Case Report

A Rare Chromosome 3 Imbalance and Its Clinical Implications

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The duplication of chromosome 3q is a rare disorder with varying chromosomal breakpoints and consequently symptoms. Even rarer is the unbalanced outcome from a parental inv(3) resulting in duplicated 3q and a deletion of 3p. Molecular karyotyping should aid in precisely determining the length and breakpoints of the 3q+/3p− so as to better understand a child’s future development and needs. We report a case of an infant male with a 57.5 Mb duplication from 3q23-qter. This patient also has an accompanying 1.7 Mb deletion of 3p26.3. The duplicated segment in this patient encompasses the known critical region of 3q26.3-q27, which is implicated in the previously reported 3q dup syndrome; however, the accompanying 3p26.3 deletion is smaller than the previously reported cases. The clinical phenotype of this patient relates to previously reported cases of 3q+ that may suggest that the accompanying 1.7 Mb heterozygous deletion is not clinically relevant. Taken together, our data has refined the location and extent of the chromosome 3 imbalance, which will aid in better understanding the molecular underpinning of the 3q syndrome.

1. Introduction

The genetic analysis of infants with multiple congenital abnormalities is a very important aid in understanding a child’s future prognosis and development. Microarray technologies are more commonly becoming the tool of choice to accurately determine the underlying genetic cause and resulting phenotype [1].

The duplication of chromosome 3q is a rare genetic disorder resulting in mental retardation, seizures, broad nose, cardiac, renal, and genital malformations [2]. The critical region of 3q+ has been defined by Aqua et al. [3] as 3q26.31-q27.3. In contrast, deletions of chromosome 3p are associated with intrauterine and postnatal growth retardation with delayed bone maturation, severe psychomotor retardation, dysmorphism including ptosis, a narrow nose, flat nasal bridge, clinodactyly, heart and kidney defects, and impaired vision [2, 4]. The size of the deletion appears to correlate with severity of the phenotype such that patients with a large deletion exhibit severe malformations and mental retardation [5]. The reported breakpoints for the 3p− syndrome appear to be variable, but the 3p− phenotype is associated with deletions in the 3pter-3p25 region [6].

Previously reported cases of patients carrying a duplication at 3q23-ter as well as a large deletion at pter-3p25 have a fatal outcome [2]. We report a case here in which the patient has a much smaller 3p deletion in combination with the 3q23-ter duplication, and discuss whether the 3p deletion size affects patient phenotype and outcome.

2. Case Report

A one-month-old male presented with a large ventricular septal defect (VSD), large posterior and anterior fontanelle, dysmorphic features, single palmar crease, under-developed testes and mild seizures. The baby was the product of a normal first pregnancy and was delivered at 41 weeks, 6 days with a birth weight of 4.1 kgs (9 lbs). Labour was complicated by foetal distress, and delivery was by caesarean section and admitted to the Newborn Intensive Care Unit (NICU) on day 2 for respiratory distress.

Ultrasound analysis revealed a thin corpus callosum and a consequent MRI of the brain and spine revealed a small right germinal matrix haemorrhage and mild craniofacial disproportion and mild micrognathia. There was also
Figure 1: Karyotype and chromosome 3 ideogram of the proband. Panel A shows the karyotype of the proband, 46,XY,rec(3)dup(3q)inv(3)(p26.3q23)mat.arr 3p26.3(56,669-1,850,707)x1,3q23q29(141,829,104-199,355,203)x3. Panel B shows the normal and derivative chromosomes 3, together with an associated ideogram. Panel C is a summary ideogram of the regions of chromosome 3 that are duplicated and deleted in the proband.

a separate choroidal fissure cyst on the left 9 mm in maximal dimension. The corpus callosum was thin, but present.

At 14 months of age, the proband had gained weight despite feeding difficulties and was breast feeding; post surgery, the child exhibited normal biventricular function with no residual VSD and no audible murmurs; he was tachypnoic with a respiratory rate of 60, but his chest was clear. He had a thickened filum, and surgery was suggested in infancy to prevent later problems with foot development. He also had reduced antigravity movement in his upper and lower limbs with reduced central tone, but increased tone in his limbs.

2.1. Cytogenetic and Microarray Analysis. Metaphase chromosomes were prepared from stimulated peripheral blood cells according to standard methods and karyotyping was performed by G-band metaphase analysis. This analysis showed a large duplication of material on the short arm of chromosome 3, which appeared 3q-like (Figure 1).

Higher resolution molecular karyotype analysis was performed to determine the extent of the 3q+ region. Briefly, genomic DNA was isolated from peripheral blood using the Gentra Puregene blood kit according to the manufacturer's instructions (Qiagen Pty Ltd., MD, USA). 0.1 micrograms of genomic DNA was labelled using the Affymetrix Cytogenetics Reagent Kit and labelled DNA was applied to an Affymetrix Cytogenetics Array (2.7 million probes) according to the manufacturer’s instructions (Affymetrix Inc, CA, USA). The array was scanned and the data analysed using the Affymetrix Chromosome Analysis Suite (ChAS; version 1.0.1) and interpreted with the aid of the UCSC genome browser (http://genome.ucsc.edu/; hg18 assembly). This analysis confirmed the copy number change as a 57.5 Mb terminal duplication from 3q23-qtter, together with an unsuspected 1.7 Mb deletion at 3p26.3 (Figure 1). The deleted region contains two genes, CNTN6 and CHL1 (Figure 2).

Parental analysis confirmed that these chromosome 3 changes arose as an unbalanced product of a meiotic recombination in the mother who has a pericentric inversion of one homologue of chromosome 3 between p26 and q23 (Figure 3).

Patients with 3p− who have been reported in the DECIPHER database exhibit a range of phenotypes (Table 1). The deletions in these patients range in length from 200 kb to 12.5 Mb, incorporating 42 known genes from 3pter-3p25. In the main, the associated clinical phenotypes of these patients do not match those identified in the proband who carries a smaller distal 3p deletion, as well as a duplication of 3q. The phenotypes that do match such as mental retardation/developmental delay, VSD, dysmorphism, and seizures are also symptoms that are associated with the 3q+ syndrome.

3. Discussion

The duplicated segment in the proband described here encompasses the known critical region of 3q26.3-q27 [3], which is implicated in the previously reported 3q+ syndrome; the proband exhibits the 3q+ syndrome phenotype [2, 3, 7]. The accompanying deleted region at 3pter is small and encompasses only two genes, CNTN6 and CHL1. Both of these genes are implicated in psychomotor retardation [8, 9], which is a phenotype exhibited by patients with the 3q+ syndrome.
Previously reported patients with a smaller 3p deletion at 3p26.1-3pter and 3p26.3-3pter exhibit a mild phenotype with no heart disease and mild or no mental retardation [9, 10], suggesting that these smaller deletions do not cause the 3p− phenotype. The 3p− phenotype has been well characterised and most reported cases have a larger deletion than the proband, from 3pter-p25 [4, 5, 11–13]. Cargile et al. [13] reported a patient with a small interstitial deletion at 3p25.3-p26.2 that had a 3p− clinical phenotype of ptosis, microcephaly, growth retardation, and developmental delay. Other reported cases of 3p− phenotypes are consistent with a larger deletion incorporating the 3p25.3-p26.2 region suggesting that the gene/genes contributing to the 3p− phenotype are within this region [9, 14–16]. Malmgren et al. (2007) reported that they consider this minimal region of overlap between the reported cases, which includes 12 genes, to contain the candidates for the 3p− phenotype.

The many genes reported as potential candidate genes in the 3p− phenotype include ATP2B2, CNTN4, ITPR1, LRRN1, SUMF1, and SRGAP3 [9, 16–18], which are present in the minimal region of overlap reported by Cargile et al. [13] at 3p25.3-p26.2; this region is not deleted in the proband described here. Evidence to suggest that genes in the 3p25.3-p26.2 region are involved in the 3p− phenotype is supported
Table 1: 3p− phenotypes reported at least twice in DECIPHER patients (15/07/2012).

| 3p− phenotype reported in DECIPHER patients | Phenotype reported in proband | Also reported in 3q+ syndrome |
|--------------------------------------------|-------------------------------|-------------------------------|
| Microcephaly                               | (Mild micrognathia)           | −                            |
| Ptosis of the eyelids                      | −                            | −                            |
| MR/DevDel                                  | ?                            | +                            |
| Small/short nose                           | −                            | −                            |
| Seizures                                   | +                            | +                            |
| AVSD                                       | +                            | +                            |
| Clinodactyly/polydactyly (Clinodactyly)     | +                            | +                            |
| Dysmorphic                                 | +                            | +                            |
| Small hands/feet                           | −                            | −                            |
| Hypotonia                                  | −                            | −                            |
| Hypertelorism                               | +                            | +                            |
| Feeding problems                           | +                            | +                            |
| Horseshoe kidney                           | −                            | −                            |
| Short stature                               | −                            | −                            |

DECIPHER patient numbers used: 256371, 249344, 261155, 256542, 251667, 1876, 253652, 249965, 253231, 248772, 258577, 248715, 248716, 1372, 1213. These data were taken from the DECIPHER Consortium database (http://decipher.sanger.ac.uk/).

by a case with a de novo balanced translocation between chromosomes 3 and 10 that disrupted the CNTN4 gene. This patient exhibited a 3p− phenotype [19].

Most patients reported with a deletion/duplication of chromosome 3 have a larger deletion from 3pter-p25 with a duplication at either 3p21 or 3p23 and have a very poor outcome with a clinical picture of growth deficit, delayed bone maturation, microcephaly, narrow nose and multiple malformations [2]. The clinical phenotype of our patient is more consistent with a diagnosis of the 3q+ syndrome phenotype alone. The patient had a high birth weight and broad nose, which is not consistent with the deletion phenotype. Microarray analysis confirmed that this patient has a smaller accompanying 1.7 Mb deletion from 3pter-p26.3. The size of the deletion appears to have minimal impact on the phenotype of this patient and this is consistent with previously reported cases. The principal conclusion, therefore, is that the patient’s clinical progression should follow a 3q syndrome phenotype.

4. Conclusion

Taken together, our data has refined the location and extent of chromosome 3 imbalances. Molecular karyotyping has led to a better understanding of the molecular underpinning and phenotypic outcome in the proband reported here and should be considered in future cases to aid a prognosis.

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