P1148A in fibrillin-1 is not a mutation anymore

Sir — Like mutations in most heritable disorders of connective tissue, fibrillin-1 (FBN1) mutations in the spectrum of the Marfan syndrome (MFS) are most often private (see ref. 1 for review). Thus, finding an identical molecular change in more than one affected individual or family has been rare. One exception is the substitution of alanine for proline at position 1148 (P1148A) in exon 27 of FBN1. Tynan and co-workers² were the first to report this mutation in 14 individuals, of which 6 were probands. All but one of these individuals had classic MFS (characterized by skeletal, ocular, and cardiovascular abnormalities³), late onset aortic aneurysms or were first degree relatives of an affected individual. One person in the control population was found to carry the 'mutation.' Sood *et al.*⁴ recently reported the expansion of the spectrum of FBN1 microfibrilopathies to include Shprintzen-Goldberg syndrome (SGS), a disorder characterized by Marfanoid habitus, craniosynostosis and mental retardation. They found P1148A in three of 60 affected families; one with SGS, one with classic MFS and one with late onset aortic aneurysm.

Here we report P1148A in five individuals from a mixed patient population (Table 1) but not in 120 Caucasian or 50 African American controls. Our screening protocol for FBN1 mutations includes heteroduplex analysis of amplicons generated

from each of the 65 exons of FBN1 using primers that flank each exon⁵. As we continued our analyses, we found additional changes consistent with mutational events in two of the five patients in whom P1148A was found (patients 496 and 503; Table 1). In the case of patient 503, sequencing of cloned RT-PCR products indicated that P1148A and the novel del5652T were in different FBN1 alleles.

It was of interest that three of our patients having the P1148A allele were Japanese. The ethnicity of the other two patients was Hispanic (Mexican) and Caucasian (Russian). Furthermore, five of the six probands with P1148A reported by Tynan² were of Asian descent, including the control individual. The ethnicity of patients analysed by Sood *et al.*⁴ was not reported. Therefore we studied 25 unrelated native Chinese individuals to determine whether P1148A is a polymorphism more commonly found in an Asian population. Eight of these individuals were P1148A heterozygotes. We found no homozygotes. These studies clearly show that P1148A is not, in and of itself, a deleterious change. The possibility that P1148A may exert a modifying affect on fibrillin mutations can and should be addressed in kindreds in which MFS and P1148A are both found.

Finally, these results confirm the hypothesis that P1148A is a polymorphic variant rather than a disease-causing mutation.

They are also a useful reminder that consideration of genetic variety between ethnic populations is essential.

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Table 1 • Diagnosis, phenotype and potential FBN1 mutation, if known, in patients with P1148A

Patient	Sex	Age (y)	Diagnosis	Clinical features	FBN1 sequence change
1063	M	35	Aortic aneurysm	pectus deformity mild scoliosis acute aortic dissection mitral valve prolapse	
1200	F		Familial ectopia lentis	ectopia lentis	
503	M	24	Classic MFS	Marfanoid habitus high arched palate arachnodactyly pectus excavatum pes planus aortic dilatation severe aortic insufficiency & mitral regurgitation	del 5652 T (exon 45) causing frame shift and premature stop
749	M		Neonatal MFS	arachnodactyly joint laxity flexion contractures pes planus mitral & tricuspid prolapse & insufficiency aortic root dilatation dysmorphic facies died at 4 months	
496	M		Neonatal MFS	As with patient 749 died at 12 months	T3706C (exon 29) resulting in C1236R substitution