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# Short case report: Xq23 deletion involving *PAK3* as a novel cause of developmental delay in a 6-year-old boy

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## List of key features

Heterozygous PAK3 deletion
Developmental delay
Dysmorphic features
Poor, inarticulate speech

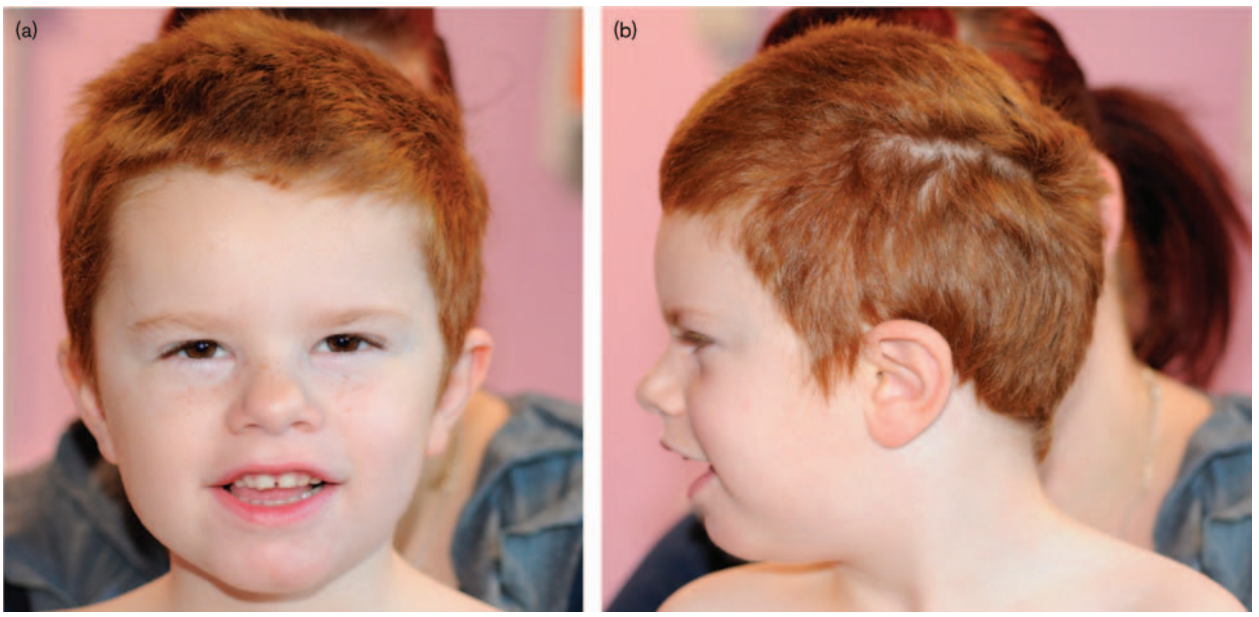
## Summary

The proband is a 6-year-old boy referred to the Clinical Genetics Service with learning difficulties, autistic spectrum disorder and intellectual disability with no significant family history. He was the third child of healthy, nonconsanguineous, White European parents. There are two healthy siblings who are fit and well. He was born following a normal pregnancy at term with a birth weight of 3.486 kg (50th centile) and there were no concerns immediately after birth. He was noted to be delayed with his development; he sat up at 14 months of age, walked at 20 months of age and was delayed with his speech. He currently attends a mainstream school, but receives full-time support and has been diagnosed with myopia and astigmatism. On examination, he was noted to have bilateral low-set ears, a bulbous tip to the nose and deep-set eyes with accessory nipples (Fig. 1). His growth parameters on presentation at 6 years of age were as follows: height 123.5 cm (91st centile) and weight 25 kg (91st centile), with a head circumference of 52 cm (25th centile).

## Investigations

Array comparative genomic hybridization (aCGH) was performed as part of ongoing investigations to elucidate the cause for the proband's learning difficulties. aCGH was performed on genomic DNA extracted from peripheral blood lymphocytes from the proband and mother.

**Fig. 1**




AQ1 (a, b) The proband, aged 6 years, showing facial dysmorphism with bilateral low-set ears, a bulbous tip to the nose and deep-set eyes.



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DNA was applied to an BlueGnome 60-mer oligoarray, printed in the 8×60K International Standard Cytogenomic Array Consortium configuration, according to the manufacturer's instructions, with pooled DNA being used as a reference (Promega Corporation, Madison, Wisconsin, USA). Slides were scanned using a Genepix Personal 4100A scanner (Axon Instruments) and analysed using BlueGnome BlueFuse-Multi (version 3.0) analysis software (BlueGnome, an Illumina Company, Cambridge, UK).

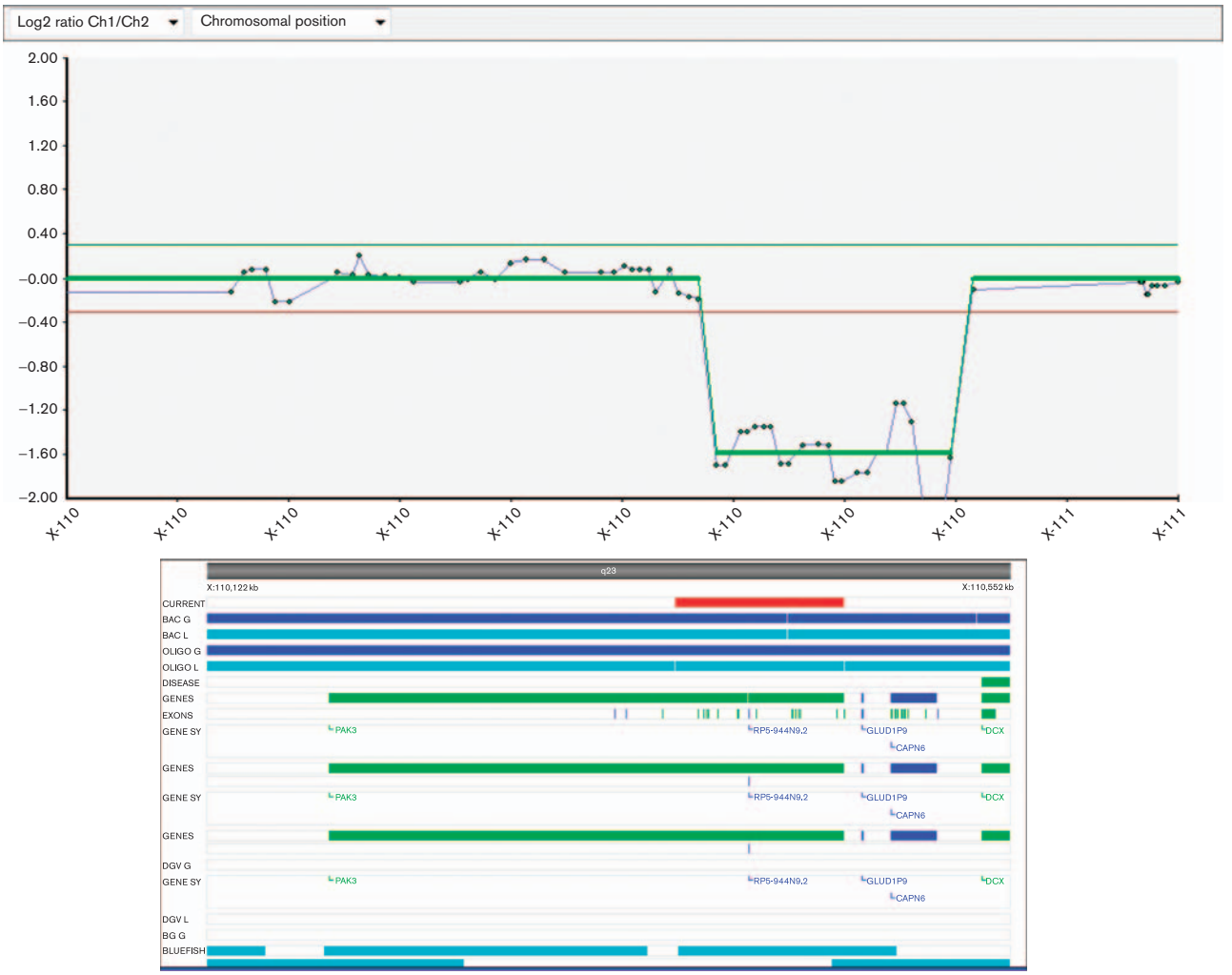
Results from 60K aCGH showed a 90 kbp deletion of Xq23 involving basepairs 110 373 400–110 464 093 (genome assembly GRCh37). Analysis of the deletion found that the region encompassed part of the *PAK3* gene (at least exons 4–15 NM_001128166.1) (Fig. 2). The mother's arrayCGH showed normal chromosome analysis with no evidence of deletion at Xq23, confirming the deletion to be *de novo* in origin. This patient had been investigated previously for Fragile-X syndrome (negative).

## Discussion

Small deletions of the X chromosome provide us with novel insights into the genetic basis of X-linked intellectual disability and correlation between the clinical phenotype and genotype. We report a child with a novel ~~de-novo~~ Xq23 deletion involving the *PAK3* gene, referred for clinical dysmorphism and developmental delay.

The PAK3 protein functions in regulating the actin cytoskeleton of cells and is also involved in neuronal stimulation and outgrowth in the foetal and adult brain (Ma *et al.*, 2012). Nonsense, missense and splice site mutations within the *PAK3* gene have all been previously associated with nonsyndromic X-linked mental retardation (Donnelly *et al.*, 1996; des Portes *et al.*, 1997; Allen *et al.*, 1998; Bienvenu *et al.*, 2000; Gedeon *et al.*, 2003;

**Fig. 2**




ArrayCGH trace indicating the de-novo Xq23 deletion in the proband.

**Table 1** **Comparison of phenotypes and genotypes of previously reported PAK3 mutations**

| | References | | | | | | |
|---|---|---|---|---|---|---|---|
| | Donnelly *et al.* (1996) and Allen *et al.*, (1998) | Des Portes *et al.* (1997) and Bienvenu *et al.*, (2000) | Gedeon *et al.* (2003) | Pieppo *et al.* (2007) | Rejeb *et al.* (2008) | Magini *et al.* (2014) | This study |
| PAK3 mutation | Missense c.199C > T p.R67C | Nonsense c.1255C > T p.R419X | Missense c.1094C > A p.A365E | Missense c.1337G > C p.W446S | Splice site c.276 + 4A > G | Missense c.1167G > T p.Lys389Asn | Heterozygous deletion of part of PAK3 |
| Study participants | 4 | 6 | 13 | 5 | 1 | 1 | 1 |
| Mental retardation | Mild | Moderate (5) Severe (1) | Borderline-mild | Mild (2) | Mild | – | Mild |
| Stature | Normal | Normal | Normal | Normal | Normal | Normal | Normal |
| Head size | Small | – | – | Small (4) | Small | Small | Relatively small |
| Facial dysmorphia | Long ears | Not specified | Long ears (7) High palate (1) Prominent nose (1) | Long ears (5) High bridged nose (5) Thin upper lip (4) Deep-set eyes (2) | Large ears Short nose with upturned tip Thick upper lip High vault palate | Long ears High palate Depressed nasal bridge, broad nasal tip | Bilateral low-set ears with fleshy ear lobes, a prominent nose and deep-set eyes |
| Language developmental delay | – | Poor, inarticulate speech (4) | Inarticulate speech (1) | Poor, inarticulate speech (4) | No speech until 6 years, poorly articulated speech | No speech | Poor inarticulate speech |

Pieppo *et al.*, 2007; Rejeb *et al.*, 2008; Magini *et al.*, 2014). Analysis of these mutations suggested that they lead to the inactivation of PAK3 protein functionality, either through loss of catalytic enzyme activity or through nonsense mutations resulting in premature termination of protein product.

To date, this is the first case in which a large deletion within *PAK3* has led to an intellectual disability phenotype. Interestingly, where the clinical phenotypes of the single nucleotide mutation families were available, comparison between them and the phenotype discussed shows a number of similarities, with facial dysmorphism, speech delay and learning/behavioural abnormalities all being present (Table 1). The phenotype of the patient reported here with the *PAK3* deletion is very similar to that of patients reported with mutations in *PAK3* with normal stature, a relatively small head or microcephaly, poor/absent speech and mild–moderate developmental delay, suggesting a possible role of haploinsufficiency causing the phenotype associated with mutations in *PAK3*.

Analysis of haploinsufficiency information for *PAK3* yields a haploinsufficiency score of 5.06% (Huang *et al.*, 2010). This finding suggests that inheritance of one normal *PAK3* allele is insufficient to maintain normal protein function within the cell. Inheritance of a single normal allele can be through deletion of *PAK3* or functional inactivation of the protein because of single nucleotide mutations as reported previously.

Given the findings here, we suggest that the developmental delay in this patient is a direct result of the deletion within *PAK3* and believe that this is the first case to report an Xq23 deletion encompassing part of *PAK3* associated with mental retardation. This finding provides further evidence for the Xq23 loci as X-linked mental retardation loci and that *PAK3* may play an important role in normal development.

## Acknowledgements

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### Conflicts of interest

There are no conflicts of interest.

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