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ORIGINAL INVESTIGATION

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Linkage studies in a kindred from Oklahoma, with familial benign (hypocalciuric) hypercalcaemia (FBH) and developmental elevations in serum parathyroid hormone levels, indicate a third locus for FBH

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Abstract A five-generation kindred (19 affected, two obligate carriers and 20 unaffected) from Oklahoma USA, in which familial benign (hypocalciuric) hypercalcaemia (FBH) was associated with a developmental elevation in serum parathyroid hormone (PTH) levels, has been investigated for linkage to the candidate chromosomal regions 3q21–q24 and 19p13.3, 11q13, and 11p15, to which the genes for FBH, multiple endocrine neoplasia type 1 (MEN1) and PTH have been mapped respectively. By means of 17 polymorphic markers from these regions, linkage was excluded [LOD scores < -2.00 at $(\theta) = 0.05$–0.25]. In addition, an analysis of multipoint crossovers and use of the LINKMAP program confirmed the exclusion from these regions. Thus, this form of FBH, designated the Oklahoma variant $FBH_{(Ok)}$, is not linked to markers that segregate with FBH, MEN1 and PTH; our results indicate further genetic heterogeneity and the presence of a third locus for FBH.

Introduction

Familial benign hypercalcaemia (FBH), which is also referred to as familial hypocalciuric hypercalcaemia (FHH), is a heritable disorder (MIM 145980, McKusick 1990) of mineral metabolism that is transmitted as an autosomal dominant trait with a high degree of penetrance (Marx et al. 1981; Law and Heath 1985). FBH is biochemically characterised by a life-long elevation of serum calcium concentrations in association with an inappropriately low urinary calcium excretion and usually a normal circulating parathyroid hormone (PTH) concentration (Menko et al. 1983). Hypermagnesaemia is also typically present (Marx et al. 1981). The disorder is considered to be benign, as patients with FBH are usually asymptomatic. However, an increased prevalence of chondrocalcinosis and pancreatitis has been reported in heterozygotes and neonatal severe primary hyperparathyroidism (NSHPT) occurs in homozygotes (Marx et al. 1982). Investigation of a five-generation kindred from Oklahoma has documented the occurrence of developmental elevations in serum PTH concentrations in association with FBH and this may give rise to difficulties in distinguishing this disorder from familial primary hyperparathyroidism (McMurtry et al. 1992). Some affected adults in the Oklahoma FBH kindred also suffer from hypophosphataemia and osteomalacia; all of these novel findings appear to represent an unusual variant of this disorder of mineral homeostasis, which we designate $FBH_{(Ok)}$. Thus, there seems to be clinical heterogeneity in FBH and family linkage studies have revealed that there is also genetic heterogeneity with one FBH locus on chromosome 3q21–q24 and another on 19p13.3. We have explored this heterogeneity by performing linkage studies with 17 genetic markers from candidate chromosomal regions 3q21–3q24 and 19p13.2–19p13.3, 11q13 and 11p15, to which the genes for FBH (Chou et al. 1992; Heath et al. 1993), multiple endocrine neoplasia type 1 (MEN1) (Larsson et al. 1988; Thakker et al. 1989) and PTH (Naylor et al. 1983) have been respectively mapped.

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Materials and methods

Patients

Venous blood was collected in tubes containing EDTA from 42 members (Fig. 1) from five generations of the previously described kindred with autosomal dominant FBH and developmental increases

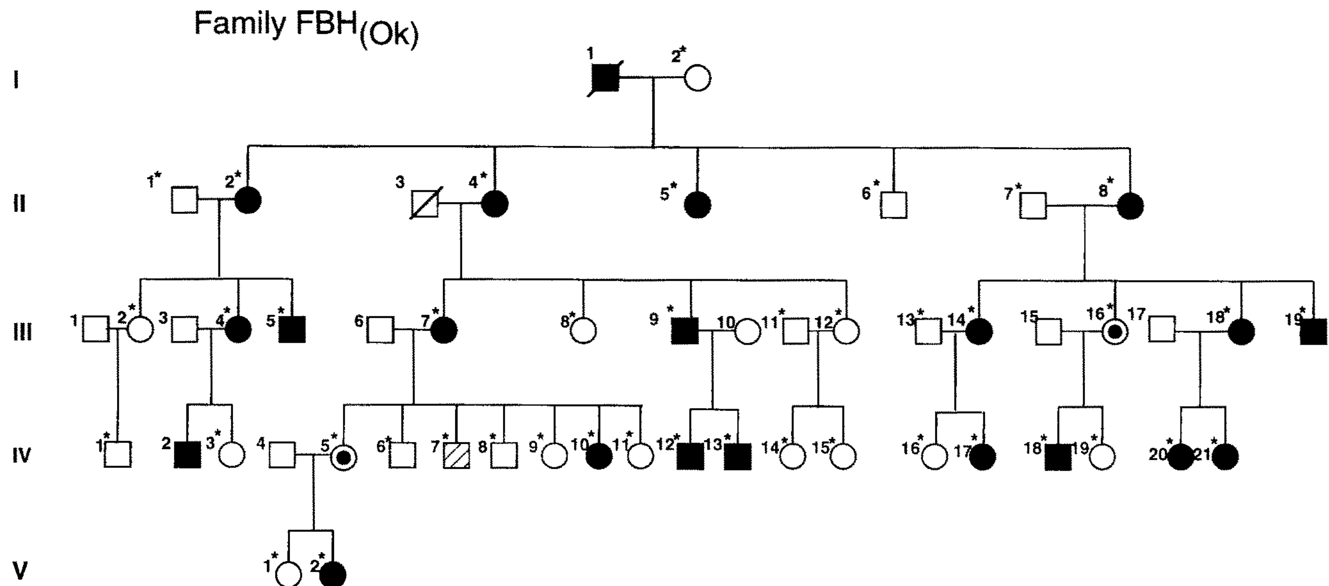


Fig. 1 Pedigree of the family with $FBH_{(Ok)}$. □ Unaffected male, ○ unaffected female, ■ affected male, ● affected female, ◉ obligate heterozygote. Individual IV.7, who suffered from idiopathic hypoparathyroidism and in whom analysis at the FBH locus was excluded, is represented as ▨. *Asterisk*, Individuals from whom blood samples were available. The two affected boys IV.12 and IV.13 are sons of an affected father (III.9), indicating male to male transmission

in serum PTH levels (McMurtry et al. 1992), and sent by express air courier from Forth Smith, Arkansas to London, UK for processing and analysis. The phenotype of FBH in these family members had been established by the finding of hypercalcaemia associated with a low ratio (< 0.010) of calcium clearance to creatinine clearance (CaCl/CrCl). Supranormal concentrations of serum PTH had been observed in patients who were above the age of 30 years (II.2, II.4, II.5, II.8 and III.7). Three adults (II.4, II.8 and III.4) who were over the age of 40 years also had evidence of osteomalacia. Individual IV.7, who suffered from idiopathic hypoparathyroidism, was excluded from the analysis at the FBH locus, and the women III.16 and IV.5 who had none of the biochemical abnormalities for FBH, but who had children affected with FBH, were considered to be obligate gene carriers. Thus, the 41 family members included for genetic analysis of the FBH locus were: 19 affected, two obligate carriers and 20 unaffected individuals.

Genetic markers

Leukocyte DNA was prepared from the venous blood samples by standard methods (Thakker et al. 1990) and used to detect restriction fragment length polymorphisms (RFLPs) and polymorphisms in microsatellite tandem repeats as previously described (Scheinman et al. 1993; Thakker et al. 1993). The DNA probes, viz. PCCB from chromosome 3q21–3q24 (Lamoneh et al. 1986), PTH from chromosome 11p15 (Schmidtke et al. 1984), D11S97 from chromosome 11q13 (Williamson et al. 1991) and D19S20 from chromosome 19p13.3 (Nakamura et al. 1989), were used to detect RFLPs as described (Thakker et al. 1990). The microsatellite polymorphisms were detected using the polymerase chain reaction (PCR) and flanking oligonucleotide primers as described for the loci D3S1215 (Hudson et al. 1992), ACPP (Polymeropoulos et al. 1991), RHO (Farrar et al. 1990), D3S47 (Donis-Keller et al. 1987), D3S196 from 3q21–3q24 (Weber et al. 1990), PTH from 11p15 (Parkinson et al. 1993), CNTF (Lev et al. 1993), D11S480, (Moffatt 1993), PYGM (Iwasaki et al. 1992), INT2 (Polymeropoulos et al. 1990), D11S533 from chromosome 11q13 (Eubanks et al. 1991), and D19S177 (Weissenbach et al. 1992), D19S216 (Weissenbach et al. 1992) and EPOR (GDB) from chromosome 19p13.2–19p13.3.

Linkage analysis

Conventional two-point LOD scores and multipoint location scores were calculated using the LINKAGE computer programs, version 5.1, on a 64-megabyte RAM Sun 4–90 computer running Sun 0S4.1.1 as described (Thakker et al. 1990; Scheinman et al. 1993). The fixed order of loci and the genetic distances between the respective intervals required for multilocus linkage analysis were deduced from published work. The order of loci for chromosome 3q21–3q24 was taken as 3cen–D3S1215–RHO–ACPP–D3S47–PCCB–D3S196–3qter (Chou et al. 1992; NIH/CEPH Collaborative Mapping Group 1992), for chromosome 11q13 as 11cen–CNTF–D11S480–PYGM–D11S97–INT2–D11S533–11qter (Thakker et al. 1993; Pang et al. 1993) and for 19p13.2–19p13.3 as 19pter–D19S20–D19S216–D19S177–EPOR–19cen (NIH/CEPH Collaborative Mapping Group 1992). The frequency of FBH and penetrance were taken as 10^{-4} and 90%, respectively; varying these values had no significant effect on the results of linkage analysis.

Results

Following the report of FBH in the five-generation kindred from Oklahoma (McMurtry et al. 1992), an additional two boys, aged 4.5 and 3 years, were observed to have FBH. These individuals (IV.12 and IV.13 in Fig. 1), are the sons of an affected father (III.9). Thus, there is male to male transmission and autosomal inheritance of $FBH_{(Ok)}$.

Simulated LOD scores were calculated, using MLINK, for linkage between $FBH_{(Ok)}$ and a four-allele genetic marker. The penetrance of the mutant gene was varied and three separate linkage analyses were performed using a gene penetrance of 100%, of 90%, and by excluding all unaffected family members by assigning them unknown phenotypes, thereby eliminating these individuals from analysis at the disease locus but allowing their genetic marker data to be used for deduction of haplotypes. The $FBH_{(Ok)}$ family (Fig. 1) was found to contain sufficient

Table 1 Two-point linkage analysis at different recombination fractions

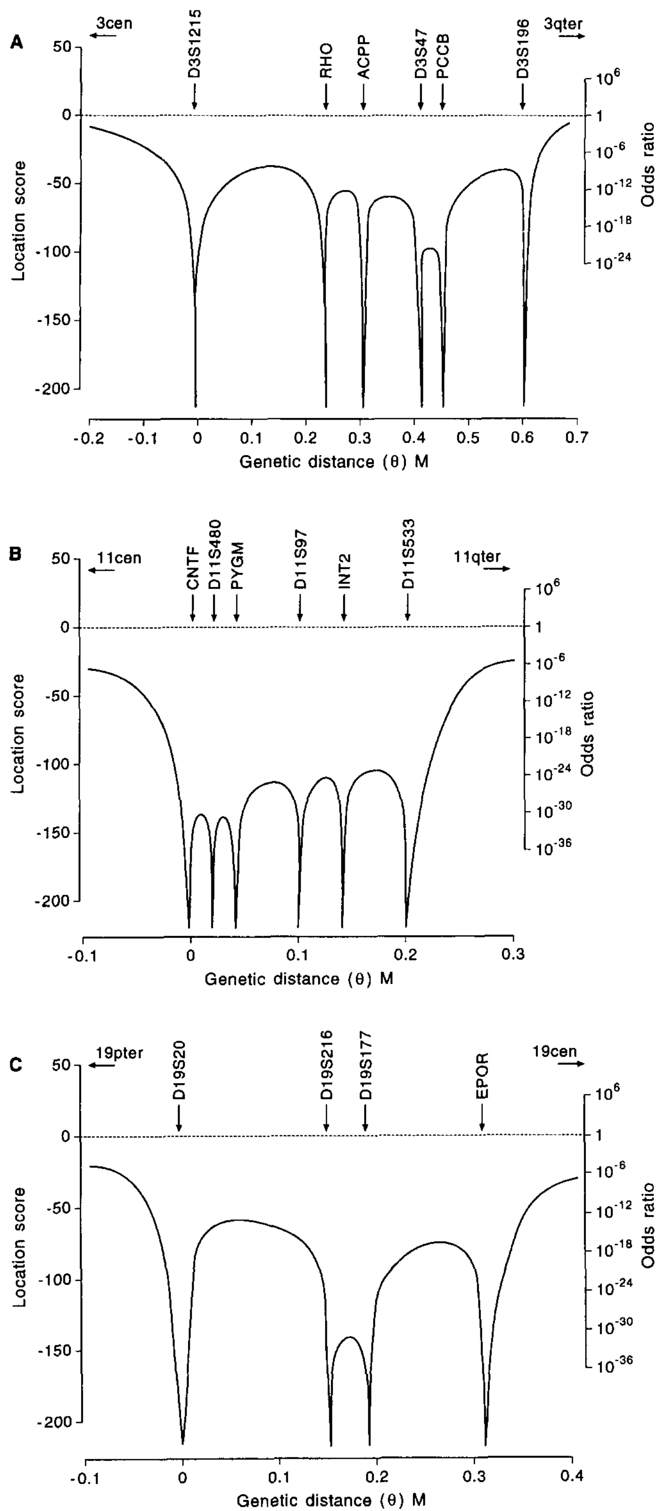
Chromosome	LOD scores Z (θ)							
	Locus	Z(0.001)	Z(0.01)	Z(0.05)	Z(0.10)	Z(0.20)	Z(0.30)	Z(0.40)
3cen-3q24								
	D3S1215	–21.83	–13.76	–7.44	–4.72	–2.18	–0.92	–0.26
	RHO	–10.60	–6.58	–3.74	–2.50	–1.30	–0.65	–0.53
	ACPP	–10.30	–7.20	–4.22	–2.83	–1.42	–0.67	–0.23
	D3S47	–18.51	–11.73	–6.21	–3.87	–1.71	–0.67	–0.15
	PCCB	–23.57	–15.61	–8.86	–5.80	–2.80	–1.26	–0.40
	D3S196	–16.27	–9.24	–4.29	–2.24	–0.50	0.13	0.24
11p15								
	PTH	–6.38	–4.21	–2.30	–1.36	–0.45	–0.05	0.07
11q13								
	CNTF	–13.26	–8.25	–4.58	–2.93	–1.32	–0.50	–0.10
	D11S480	–11.81	–6.81	–3.20	–1.68	–0.36	0.13	0.21
	PYGM	–27.83	–17.74	–10.31	–6.95	–3.58	–1.76	–0.65
	D11S97	–23.82	–14.75	–8.12	–5.18	–2.37	–0.99	–0.28
	INT2	–17.55	–11.21	–6.32	–4.11	–2.00	–0.93	–0.33
	D11S533	–23.17	–14.94	–8.15	–5.10	–2.21	–0.82	–0.15
19p13.2-19p13.3								
	D19S20	–23.28	–14.54	–8.18	–5.42	–2.75	–1.34	–0.49
	D19S216	–23.55	–15.39	–9.14	–6.13	–3.10	–1.49	–0.54
	D19S177	–31.00	–19.02	–10.57	–6.96	–3.50	–1.69	–0.61
	EPOR	–21.38	–13.31	–7.52	–4.98	–2.54	–1.27	–0.49

scorable meioses to establish linkage, at the above three-gene penetrances with respective peak LOD scores ranging from 9.03 to 3.02 (θ = 0.00–0.20), 8.58 to 3.30 (θ = 0.00–0.20), and 5.42 to 3.72 (θ = 0.00–0.05).

The family proved informative for all 17 genetic markers and the results of two-point linkage analysis at different recombination fractions are shown for each marker in Table 1. Linkage between FBH and each of these 17 genetic markers was excluded by demonstrating LOD scores of < -2 within a 10cM interval. This exclusion of $FBH_{(Ok)}$ from the chromosomal regions 3q21–3q24 and 19p13.2–19p13.3, 11q13, and 11p15 was further demonstrated by an examination of multipoint crossovers. An analysis of individual haplotypes obtained for each of these chromosomal regions demonstrated an independent segregation of $FBH_{(Ok)}$ (data not shown); this exclusion was quantitatively assessed using the LINKMAP program. The location curves obtained for chromosomes 3q21–3q24, 11q13 and 19p13.2–19p13.3 using an $FBH_{(Ok)}$ gene penetrance of 90% are shown in Fig. 2. A location of the $FBH_{(Ok)}$ gene in each of these regions was excluded with significant negative location scores ranging from –40 to –118 for loci from chromosome 3q21–3q24, with respective odds ratios of 2.1×10^{-9} to 2.4×10^{-26}, –105 to –138 for loci from 11q13, with respective odds ratios of 1.6×10^{-23} to 1.1×10^{-30}, and –58 to –140 for loci from chromosome 19p13.2–19p13.3, with respective odds ratios of 2.5×10^{-13} to 4.0×10^{-31}. Varying the penetrance of the mutant gene had no significant effect on these results. For example, an analysis with all the unaffected family members excluded yielded significant negative location scores ranging from –36 to –96 for loci from chromosome 3q21–3q24, with respective odds ratios of 1.5×10^{-8} to 1.4×10^{-21}, –97 to –129 for loci from 11q13, with respective odds ratios of 8.6×10^{-22} to 9.7×10^{-29}, and –58 to –129 for loci from chromosome 19p13.2–19p13.3, with respective odds ratios of 2.5×10^{-13} to 9.7×10^{-29}. Thus, the gene causing $FBH_{(Ok)}$ has been excluded from the chromosomal regions 3q21–3q24, 19p13.2–19p13.3, 11q13 and 11p15; our results, which demonstrate further genetic heterogeneity, indicate that there is a third FBH locus.

Discussion

Our linkage study of $FBH_{(Ok)}$ using 17 polymorphic genetic markers has excluded linkage between $FBH_{(Ok)}$ and the chromosomal regions 3q21–3q24, and 19p13.2–19p13.3 to which genes causing FBH have previously been mapped (Chou et al. 1992; Heath et al. 1993). Two point LOD scores of < -2 were obtained between $FBH_{(Ok)}$ and each of the genetic markers, and linkage was excluded to a distance of at least 10cM from each locus. These exclusions were confirmed by multipoint analyses that revealed independent segregation of $FBH_{(Ok)}$ and each of these candidate regions, with an odds ratio of more than 6.7×10^{7} against linkage. These results indicate further heterogeneity in FBH and the presence of a third locus that we propose to designate $FBH_{(Ok)}$ for the Oklahoma variant of this disorder. In addition, linkage has also been excluded between $FBH_{(Ok)}$ and candidate chromosomal regions 11q13 and 11p15 to which MEN1 (Larsson et al. 1988;



◀ **Fig. 2** Location scores of FBH$_{(Ok)}$ versus chromosomal regions 3q21–3q24 *(panel A)*, 11q13 *(panel B)* and 19p13.2–19p13.3 *(panel C)*. The *horizontal axis* is the genetic distance in Morgans and an arbitrary centromeric or telomeric locus on each of the chromosomal segments analysed was selected as the *origin*. The genetic distances for multilocus analysis were calculated as described previously (Thakker et al. 1990) by converting the published recombination frequencies (θ) to genetic distances *(d)* with Haldane's mapping function, $d = -0.5\ ln\ (1-2\theta)$, which assumes no interference. The *right vertical axis* is the odds ratio for the location of FBH$_{(Ok)}$ at a given distance compared with a location of FBH$_{(Ok)}$ at an infinite distance from the markers in each of the chromosomal regions. The *left axis* is the location score, defined as twice the natural logarithm of the odds ratio. FBH$_{(Ok)}$ was excluded form each of these chromosomal regions

Thakker et al. 1989) and PTH (Naylor et al. 1983) have been localised, respectively.

Our findings of further heterogeneity in the FBH disorders indicates that there may be a family of causal genes, for example, of the G-protein-coupled parathyroid calcium-sensing receptors, e.g. PCaR1 (Brown et al. 1993). Heterozygosity for PCaR1 mutations at 3q21–q24 has been established in FBH kindreds (Pollak et al. 1993; Pearce et al. 1994; Heath et al. 1994) and homozygosity for a mutation of PCaR1 has been reported in one child with NSHPT (Pollak et al. 1994). The PCaR1 belongs to the group of G-protein-coupled cell-surface receptors that may regulate PTH secretion through a phospholipase C dependent pathway (Brown et al. 1993; Pollak et al. 1993). By homology with the other families of G-protein-coupled receptor genes, e.g. the melanocortin receptor genes (Mountjoy et al. 1992), it is likely that a family of such calcium-sensing receptor genes exists. Thus, the genes for FBH$_{19p}$ and FBH$_{(Ok)}$ may be members of this family of genes and the heterogeneity observed in FBH may reflect aberrations in this gene family. Characterisation of the genes causing the FBH disorders should help to elucidate the roles of these important regulators of calcium homeostasis.

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