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Clinical and molecular characterisation of the first familial report of 1p32 microdeletion

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ABSTRACT

Objectives: Structural rearrangements of chromosome band 1p31p32 are rare, and their phenotypic consequences remain poorly delineated. Up to 12 patients with learning difficulties, developmental delay, multiple congenital anomalies and microdeletion of the chromosome band 1p31p32 have been described. Inheritance of this deletion has not been previously reported. We describe the inheritance of 1p32 deletion and discuss the relevance of this deletion to the described phenotype. The differences in clinical and molecular characteristics between the proband and others published reports is reviewed. **Methods:** Patients were evaluated in OI-Genetics clinic with appropriate history, examination and investigation. Existing literature on interstitial deletions of 1p was reviewed. **Result:** Here we report on a three generation family, where the index patient was an adult female with learning difficulty, dysmorphic features, microcephaly, ambiguous genitalia, congenital hip dislocation and brachydactyly in whom a maternally inherited 1.45Mb interstitial deletion was detected at 1p32.3. Her mother and maternal grandmother both have learning difficulties and dysmorphic features. There are 14 OMIM genes in the deleted region including *LRP8* and *DMRTB1*. *NFIA* gene is not deleted in this family. **Conclusion:** The first report of a familial 1p32 microdeletion in three generations of a family carrying the smallest reported deletion involving this region and brachydactyly as a previously unreported feature.

KEYWORDS: 1p31p32 deletion, 1p, short arm of chromosome 1, developmental delay, learning difficulty.

LIST OF THE KEY FEATURES

Microcephaly, Ambiguous genitalia, Congenital hip dislocation, Brachydactyly, Developmental delay, Learning difficulties, Behavioral problems, Micrognathia, High palate, Prominent nasal bridge.

INTRODUCTION

Interstitial deletions of the short arm of chromosome 1 are rare, except for 1p36 deletions. The overall number of the reported patients is small and most have different sized deletions, some of the earlier patients have uncertain breakpoints. Despite the widespread use of genome wide microarray technology, reports of deletions in this region of chromosome 1 remain rare. Therefore, there are clear limitations in our knowledge concerning the phenotypic consequences of this deletion. So far, the case reports highlighted both common clinical features and phenotype variations among described patients, likely due to different size and position of the deletions and their gene content. The interstitial deletion of the short arm of chromosome 1, so far, have breakpoints in p13, p21, p22, p31, p32, p34, p35 and p36 (Labonne et al., 2016). The majority of the deletions have breakpoints in bands p31 or p32 of chromosome 1 (Labonne et al., 2016).

In 1995, Barton described the first patient with chromosome 1p32.1p32.3 deletion in an 18-month-old girl with developmental delay and dysmorphic features (Barton et al., 1995). Since then, at least 11 patients with deletions involving 1p32 have been reported including a sib-pair (Coci et al., 2016; Ji et al., 2014; Kehrer et al., 2015; Koehler et al., 2010; Lu et al., 2007; Mulatinho et al., 2008; Zinner and Batanian 2003). The reported patients have deletions within p32 and deletions between 1p31 and 1p32. The consistent features in all

the reports are learning difficulty/ developmental delay and dysmorphic features. Other breakpoints that involve 1p32 have also been rarely reported. A deletion between 1p21 and 1p32 was reported in a 14-year old girl with severe learning difficulties, dysmorphic features, short stature and overweight (Bene et al., 1979). There is one report of a female baby with a 1p32.3p34.1 deletion. She was dysmorphic with dilated lateral ventricle, hydronephrosis, dilated ureter and mild developmental delay (Yoshino et al., 1991). All the described deletions, so far, have been *de novo* deletions except for a sib-pair whose interstitial deletion was the result of a balanced translocation inherited from their phenotypically normal mother (Lu et al., 2007).

We describe the clinical and molecular features of a 20-year old patient with learning difficulty, dysmorphic features and a maternally inherited 1.45Mb deletion within the band p32.3 of chromosome 1. Her mother and maternal grandmother have learning difficulties and similar dysmorphic features.

SHORT CLINICAL SUMMARY

The proband was the first child born to non-consanguineous, White European parents. She was born at 38-weeks gestation by normal vaginal delivery. At birth, she had a head circumference of 33.5cm (2^{nd} centile) and weight of 2.6kg (9^{th} centile). She was noticed to have ambiguous genitalia with hypertrophy of the labia minora and bilateral congenital hip dislocation. She was

otherwise healthy. She had mild delay in obtaining motor skills. Her language skills were within normal range. The first clinical genetics evaluation was performed at the age of 6 years and 6 months. She was referred for assessment for learning difficulties and behavioural problems. She attended a mainstream school where she was in special needs class. She was friendly with no sense of danger. On examination, her head circumference measured 48.2 cm, which is below 0.4th centile, height was on the 9th centile and weight was on the 75th centile and a normal inter pupillary distance of 48mm. Her physical features showed a narrow forehead, prominent nasal bridge, low hanging columella, thick upper lip vermilion, high palate, micrognathia, brachydactyly and a large café au lait patch on her left shoulder (Fig 1a-b with progression of facial dysmorphism on subsequent reviews aged 10: Fig 1c-d and aged 12: Fig 1e-f). Examination of the hand showed short hallux, tapering fingers and 5th finger clinodactyly. She had a congenital hip dislocation, which was surgically repaired. She wears glasses for myopia. She had mild hearing loss and needed bilateral grommets. She had her first menstrual cycle at 13-years of age. She had a number of investigations, which were all normal including, standard karyotyping, neonatal cranial ultrasound scan, echocardiogram, abdominal ultrasound scan. Pelvic ultra-sound scan showed a normal sized uterus. A bilateral hand X-ray showed symmetrical brachyphalangia with shortened middle phalanges of the index fingers and oblique joint lines giving rise to some ulnar deviation of the distal phalanges on these fingers. Formal intellectual assessment at 18 years of age using Worschsler Adult Intelligence scale (WAIS IV) showed a full scale IQ of 61 (95% confidence interval 58-66). This result is

indicative of significant intellectual disability. Of note was the difference between her Working Memory Index (WMI) and her Processing Speed Index. Her WMI, which indicates how well she stores information in order to solve a problem, was 74, this is in the borderline range but her PSI, which is the speed at which she processes information in order to solve the problem, was 53, which is in the extremely low range. She is now 20-years old and dependant on carers for her personal care and safety.

The proband's mother, who had the diagnosis of Tourette's syndrome, was assessed by clinical genetics at 29 years of age. She had learning difficulties and congenital conductive deafness. She had dysmorphic features similar to the proband (Fig 2) with prominent nasal bridge, high palate and similar hand shape. She required help from family members to perform some daily activities. Her head circumference measured 52.7cm (2nd centile).

Maternal grandmother has learning difficulties and seizures. She is dysmorphic with a prominent nasal bridge and 5th finger clinodactyly. Her head circumference measured 53.3 cm (3rd centile).

RESULTS

Comparative genomic hybridization (OGT 60K v2.0 ISCA microarray) demonstrated a 1.45Mb deletion at 1p32.3, which included 33 protein-coding genes. The breakpoints were reported as 1p32.3 (53301963-54756872). There

are no reported familial or *de novo* patients with the same deletion breakpoints in medical literature. Figure 3 illustrates the deletion in comparison to the previously reported patients. This region contains 23 protein-coding genes, 14 of which are OMIM genes and 3 are disease-causing genes (Table 1). This result was confirmed by Fluorescence *in situ* hybridization, which showed a deletion of the short arm of chromosome 1 within band p32.3. The proband's mother was found to have the same deletion.

DISCUSSION

Interstitial deletions involving p32 band of chromosome 1 are rare and their phenotypic consequences remain poorly defined. The sizes of the reported deletions are far from similar, with deletions ranging from 22.9Mb in the patient reported by Ji et al. (2014) to 1.45Mb in our patient. More importantly, the deleted regions contain different genes. Hence, the reported patients have different clinical characteristics, which make comparing exact phenotypic features difficult and not particularly helpful.

The proband in this study had dysmorphic features and learning difficulties with a maternally inherited 1.45Mb deletion within band p32.3 of chromosome 1. Her mother and maternal grandmother have learning difficulties and similar dysmorphic features. There are no previous reports of inheritance in 1p32 deletions, but the phenotype in this family appear to be variably expressed

across three generations. This is similar to many other chromosome aberrations.

Looking at all the reported patients that involve 1p31p32 band, developmental delay/ learning difficulties and dysmorphic features appear to be the shared clinical characteristics. Only 4 out of the 12 reported patients (Kehrer et al., 2015; Lu et al., 2007; Mulatinho et al., 2008) and 5 patients on DECIPHER database (Firth et al., 2009) partially overlap with the deletion observed in our patient. The deletion described here is smaller than any of the overlapping deletions previously reported in this region.

There is limited literature on the genes involved in the phenotype associated with deletion of short arm of chromosome 1 in general, and deletion of 1p32 in particular. There are three disease-causing gene in the deleted region in our patient, namely *LRP8, SCP2, CPT2*. There are no confirmed developmental delay genes in the current reported deletion. Nevertheless, the proband has moderate to severe learning difficulties. One gene that may be contributing to the phenotype is *LRP8* (LDL receptor related protein 8) gene. *LRP8* is a key component of reelin pathway, a pathway that controls neuronal layering of the forebrain during embryonic brain development. *LRP8* can also influence neighboring genes like *DAB1*, a gene important for brain development, through the same pathway (Telese et al., 2015). The deleted region in our patient contains *CPT2* and *SCP2* genes, which are known to play a role in fatty acid oxidation and cholesterol metabolism (Mulatinho et al., 2008).

At least 2 patients have been reported to have low cholesterol level and deletion of *CPT2* and *SCP2* has been proposed as the possible cause (Kehrer et al., 2015; Mulatinho et al., 2008). The proband has myopia, which is also a feature in the patient reported by Mulatinho et al. (2008). Congenital hip dysplasia is a shared feature in our patient and DGAP205-1s reported by Lu et al. (2007). The current patient and the patient reported by Kehrer et al. (2015) are the only reports of microcephaly, while all other reported patients had large or normal head circumference. Despite sharing some clinical features, the non-specific nature of the reported dysmorphic features make it difficult to establish a clinical phenotype in relation to regional deletions in 1p32. The patient reported here had ambiguous genitalia at birth in the form of large labia. Ambiguous genitalia has also been reported in 2 patients of 1p deletion involving p32 (Sivasankaran et al., 1997; Lu et al., 2007). However, there is no overlap in the deleted region between those 2 patients and our patient. A gene that could plausibly contribute to this phenotypic feature in our patient is *DMRTB1* gene. *DMRTB1* is highly expressed in ovary and testis and believed to play a role in sex differentiation (Ottolenghi et al., 2002). Deletion of *DMRTB1* in our patient may be contributing to genital ambiguity. In addition to the features previously mentioned, our patient had brachydactyly, which has not been previously reported in association with 1p32 deletion. The clinical and molecular characteristics of the current patient were compared to the 4 reported patients with overlapping deletions (see table 2). Haploinsufficiency of *NFIA* gene has been proposed to be the cause of central nervous system (CNS) malformations and urinary tract abnormalities, which appear to be recurring

features in many of the reported patients (Lu et al., 2007). This gene is not deleted in our patient.

Increasing number of reported patients and detecting smaller deletions with fewer genes is going be helpful in investigating the contribution of candidate genes to the phenotype associated with this deletion. Detailed and systematic characterization of clinical and molecular data in newly reported patients is expected to identify candidate genes and link it to the specific features of the 1p32 deletion. Furthermore, functional studies in candidate genes may contribute to a better understanding of their function and help gain more insight into genotype-phenotype correlation.

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