SHORT REPORT

Homozygosity mapping of a Desbuquois dysplasia locus to chromosome 17q25.3

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Desbuquois dysplasia is a rare autosomal recessive chondrodysplasia characterised by short stature, joint laxity, facial dysmorphism, a “Swedish key” appearance of the proximal femur, advanced carpal and tarsal bone age, and hand anomalies consisting of phalangeal dislocations and an extra ossification centre distal to the second metacarpal. However, the latter changes are not consistently observed in all Desbuquois patients, defining two distinct groups, based on the presence or absence of hand anomalies. We have performed a genome wide search in four inbred Desbuquois families with typical hand anomalies originating from France, Sri-Lanka, the United Arab Emirates, and Morocco. Here, we report on the mapping of a disease gene to chromosome 17q25.3 ($Z_{\max}=4.61$ at $\theta=0$ at locus D17S1806) in the 9.5 cM interval defined by loci D17S802 and D17S1822. The present study supports the genetic homogeneity of the clinical subtype with hand anomalies and will hopefully help in identifying the Desbuquois dysplasia gene.

Desbuquois dysplasia is a rare condition of autosomal recessive inheritance, first described by Desbuquois *et al* in 1966. Patients are characterised (1) clinically by markedly short stature of prenatal onset, joint laxity, and spe-

cific facial dysmorphism including a round face, prominent, bulging eyes, and midface hypoplasia, and (2) radiologically by a “Swedish key” appearance of the proximal femur and advanced carpal and tarsal bone age. Other characteristic hand changes include an extra ossification centre distal to the second metacarpal, delta phalanx, bifid distal phalanx of the thumb, and phalangeal dislocations (fig 1), but these typical features are only reported in a third of the patients.² The pathogenesis of Desbuquois dysplasia is unknown, but histological and transmission electron microscopy studies are suggestive of an impairment of the extracellular matrix. Indeed, analyses of bone specimens have shown enlarged chondrocytes in the reserve zone of the growth plate cartilage and decreased amounts of proteoglycans and collagens, with unusual grouping of banded collagen fibrils in the resting cartilage matrix.^{3,4}

Here, we report on the homozygosity mapping of a Desbuquois dysplasia gene in four inbred families of various ethnic origins (fig 2).

MATERIALS AND METHODS

Three out of the four families had been previously reported.^{2,3,5} Their main clinical and radiological features are summarised in table 1. All affected subjects fulfilled the criteria for Desbuquois dysplasia, namely short stature of prenatal onset, joint laxity, specific facial dysmorphism, a “Swedish key” appearance of the proximal femur, and advanced carpal and tarsal bone age. In order to guarantee homogeneity of the

Figure 1 (Left) AP radiograph of patient 1, family 1 at 4½ months of age showing bifid terminal phalanx of the first digit, unusual ossification at the base of this phalanx with an extra ossification centre close to both the distal portion of the second metacarpal and the proximal phalanx of that digit, accelerated carpal ossification, and phalangeal dislocations. (Right) AP radiograph of a Desbuquois dysplasia patient at 8 months of age showing a flat acetabular roof, two ossification centres for each of the capital femoral epiphyses, and “Swedish key” configuration of the proximal femora.

Figure 2 Pedigrees and haplotypes of families 1–4. Genetic distances between microsatellite polymorphic markers were ascertained from the Genethon map. Distances between markers from D17S1790 to D17S928 were 1.3 cM, 4.1 cM, 1.7 cM, 1.4 cM, 2.3 cM, 0 cM, and 11 cM. The orders of the microsatellite polymorphic markers were obtained from the Human Genome Working Draft database.

samples, only patients with Desbuquois dysplasia and typical hand anomalies were included in this study.

Informed consent and blood samples were obtained from all family members. Genomic DNA was purified from peripheral blood leucocytes according to standard techniques. Microsatellite DNA markers from the entire genome were used at an average spacing of 10 cM. For regions of interest, all samples were analysed with extra markers of the Génethon map using a single set of primers in each amplification reaction. The homozygosity mapping strategy was based on the assumption that affected subjects of the same kindred are homozygous by descent⁶ and two point linkage analyses using the MLink option of the LINKAGE package version 5.1 were performed.⁷ The disease gene frequency was set to 0.001 assuming an autosomal recessive mode of inheritance with complete penetrance. We took into account the inbreeding loops and allele frequencies were set according to the Genethon published figures.

RESULTS

The three affected subjects from families 1, 2, and 3 were initially tested and all three were homozygous for marker D17S784. Affected subjects from families 1 and 2 were also homozygous for contiguous markers at the

D17S928 locus. Pairwise linkage between polymorphic markers and the disease locus gave a cumulative maximum lod score of $Z=4.61$ at $\theta=0$ at the D17S1806 locus (table 2). An ancestral recombination event between loci D17S1847 and D17S802 in family 2 defined the proximal boundary of the genetic interval and another ancestral recombination event between loci D17S1806 and D17S1822 in family 4 defined the distal boundary of the genetic interval (9.5 cM, fig 2). No common founder haplotypes could be noted.

Nine genes were considered as possible candidate genes by their position, namely the STAT induced inhibitor-3 gene (*SSI-3*), the phosphatidylglycerophosphate synthase gene (*PGS1*), the dynein axonemal heavy polypeptide 17 gene (*DNAH17*), the Pleckstrin homology Sec 7 and coiled/coiled domains 1 gene (*PSCD1*), the human tissue inhibitor of metalloproteinases 2 gene (*TIMP2*), the C1q and tumour necrosis factor related protein 1 gene (*CIQTNF1*), the apyrase gene (*SHAPY*), the lectin, galactoside-binding, soluble, 3 binding protein gene (*LGAL3BP*), and the chromobox homologue 8 gene (*CBX8*). *TIMP2* was regarded as a good candidate gene by its function^{8,9} as the clinical features in Desbuquois dysplasia were consistent with a disorder of the extracellular matrix. Similarly, *CIQTNF1* was also considered as a candidate gene because of the

Table 1 Clinical and radiographic features of four Desbuquois dysplasia patients

	Patient 1, family 1	Patient 2, family 2	Patient 3, family 3	Patient 4, family 4
Previous report	Le Merrer <i>et al</i> ^a , case 1	Not reported	Al-Gazali <i>et al</i> ^a	Gillissen-Kaesbach <i>et al</i> ^a , case 3
Origin	French	Sri-Lanka	United Arab Emirates	Morocco
Sex	M	M	M	M
Parental consanguinity	+	+	+	+
Early death	–	+	–	+
Birth length	43 cm	34 cm	?	37 cm
Facial dysmorphism	+	+	+	+
Joint laxity	+	+	+	+
Dislocated joints	+	+	+	+
Mental retardation	–	?	?	+
Visceral malformations	–	Atrial septal defect	–	–
"Swedish key"	+	+	+	+
Advanced carpal/tarsal bone age	+	+	+	+
Typical hand anomalies	+	+	+	+

?: unknown.

Table 2 Two point lod scores for linkage of a Desbuquois dysplasia locus to chromosome 17q25.3

Loci	Distance*	Recombination fraction of					Zmax	θ
		0.00	0.05	0.10	0.20	0.30		
D17S1847	1.7	2.51	2.16	1.82	1.22	0.72	2.51	0.00
D17S836	1.4	2.61	2.23	1.86	1.17	0.62	2.61	0.00
D17S1806	2.3	4.61	4.01	3.41	2.26	1.27	4.61	0.00
D17S1822		0.82	2.02	1.86	1.31	0.72	2.02	0.05

*The distance is given in centimorgans according to the Généthon map.

presence of a collagenic domain and its expression in bone and cartilage. Direct sequencing on genomic DNA in *TIMP2* and *CIQTNF1* failed to detect any deleterious mutations in the patients (data not shown).

DISCUSSION

It is currently unknown whether Desbuquois dysplasia with and without typical hand anomalies is a homogeneous condition. Analysis of rare pairs of sibs showed homogeneity with respect to radiographic features of the hands.^{1,4,10} For these reasons, only patients with typical hand anomalies were included in this study. Nevertheless, it would be of great interest to test patients with no typical hand anomalies to investigate the genetic homogeneity of the condition further.

In conclusion, this study shows that the Desbuquois dysplasia gene maps to chromosome 17q25.3 and supports the genetic homogeneity of the clinical subtype with hand anomalies. Ongoing studies will hopefully identify the disease gene and help to elucidate the pathogenesis of Desbuquois dysplasia.

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