

Desbuquois Syndrome Atypical Hands Subtype with No Mutation in *FLNB* Gene

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Abstract Desbuquois syndrome is characterised by craniofacial dysmorphism, carpotarsal, vertebral and joint abnormalities; with associated developmental delay. It is genetically heterogeneous and has been subdivided into two groups, the "typical hands" and "atypical hands" groups. We hypothesised that the "atypical hands" subgroup may be due to Filamin B (*FLNB*) mutations, and the objective of this study is to evaluate if mutation in *FLNB* gene is associated with this clinical subgroup. After sequencing the whole *FLNB* gene, we report that no mutation was found in our case of Desbuquois syndrome.

Key words Atypical hands; Desbuquois syndrome; *FLNB* gene; Skeletal dysplasia

Introduction

Desbuquois syndrome (DS) is a rare autosomal recessive osteochondrodysplasia that is characterised by prenatal onset of short stature, facial dysmorphism of round flat midface and prominent bulging eyes, joint laxity or dislocation, advanced carpal and tarsal bone age, swedish key appearance of the proximal femur with flat proximal femoral metaphysis and exaggerated lesser trochanter, and variable degree of mental retardation.

The condition was initially reported by Desbuquois et al in 1966,¹ and subsequent reports of cases divided Desbuquois syndrome into two subgroups based on presence (46%) of a supernumerary ossification centre distal to second metacarpal, and variable thumb changes, being regarded as typical hand changes; or the slightly more common group (54%) with absence of above hand changes,

regarded as atypical subtype changes.²

Spondylocarpotarsal synostosis, Larsen syndrome and Desbuquois syndrome share in common similar clinical features with variable degree of severity consisted of advancement of carpotarsal ossification, joint formation, vertebral and bones developmental abnormalities. Krakow et al reported Filamin B (*FLNB*) gene mutation in Spondylocarpotarsal synostosis and dominant form of Larsen syndrome.³ Since Desbuquois syndrome with typical hand changes was linked to 17q25.3 and the same group reported exclusion of 17q25.3 locus in Desbuquois syndrome with atypical hand changes.^{2,4} We hypothesised that Desbuquois syndrome with atypical hand changes are due to mutations in *FLNB* gene at chromosomal locus 3p14.3, and the objective of this study is to evaluate if mutation in *FLNB* gene is associated with this clinical subgroup.

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Subject and Methods

The case was previously reported by Lam et al,⁵ and was initially referred to our Clinical Genetic Service on day 2 of life for suspected skeletal dysplasia. The proband and her sister were born to consanguineous parents; and both siblings were developmentally delayed and similarly affected with DS.

Genomic DNA was extracted from peripheral blood of

Proband and her parents using QIAamp DNA blood mini kit (Qiagen). DNA was amplified in a final reaction volume of 50 μ l by using 100 ng genomic DNA, 1 x FX buffer, 0.2 mM of each dNTPs, 20 pmole primers and 1 unit AmpliTaq Gold polymerase. Primers and the annealing temperatures were self-designed and are available on request. PCR cycling conditions consisted of an initial denaturation step at 95°C for 10 min following by 35 cycles of 94°C for 1 min, the specified annealing temperature for 1 min, 72°C for 1 min and ending with a final elongation step at 72°C for 7 min.

PCR products were purified using QIAquick PCR purification kit (Qiagen) and then subjected to cycle sequencing in a 20 μ l reaction with the ABI BigDye Terminator V1.1 cycle sequencing kit. Each reaction contained 3.2 pmole forward or reverse primer, 8 ng template DNA, 2 μ l BigDye Terminator ready reaction mix, 3 μ l of BigDye sequencing buffer and using water to make up to 20 μ l. Cycle sequencing conditions consisted of an initial denaturation step at 96°C for 1 min following by 25 cycles of 96°C for 10 sec, 50°C for 5 sec, and 60°C for 4 min. Unincorporated dye and other contaminants were removed using the CentriSep columns (Applied Biosystems). The purified extension products were then sequenced on an ABI 3100 Genetic Analyzer (Applied Biosystems).

Parental consent for publication was kindly given and signed.

Results

After sequencing the whole *FLNB* gene (exon 1 to 46), we found no mutation in either of our proband or her parents.

Discussion

DS shares in common with the recessively inherited Spondylocarpotarsal synostosis (SCT) and the dominant form of Larsen syndrome (LS) in certain phenotypic features namely craniofacial dysmorphism; carpotarsal, vertebral and joint abnormalities. Faivre et al (2003) demonstrated genetic heterogeneity by mapping Desbuquois syndrome with "typical hands" to 17q25.3 and excluded the same locus in the syndrome with "atypical hands".^{2,4} Our case as reported by Lam et al (2003) falls in the atypical hands group. As Krakow et al (2004) reported

FLNB mutations in SCT and LS, *FLNB* should be considered a likely candidate gene for DS.

Sheen et al (2002) reported that both Filamin A (*FLNA*) and Filamin B (*FLNB*) proteins, apart from forming *FLNA* homodimers and *FLNB* homodimers, they also closely interact by forming heterodimers.⁶ While *FLNA* was widely expressed in all cortical layers and *FLNB* was highly expressed in ventricular and subventricular regions during brain development, it would not be surprising for patients with *FLNB* mutations to have variable degree of developmental delay. Since *FLNA* gene is X-linked therefore it is unlikely to be responsible for DS, which is an autosomal recessive condition. Therefore we hypothesised that DS with atypical hands may be caused by *FLNB* mutations. After sequencing the whole *FLNB* gene, we found no mutation in this case. The reasons may be that it is due to some other forms of mutation not detected by our current methods for example, mutations in the gene promoter region, deep intronic mutations, exon deletions or duplication; or it may not be due to *FLNB* mutations at all. This is significant because Larsen syndrome is a major differential diagnosis of Desbuquois syndrome. Since *FLNB* mutations have been found in Larsen syndrome patients, mutations in *FLNB* must be strongly suspected in Desbuquois syndrome. Our results suggested that Desbuquois syndrome is not part of the recently defined Filamin B "Filaminopathy" spectrum; and a gene other than *FLNB* that is involved in craniofacial, carpotarsal, vertebral and joint development, and at the same time may also be expressed in the brain, causes Desbuquois syndrome.

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