial muscles was noted. Cognitive functioning was in the range for the mildly retarded (IQ 50–70). Blood pressure, pulse, total cholesterol, blood glucose, Doppler ultrasound examination of the precrerebral arteries, and an electroencephalogram were normal. Molecular genetic studies of the ARX gene demonstrated a 428–451dup (24 bp) mutation in exon 2. The pathogenetic mechanism of this duplication, which results in addition of 8 extra alanine residues to the ARX protein, is currently not understood.

MRI examination showed fluid filled cavities in both cerebral (fig 2A) and cerebellar hemispheres (fig 2B). The
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have been associated with malformations in the central nervous system, including the ocular region. Unilateral microphthalmia and structural brain asymmetry occurred in a boy with infantile spasms who had a deletion mutation of exon 5 of the ARX gene. The frequency of congenital cysts associated with mutations may not be high, although several affected individuals have not yet been studied with MRI. Interestingly, a large posterior fossa cyst was reported in one other case with an ARX mutation, a missense mutation of exon 2 associated with myoclonic epilepsy.

In conclusion, it was most likely that the cystic cavities were related to the mutation in the ARX homeobox gene. The spectrum of phenotypes caused by mutations in this gene will probably expand as more cases become diagnosed.

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