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CASE REPORT

Clinical and molecular characterization of a patient with a combination of a deletion and a duplication of 22q13 using array CGH

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Abstract: Phelan–McDermid syndrome is caused by the loss of terminal regions of different sizes at 22q13. There is a wide range of severity of symptoms in patients with a 22q13 deletion, but these patients usually show neonatal hypotonia, global developmental delay, and dysmorphic traits. We carried out a clinical and molecular characterization of a patient with neonatal hypotonia and dysmorphic features. Array-based comparative genomic hybridization showed an 8.24 Mb terminal deletion associated with a 0.20 Mb duplication. Characterization of patients with Phelan–McDermid syndrome both clinically and at the molecular level allows genotype-phenotype correlations that provide clues to help elucidate the clinical implications.

Keywords: 22q13 deletion, subtelomeric rearrangements, Phelan–McDermid syndrome, genotype–phenotype correlations

Introduction

The 22q13.3 deletion syndrome, also known as Phelan–McDermid syndrome (PMS, OMIM # 606232), is characterized by global developmental delay, absent or impaired speech, neonatal hypotonia, autistic traits, and mild dysmorphic features.[1,2] This syndrome results from loss of segments of varying sizes involving the terminal region of long arm of chromosome 22, due to a simple deletion (75% of PMS cases), ring chromosomes, or unbalanced translocations.[3–5] Affected individuals have deletions ranging in size from 95 Kb to 9.22 Mb, and no common breakpoint has been observed.[6,7]

Due to lack of clinical recognition, the cryptic nature of this deletion in a significant fraction of cases, and the difficulty of performing an appropriate diagnostic test, PMS is considered to be underdiagnosed and its true prevalence is unknown.[4] A subtelomeric fluorescence in situ hybridization analysis of more than 11,000 patients with developmental disabilities suggested that deletion 22q13 was second to deletion 1p36 as the most frequent subtelomeric rearrangement, and was identified in 0.2% of those evaluated.[8] The number of malformation syndromes attributed to these microdeletions is increasing as more are being identified through molecular diagnostic techniques. Until recently, the diagnosis was based on cytogenetic banding and fluorescence in situ hybridization. Oligo-array comparative genomic hybridization (CGH) is able to detect smaller deletions and accurately measure deletion size and breakpoints.

Most of the published reports consider that the haploinsufficiency of *SHANK3*, which encodes a synapse structural protein and is located approximately 130 kb from the telomere, was responsible for the major neurobehavioral symptoms of this syndrome.[9,10] A patient with developmental delay, speech delay and minor

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dysmorphic facial features (ptosis, epicanthal folds and cupper ears) carrying a de novo interstitial deletion disrupting only *SHANK3* gene, supported that happloinsufficiency of *SHANK3* alone, and no other genes telomeric to it, was responsible for PMS.[10]

Recent genotype–phenotype studies have shown more severe phenotypes associated with larger deletions.[5,6,11] These results suggested that other genomic regions proximal to *SHANK3* are responsible for speech and developmental delay, and some dysmorphic features, when deleted.

Clinical report

The patient is a Caucasian male, the first child of healthy parents. His mother was 29 and his father 30 years old when he was born. The father, grandfather, and great-grandfather presented toe syndactyly. First fetal movements were felt by the mother at 21 weeks. The pregnancy was complicated by maternal preeclampsia. He was born at gestational age 38 weeks by cesarean. Fetal monitoring before labor registered few movements. Birth weight was 2770 g, length 48 cm, and cranial perimeter 35.5 cm.

In the neonatal period, echocardiography showed a persistent ductus arteriosus and patent foramen ovale. Axial hypotonia was present. A cerebral scan was performed with a normal result. Dysmorphic features have been described in Table 1 and can be seen in Figure 1. He showed facial features that included large ears, full cheeks and pointed chin, large extremities, and a short webbed neck.

At 23 months old he had a bilateral hearing deficit and recurrent respiratory infections. Sacral ultrasound demonstrated renal crystal depositions.

Cytogenetics

The deletion was cytogenetically visible by conventional G-banding karyotype (Figure 2A). The parents were tested, displaying normal karyotypes, so the deletion was considered as de novo. Molecular testing for fragile X was negative.

High resolution CGH-array (400K; Agilent Technologies, Santa Clara, CA) was carried out to determine the size and extent of the deletion (Figure 2B). This was determined to be a terminal deletion of 8.24 Mb associated with a duplication of 0.20 Mb adjacent to the deleted region, 46,XY,arr cgh 22q13.2(42694206-42889651)x3, 22q13.22q13.3(42944814-51186390)x1 (location according NCBI Build 37.3). The deleted region has 137 genes in the Genes on Sequences NCBI map, of which 61 are in the OMIM database. The duplicated region contains two genes, one of which (*NFAM1*) is in the OMIM database.

Discussion

The clinical features of PMS are highly variable. Patients' deletion sizes are also highly variable. Recent genotype–phenotype studies using CGH-array have found correlations between deletion size and the severity of selected phenotypes.[6,7] Different features have been associated with larger deletions including large hands,[7] and dysmorphic features related to ears, toenails, and philtrum, as well as male genital anomalies.[6,12] Our patient has a phenotype similar to those reported with similar deletion sizes. This genotype–phenotype correlation suggested that there are clinically important genes located proximal to *SHANK3* contributing to PMS phenotype. In agreement with this, Wilson et al[11] reported two cases with intact *SHANK3* that showed development delay and dysmorphic features.

The interval deleted in our patient contains 137 genes. Some of these genes (besides *SHANK3*) are responsible for clinically significant disorders: *UPK3A* (renal adysplasia), *FBLN1* (synpolydactyly associated with metacarpal and metatarsal synostoses), *ATXN10* (spinocerebellar ataxia 10), *TRMU*

Table 1 Dysmorphic features of the patient described in this study

Craniofacial	Extremities	Trunk	Genital
• Low set large and dysplastic ears • Flat forehead • Full cheeks • Downslanting palpebral fissures • Hypertelorism • Epicanthal folds • Long filtrum • Microstomia • Retromicrognatia • High arched palate • Pointed chin	• Large extremities • Large fleshy hands • 2–3-toe syndactyly • Left talus valgus deformity • Dysplastic toenails	• Laterally displaced hypoplastic nipples • Short webbed neck	• Large penis and testes

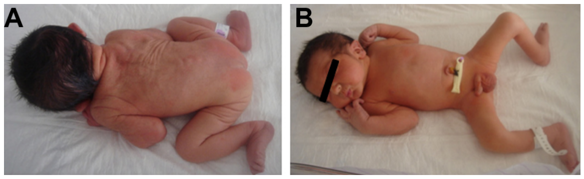

Figure 1 Dysmorphic features of patient described in this study. (**A**) Short webbed neck. (**B**) Large extremities, left talus valgus deformity, large penis and testes.

(liver failure, transient infantile, deafness, aminoglycoside-induced).

Our patient carries an 8.24 Mb deletion associated with a 0.20 Mb duplication. Only two similar cases with deletion-duplications in 22q13 have been previously reported,

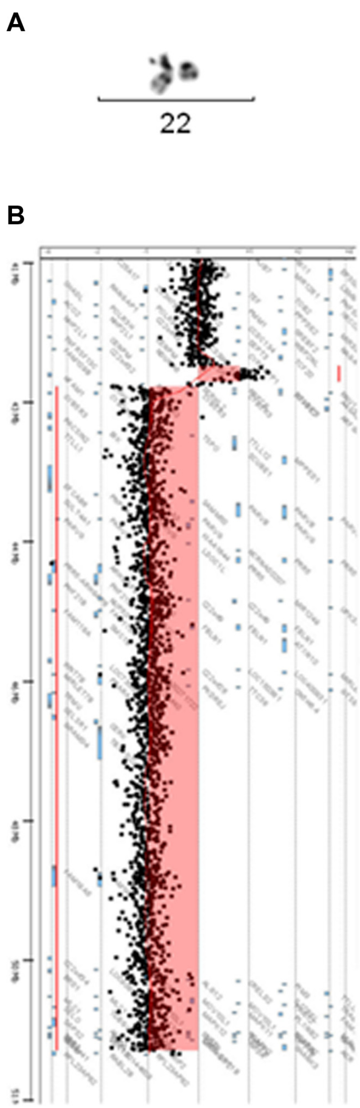

Figure 2 Characterization of the deletion: cytogenetic and molecular studies. (**A**) Conventional G-banding chromosome 22. The deleted chromosome is on the right. (**B**) CGH-array. Reduced dosage for probes is shown to the left of the control two-copy line and increased dosage is shown to the right.
Abbreviation: CGH, comparative genomic hybridization.

although these were not the same as our patient's. Lindquist et al[13] described a patient with a 7.9 Mb duplication and a 4.2 Mb deletion of 22q13 who had generalized developmental delay, delayed speech, hypotonia, dysmorphic features (including epicanthal folds, flat midface, and full cheeks), apneic spells with seizures, persistent ductus arteriosus and Pierre Robin sequence (never reported before in PMS). Koolen et al[5] reported a case with a 3.9 Mb subtelomeric deletion associated with a 2.0 Mb duplication. This patient had signs of retinitis pigmentosa (never reported before in PMS). There are a growing number of similar cases that have been reported at different chromosomal ends: 1p, 2q, 4p, 5p, and 8p.[14–18] This type of chromosome rearrangement may be more common than previously thought, and it can be detected by high-resolution CGH-array.

A phenotype present in our patient had never been observed in 22q13 deletion: short webbed neck. This feature had been previously observed in 22q13 duplication syndrome.[19] This feature is only present when 22q13.2 is duplicated. Patients with duplications 22q13.3-qter do not show short neck. So, this phenotype is possibly attributable to the duplication.

In summary, this study underscores the utility of array CGH for the characterization of the size and nature of subtelomeric rearrangements and to predict the severity of phenotypes. Associations between phenotypes and deleted/duplicated regions provide valuable information about clinically important genes, micro-RNAs or regulatory elements, and will allow investigation of their role in the phenotypes of this syndrome.

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Disclosure

The authors report no conflicts of interest in this work.

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