Isolated autosomal dominant type E brachydactyly: exclusion of linkage to candidate regions 2q37 and 20q13

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Abstract

Type E brachydactyly is a digital malformation which characteristically causes an asymmetrical shortening of one or more metacarpals or metatarsals or both. Although commonly seen as part of a syndrome, it can be inherited as an autosomal dominant characteristic, the gene acting with variable expressivity, but complete penetrance. As an Albright hereditary osteodystrophy (AHO)-like syndrome including brachydactyly type E and mental retardation may be caused by (micro) deletions at chromosome 2q37, this region together with the AHO locus at chromosome 20q13 were considered as

candidate loci for brachydactyly type E. In this paper we describe a family with isolated autosomal dominant type E brachydactyly in whom molecular analysis excludes linkage to these regions, providing support for further genetic heterogeneity of this trait.

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Key words: brachydactyly type E; Albright hereditary osteodystrophy; Gsα gene.

The brachydactylies are a heterogeneous group of digital anomalies classified by Bell in 1951.¹ Bell reviewed 124 pedigrees containing 1336

Figure 1 Brailsford's original family with autosomal dominant brachydactyly type E, pedigree updated 1995.

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Table 1 Summary of clinical features described

Subject	Metacarpal shortening		Metatarsal shortening	
	Left hand	Right hand	Left foot	Right foot
IV.2	3, 4	3, 4	1, 4	1, 4
IV.3	3	3	1, 4	1, 4
V.1	3	3	3, 4	3, 4
V.3	3	3	1, 4	1
V.5	3, 4	3	3, 4, 5	4, 5

people with this malformation and on anatomical grounds defined seven clear groups. Type E brachydactyly is distinguished by shortening of one or more of the metacarpals or metatarsals or both. A striking feature is the common lack of symmetry and lack of shortening of corresponding bones of the hands and feet, together with intrafamilial variation. At that time Bell¹ also recognised that this type of brachydactyly was heterogeneous, featuring in several genetic conditions (notably Turner syndrome and Albright hereditary osteodystrophy) in addition to being inherited as a distinct autosomal dominant characteristic. In 1995, chromosome 2q37 was suggested as a candidate region for type E brachydactyly,² based on the presence of (micro)deletions in five patients with short metacarpals, mental retardation, and other dysmorphic features similar to that observed in Albright hereditary osteodystrophy, which is caused by mutations

in the *Gsα* gene located on chromosome 20q13.³⁻⁵ The purpose of this study was to evaluate these chromosomal loci as possible candidate regions for familial brachydactyly type E, and in particular to assess whether microdeletions on chromosome 2q37 might represent a contiguous gene syndrome involving a gene for brachydactyly type E.² Molecular analysis was therefore performed in eight members of a family with autosomal dominant brachydactyly type E using six microsatellite markers and a single VNTR on chromosome 2q37, together with three markers on chromosome 20q13.

Patients, materials, and methods

We recontacted surviving members of a brachydactyly type E family originally described by Brailsford⁶ (fig 1). The clinical features of those with the characteristic are summarised in table 1. Hand x rays of IV.3 showing bilateral shortening of the third metacarpals and x rays of the feet showing bilateral shortening of the first and fourth metatarsals are shown in fig 2. Other congenital malformations, short stature, and mental retardation were not observed.

DNA STUDIES

Genomic DNA was isolated from peripheral leucocytes using standard methods. Genotypes

Figure 2 X rays of hands and feet of IV.3.

Figure 3 Chromosome 20q13 haplotype data.

for chromosome 20 markers were determined using an endonuclease restriction site polymorphism (*FokI*) in exon 5 of *Gsα*,³⁷ a dinucleotide repeat in intron 3 of the same gene,⁸ and a highly polymorphic tetranucleotide repeat (D20S93) which maps to a maximum distance of 4 cM distal to the *Gsα* gene.⁹ PCR amplification of D20S93 was performed in the buffer described by Wilson *et al*² for 23 cycles at an annealing temperature of 62°C. The dinucleotide repeat markers D2S125, D2S395, D2S345, D2S336, and D2S338 were PCR amplified in the presence of [α^{32} P]-dCTP at annealing temperatures of 55°C, 62°C, 60°C, 60°C, and 60°C respectively. The first four markers were amplified in the same buffer as that used in the D20S93 study while marker D2S338 was amplified in the buffer used for exon 5 amplification in the presence of 1 mmol/l MgCl₂. The PCR products of a further marker, D2S140, were radiolabelled using a reverse primer end labelled with [γ^{32} P]-ATP in a reaction with the D20S93 buffer at an annealing temperature of 56°C. All PCR reactions were performed for 23 cycles, subjected to electrophoresis on 6% denaturing polyacrylamide

gels, and visualised by autoradiography.¹⁰ The primer sequences were described by Gyapay *et al*.¹¹ The genotypes for the VNTR D2S90 were determined as previously described by Wilson *et al*.²

Results

The family analysed in this study contained six people with classical type E brachydactyly. The results of the chromosome 20q13 study are summarised in fig 3. The family was uninformative for both polymorphisms in *Gsα* and fully informative for the flanking marker D20S93. Direct inspection showed that no common haplotypes are shared by all affected people and the data therefore exclude the *Gsα* gene in the development of the brachydactyly E phenotype in this family. The genotypes for each marker on terminal chromosome 2q were determined and haplotypes inferred (fig 4). Inspection failed to show a common haplotype shared by all affected subjects, excluding linkage of autosomal dominant brachydactyly type E in this family to this region of the genome. Two point linkage analysis of disease locus against each marker at 2q confirmed the absence of linkage for all markers using MLINK, with exclusion ($\text{lod} \leq -2$) to recombination fractions (θ) of 0.15 or more (data not shown).

Discussion

We chose to study two candidate loci because of the known association of brachydactyly type E with Albright hereditary osteodystrophy, caused by mutations in the *Gsα* gene on chromosome 20q13 and an AHO-like syndrome recently defined by (micro)deletions at chromosome 2q37, which could be a contiguous gene defect involving a locus for brachydactyly type E.² These results show no evidence of linkage to these two regions of the genome and give no evidence of support for a contiguous gene defect in the AHO-like syndrome. Other syndromes featuring brachydactyly type E include Biemond syndrome I and Ruvalcaba syndrome and their localisation will enable further candidate loci for familial isolated brachydactyly type E to be considered. In addition, homeobox containing genes and genes encoding growth factors, both classes of genes implicated in the control of distal limb development, should be considered. Indeed the genes *HOXD*, *MSX1*, *MSX2*, *FGF-1*, and *FGF-2* have recently been excluded in two families with type A1 brachydactyly.¹² These genes should clearly be considered in other subtypes of brachydactyly.

The first two authors contributed equally to this work.

- 1 Bell J. *The treasury of human inheritance*. Volume V. On hereditary digital anomalies. Part I. On brachydactyly and symphalangism. Cambridge: Cambridge University Press, 1951.
- 2 Wilson LC, Leverton K, Oude Luttikhuis MEM, *et al*. Brachydactyly and mental retardation: an Albright hereditary osteodystrophy-like syndrome localised to 2q37. *Am J Hum Genet* 1995;56:400-7.
- 3 Wilson LC, Oude Luttikhuis MEM, Clayton PT, Fraser WD, Trembath RC. Parental origin of *Gsα* gene mutations in Albright's hereditary osteodystrophy. *J Med Genet* 1994; 31:835-9.