Case Report

Pure Duplication of the Distal Long Arm of Chromosome 15 with Ebstein Anomaly and Clavicular Anomaly

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1. Introduction

Reported cases of duplication of distal chromosome 15 are uncommon. Most of these are due to the inheritance of an unbalanced product of a translocation with an additional monosomic component. There are only very few reported cases of “pure” duplication of 15q24-qter region (Table 1) [1–6]. Of the 10 reported patients, seven patients had trisomy of 15q25/q26-qter. These patients presented with evidence of prenatal overgrowth and developed postnatal overgrowth. Overgrowth has been attributed to overexpression of the insulin-like growth factor (IGF1R) gene, which is located in 15q26.3 and is known to play a critical role in the somatic growth of the mammalian embryo and fetus and in postnatal growth. In general, these patients also had mild developmental problems and minimal dysmorphism, the latter encompassing abnormal slant or size of the palpebral fissures, ptosis, long fingers, and overlapping toes.

In the three remaining patients, the trisomy involved the 15q24-qter region [2, 6]. Interestingly, these patients exhibited growth retardation, together with more significant developmental delay compared to those patients described above. It is tempting to speculate that overexpression of genes that lie in the 15q24 region rule out the effect of increased expression of IGF1R, leading to short instead of tall stature.

In this report we present a patient with a pure duplication of 15q24-qter. Our patient has unusual phenotypes that are not commonly associated with previously reported dup15q patients. Among her many dysmorphic findings are two atypical features. The first is Ebstein anomaly, which has been reported in only two other cases that carry trisomy for 15q22/q24-qter, but these patients also carried monosomic regions [6]. Ebstein anomaly is a distinctive abnormality of the leaflets of the tricuspid valve in which deformed septal and posterior valve leaflets are displaced apically and adherent to the wall of the right ventricle. The second atypical feature is an unusual radiologic appearance of the clavicles.

2. Clinical Report

The propositus was born prematurely at 33 weeks gestation to a G2, P1 mother. Her first pregnancy resulted in an early
|                  | Present case | Okubo et al. | Roggenbuck et al. | Bonati et al. | Kant et al. | Tatton-Brown et al. | Miller et al. |
|------------------|--------------|--------------|-------------------|---------------|-------------|---------------------|---------------|
|                  | Twin1 Case 1*| Twin1 Case 2 | Case 3           | Case A        | Case A      | Case 1A             | Case 2-A      |
|                  | Twin2 Case 2 |             |                   | Case 1-B      | Case 2-B    | Case 2-B            | Case 1        |
|                  | Case 1-B     | Case 2       |                   | Case 2-B      | Case 2-B    |                     | Case 2        |
| Sex              | M            | M            | F                 | M             | M           | F                   | M             |
| Trisomic segment | 15q24.2-q26.3| 15q24-q26.3  | 15q25.2-q26.3     | 15q26.1-q26.3 | 15q26-q26.3 | 15q26-q26.3         | 15q26-q26.3   |
| Monosomic segment| 15p11.2      | 15p11.2      | none              | none          | none        | 15p12-pter          | 14p11.2-pter  |
| Dysmorphic features |            |              |                   |               |             |                     |               |
| Postnatal growth retardation | −           | +            | +                 | −             | −           | −                   | +             |
| Tall stature     | +            | −            | −                 | +             | +           | +                   | +             |
| Mental retardation/Developmental delay | +       | +            | +                 | +             | +           | +                   | +             |
| Micrognathia     | +            | +            | −                 | −             | −           | −                   | +             |
| Long-tapered fingers | +         | −            | −                 | +             | −           | −                   | +             |
| Clinodactyly     | +            | +            | +                 | −             | −           | −                   | +             |
| Incurving and overlapping toes | +       | +            | −                 | −             | −           | −                   | +             |
| Unusual palpebral fissures | Small    |              | Uplslanting       | Down-slanating | −           | Down-slanating     |              |
| Hypoplastic genitalia | +         |              |                  |               |             |                     |               |
| Cardiac anomaly  | Ebstein anomaly |          | Ventricular septation | VSD+ASD |                 |                     | Ebstein anomaly |
| Other            |              |              |                   |               |             |                     |               |
| Anencephaly      |              |              |                   |               |             |                     |               |
| Microcephaly     |              |              |                   |               |             |                     |               |
| Brachycephaly    |              |              |                   |               |             |                     |               |
| Seizure          |              |              |                   |               |             |                     |               |
| Wide nasal bridge |              |              |                   |               |             |                     |               |
| Frontal bossing  |              |              |                   |               |             |                     |               |
| Horseshoe kidney |              |              |                   |               |             |                     |               |
| Strabismus       |              |              |                   |               |             |                     |               |
| Long prominent nose |              |              |                   |               |             |                     |               |
| Dolichocephaly   |              |              |                   |               |             |                     |               |
| Microcephaly     |              |              |                   |               |             |                     |               |
| Prominent nose   |              |              |                   |               |             |                     |               |
| Other             |              |              |                   |               |             |                     |               |

M: male; F: female; +: feature present; −: feature absent; blank: not known; VSD: ventral septal defect; ASD: atrial septal defect.

* Died soon after birth
2.1. Cytogenetic and Molecular Studies. Conventional G-banded chromosome analysis was performed on peripheral blood samples taken from the proband and her mother (a blood sample from her father was not available). Analysis of the mother identified a pericentric inversion in one homologue of chromosome 15, with breakpoints at 15p11.2 and q24: 46,XX,inv(15)(p11.2q24) (Figure 2(a)). Analysis of the proband revealed additional chromosomal material on distal 15p, with a karyotype of 46,XY,rec(15)dup(15q)inv(15)(p11.2q24)mat (Figure 2(b)).

Genomic DNA was isolated from peripheral blood of the proband using the Gentra Puregene blood kit according to the manufacturer’s instructions. 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. The array was scanned and the data was analysed using the Affymetrix Chromosome Analysis Suite (ChAS; version 1.0.1) and interpreted with the aid of UCSC genome browser (hg18 assembly). The proband’s molecular karyotype identified a terminal duplication of 27 Mb; arr 15q24.2q26.3(73,237,973-100,215,737)x3 (Figure 3).

3. Discussion

The patient described in this report exhibited normal growth parameters at birth, but it is too early to assess postnatal growth and developmental progress. Some of the noted dysmorphic findings, namely the small palpebral fissures, micrognathia, long slender fingers, incurving and overlapping of toes, and hypoplastic genitalia, are similar to those previously reported in patients with pure 15q24-qter duplications. The more significant developmental delay reported for these patients, compared to those with a more distal duplication (15q25/26-qter), may be due to the overexpression of genes located in the 15q24 region [7]. Of relevance are the genes LINGO-1 and CSPG4. Overexpression of LINGO-1 has been implicated in delayed myelination in mouse models [8, 9], and cells expressing CSPG4 play a role in brain repair [10, 11].

Our patient exhibits Ebstein anomaly, which is uncommon, comprising only 0.5% of all patients with a congenital heart defect [12]. The formation and liberation of the tricuspid valve leaflets occurs by a process of delamination from the underlying myocardium, starting at 8 weeks of fetal...
Figure 2: Partial karyotype and ideograms of chromosomes 15 of proband and mother. (a) The mother’s partial karyotype and ideogram shows a normal chromosome 15 (left) and inverted chromosome 15 (right). (b) The proband’s partial karyotype and ideogram shows the normal chromosome 15 (left) and recombinant chromosome 15 (right).

Figure 3: Schematic of the chromosome 15 region that shows increased dosage in the proband. (a) Shows an ideogram of chromosome 15, together with the location and extent of the duplication detected in the proband (15q24.2-qter; boxed in red); the base pair coordinates of the light and dark staining G-bands are also shown. (b) Shows the RefSeq genes that are localised to 15q24.2-15q24.3; LINGO-1 and CSPG4 are shown in red boxes. These data and graphics were taken from the UCSC genome browser (http://www.genome.ucsc.edu).
gestation. Ebstein anomaly is linked to a deficiency in this delamination process of the septal and posterior tricuspid valve leaflets [13]. The cases associated with chromosomal abnormalities, as well as the multiple cases of familial Ebstein anomaly, support the hypothesis that several genes may act in the regulation of delamination during cardiogenesis. To date, only two human genes have been linked to Ebstein anomaly: TBX5 at 12q24.1, which is associated with Holt-Oram syndrome [14], and the cardiac transcription factor, NKX2-5, at 5q34 [15].

There are only two reported cases of patients with duplication of distal 15q and Ebstein anomaly (Table 1) [6]. The first patient was trisomic for the 15q22-pter region and monosomic for 7q36-pter. The second patient was trisomic for the 15q24-pter region and monosomic for 21q22.2 region. No previous cases of Ebstein anomaly have been reported in patients with terminal 7q or 21q monosomies. Thus, these two cases, together with the present case, raise the possibility that overexpression of a gene, likely within the 15q24 band, disrupts normal development of the tricuspid valve. The identity of this gene is unclear based on a search of all the genes within 15q24.2-q24.3 (see supplementary Table of Supplementary Material available at doi:10.1155/2011/898706).

The described skeletal anomalies of our case have not been previously reported in patients with partial trisomy 15q. Of particular interest is the unusual radiologic appearance of the clavicles. A similar appearance of the midportions of the clavicles has been previously reported in an infant with mosaicism of ring 21 [16]. A subsequent letter to the journal’s editor raised the possibility that this anomaly may represent pseudarthrosis of the clavicles [17]. We have ruled out this possibility both clinically and radiologically in this case. Unfortunately, there are no known human genes in the 15q24-q26.3 region that appear to be involved in the development of the unusual phenotypes presented here.

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