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 specific 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. 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. 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. 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 dysmorphisms, a “Swedish key” appearance of the proximal femur, and advanced carpal and tarsal bone age. In order to guarantee homogeneity of the

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**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.
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 Généthon 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 descent and two point linkage analyses using the MLink option of the LINKAGE package version 5.1 were performed. 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 D17S928. 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 candidates 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/coil domains 1 gene (PSCD1), the human tissue inhibitor of metalloproteinases 2 gene (TIMP2), the C1q and tumour necrosis factor related protein 1 gene (C1QTNF1), 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 as the clinical features in Desbuquois dysplasia were consistent with a disorder of the extracellular matrix. Similarly, C1QTNF1 was also considered as a candidate gene because of the
presence of a collagenic domain and its expression in bone and cartilage. Direct sequencing on genomic DNA in TIMP2 and C1QTNF1 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.1-5 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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**REFERENCES**


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

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