PKD3—to be or not to be?

Sir,

In the March 1999 issue of *NDT*, de Almeida and colleagues [1] followed up a previous report of a family which they have described to be unlinked to either *PKD1* or *PKD2* [2]. We have shown elsewhere that multiple inter-marker recombination events are necessary on certain *PKD1* haplotypes in this family [3]. These findings raise the possibility that genotyping errors or sample mix-up may lead to the apparent absence of linkage to the two known loci as observed. In conclusion, it is unclear at present whether this family is truly unlinked to *PKD1* or *PKD2*. The interpretation of the phenotypic findings of this family as due to a third gene for ADPKD is therefore premature.

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Reply

Sir,

Drs Paterson and Pei published a few months ago a comment where the existence of a third genetic locus for autosomal dominant polycystic kidney disease was questioned [1]; while small number of patients and only two *PKD1* markers are pointed to question the conclusion in other families, in the family we reported [2], which is large and several markers were tested, sample mix-up or genotyping error is invoked to explain four inter-marker recombination events between two markers 9 cM apart in one patient. We agree with Dr Paterson in the assumption that four inter-marker recombination between 3'HVR and SM7 is rare and, therefore, some mistake has occurred. Our first suspicion was a misinterpretation of the Southern blots when using 3'HVR, 2BP5 or 218EP6 probes. Actually when we performed the *XmnI* blots using probe 2BP5 we observed a yet unknown allele, 27 Kb long; as we believed that this allele had not described before, this finding was submitted to *Nucleic Acids Research*, in 1999. Careful inspection of the blots revealed that this extra allele probably resulted from incomplete *XmnI* digestion. Therefore, subject II-20 in the pedigree, should be homozygous with respect to allele 1; her son, III-33, and her daughter, III-37, inherited allele 2 from their affected father and allele 1 from their mother. Redrawing the pedigree with the new information, only two recombination events are found, and one of them (between HBPA1 and 3'HVR), has occurred within a recognized recombination hot spot [3].

However, the exclusion of linkage to *PKD1* does not depend on the genotyping of this particular patient; in fact, there are several reasons why we believe that this family is unlinked to *PKD1*. First, when genetic studies in this family started in 1991, Dr Peter Harris (personal communication), from Oxford, was the first to suggest that this family was unlinked to *PKD1* based on the observation of the segregation of 3'HVR, SM7 and SM6 polymorphisms. Second, simple inspection of the haplotype segregation in this family, e.g. between the twins (II:19 and II:17), is clearly compatible with absence of linkage. In fact, a rather different haplotype is segregated by subjects II:17 and II:19, to the next generation (Figure 1 p. 2966).

It is our purpose to retype all the family in order to confirm our analysis; as scientists we are open to any suggestions and able to collaborate with any group, in order to find a definitive answer to this question.

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Fig. 1. Partial pedigree of a non-PKD1/non-PKD2 family showing that a different haplotype is segregated to the next generation by subjects II:17 and II:19, who are dizygotic twins, consistent with an absence of linkage to PKD1. 2BP5 alleles were corrected according to new information (see text for details). Reproduced with permission from Human Genetics [2].