DA5 (5'-GATCCGTATCCCAGGCCTGC-3'), a 0·9 kb fragment was amplified from the genomic DNA, which carried the intronic sequence between cDNA nucleotide positions 1234 and 1235 (data not shown). Cleavage by *Sac*I of the PCR product from normal genomic DNA yielded a 54 bp shorter fragment than the untreated one (fig 2). The 54 bp fragment was not detectable on the gel system used. In the study of genomic DNA from the family members, the fragments from patients 1 and 2 were not digested with *Sac*I, whereas cleaved bands were observed for the father and a second unaffected sib as well as normal subjects (fig 2). Half the PCR product from the mother was digested with *Sac*I, indicating carriage of the mutation by one of the alleles. The *Sac*I restriction site was present in the DNA from all of 10 unrelated Japanese females (20 alleles) investigated (data not shown). Cosegregation of the mutation with the disease provides evidence that it is directly causative. The present approach clearly offers advantage for carrier detection and prenatal diagnosis.

The affected leucine is within the SH2 domain of Btk and is highly conserved in the SH2 domains of other non-receptor tyrosine kinases.[7] SH2 domains have been shown to bind tyrosine phosphorylated ligands.[8] While the mutation of the highly conserved leucine would therefore be expected to affect the conformation or function of Btk, further analysis of the protein is required before such a conclusion can be definitely drawn. While heterogeneous mutations of the btk gene have been found in XLA patients,[2 9 10] the three previously reported missense mutations resulting in Arg-288 to Trp, Arg-307 to Gly,[11] and Tyr-361 to Cys[12] within the SH2 domain, the mutation in our patient is a new missense mutation within the SH2 domain.

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Exclusion of retinoic acid receptor and a cartilage matrix protein in non-syndromic CL(P) families

We read with interest the report of Vintiner *et al*[1] excluding linkage to RARA (17q21), F13A1 (6p24-25), and CRTL1 (5q15) loci in eight multigeneration white families with autosomal dominant non-syndromic cleft lip with or without cleft palate (CL(P)). These candidate genes were chosen on the basis of their mapping close to translocations with associated syndromes which include CL(P), proximity to loci known to cause syndromes which include CL(P), and from previously published association and linkage studies.[1]

We have also tested linkage to the same loci in ten non-syndromic CL(P) white families at these same loci, and can confirm the reported exclusions.[1] The *Pst* RFLP in RARA was tested using Southern gel and Genius non-radioactive techniques.[2] Tightly linked flanking short tandem repeat PCR markers at the RARA locus, Thra1, Mfd188 (D17S579), D17S800, and Hox2B and CRTL were amplified and separated on 8% sequencing gels,[2] and visualised by silver staining using the GELCODE® system.[3] Linkage was tested by using MLINK and LIPED, assuming a dominant mode of inheritance for CL(P) with a penetrance of 0·32 in males and 0·24 in females and with a 0·001 allele frequency.[4]

The lod scores at $\theta = 0$ were 1·14, −9·57, −9·72, −8·87, and −2·49 for RARA, Thra1, D17S579, D17S800, and Hox2B, respectively. The summed lod scores are shown in the table. Although RARA showed a small positive lod score, the families were generally uninformative. However, haplotype analysis of flanking markers (Thra1, RARA, D17S800) excludes this region in these multigenerational families. Hox2B was tested as a candidate gene for clefting and was excluded. We have also tested linkage to the CRTL1 locus and the lod score of −2·1 at $\theta = 0·1$ also excluded this gene. We have previously reported exclusion of the F13A1 locus and the entire region spanning from F13A1 to TCTE, which included the HLA region.[3]

Our findings and those of Vintiner *et al*[1] suggest that RARA, CRTL1, and F13A1 do not have a major causal role in the aetiology of CL(P) in the 18 families tested. However, as previously suggested, we can not distinguish whether RARA plays a modifying role in the aetiology of CL(P).[5]

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Further report of a patient with humeroradioulnar synostosis and hydronephrosis

A case of humeroradioulnar synostosis with lambdoid synostosis was published recently in this journal.[1] We report on a male baby with clinical and skeletal abnormalities very similar to those previously reported.[1–4]

The proband was the first child of young and healthy non-consanguineous parents. He was born at term following caesarean section because of cephalopelvic disproportion. Birth weight and length were 3490 g and 51 cm, respectively. Apart from the upper limb defects and a midline capillary haemangioma, no other abnormality was found on physical examination.

At 11 months he measured 73·5 cm (50th centile), head circumference was 47 cm (50th centile), and weight was 8300 g (10th centile). Psychomotor development has been normal. Both upper limbs were short, the left one more malformed than the right. Both shoulders had normal range of movement. The left upper limb was shorter than the right and kept in a fixed position; there were two digits joined

Lod scores for CLP v chromosome 17 markers and in CL(P) families

	Recombination fraction (θ)						
Marker	*0·00*	*0·001*	*0·01*	*0·05*	*0·10*	*0·20*	*0·30*
Thral	−9·57	−9·12	−7·47	−4·61	−2·80	−1·33	−0·63
RARA	1·14	1·14	1·09	0·90	0·69	0·37	0·16
D17S579	−16·35	−14·11	−9·38	−4·80	−2·85	−1·25	−0·57
D17S800	−8·87	−7·01	−3·76	−1·25	−0·33	0·31	0·43
Hox2b	−2·49	−2·27	−1·29	−0·06	0·38	0·53	0·39