excluded[6] and a recessive family in whom no linkage analysis had been undertaken.[15]

We agree with Shastry and Trese in that the variable phenotype observed in FEVR patients could well be due to modifying genes at other loci as well as environmental effects. However, to prove such a link, evidence must be presented showing that individuals containing two mutant alleles consistently have a different phenotype (either more severe or milder) than those with only one. The results presented by Shastry and Trese are interesting but anecdotal, since they provide no statistically significant evidence that factor V Leiden has an effect on the FEVR phenotype. We understand that the authors have very carefully worded their discussion so that they do not actually come to any conclusions about their finding and only suggest possibilities, but the fact that this cosegregation could be simply due to chance is not discussed. Indeed, the authors state that 'the cosegregation of unlinked genes in such a small family is statistically unlikely'. As we have shown, this statement is not supported by the data these authors presented. Furthermore, the lack of Leiden mutations in our FEVR patient cohort suggests that the factor V Leiden does not play a significant role in FEVR severity and that further studies are needed to dissect out the complexities of the variable phenotypes observed in FEVR patients.

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Helen M Bottomley[1], Louise M Downey[1], Chris F Inglehearn[1] and Carmel Toomes*[,1]
[1]*Molecular Medicine Unit, School of Medicine, University of Leeds, UK*

**Correspondence: Dr C Toomes, Molecular Medicine Unit, Clinical Sciences Building, Level 6, St. James's University Hospital, Leeds, LS9 7TF, UK.*
Tel: +44 113 206 6612; Fax: +44 113 2444475;
E-mail: c.toomes@leeds.ac.uk

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Reply to Bottomley *et al*

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We welcome additional studies by Dr Bottomley *et al* on factor V Leiden mutation in other FEVR families and happy to note that they find our report 'interesting'. However, it is not surprising that they did not find additional families containing this mutation in their cohort. We have discussed in our short report most of the limitations of our study mentioned by Bottomley *et al* in their comments. Additionally, as correctly stated by Bottomley *et al*, we have not claimed the effect of mutation on phenotype or its association in other FEVR families but we speculated and

hypothesized that similar thing could be involved in variable phenotype. For instance, we discussed that such digenic mutation is not widespread (abstract), segregation observed is suggestive of linkage or unlikely (discussion), there is no correlation between the genotype and phenotype (discussion), FZD4 mutation alone is sufficient to cause a severe phenotype in other families (discussion) and lack of functional studies or availability of proper patients to understand the contribution of Leiden mutation in the presence of FZD4 gene mutation (discussion). In addition, we are aware of the fact that 5% of the population contains Leiden mutation, but it still does not address the question why only the affected individuals in the family have the mutant allele and not the unaffected individuals? Finally, we do agree that further studies are needed to understand the variable phenotypes in FEVR patients.

Barkur S Shastry and Michael T Trese
Department of Biological Sciences, Oakland University, Rochester, MI, USA