A recurrent fibrillin-1 mutation in severe early onset Marfan syndrome.
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Marfan syndrome (MFS) is a well-recognized, autosomal dominant, multisystemic disorder of connective tissue caused by mutations in fibrillin-1 (\textit{FBN1}). A subset of patients present with severe, early onset, and rapidly progressive disease, referred to as early onset MFS. Mutations in early onset MFS almost exclusively localize to exons 24-32 of \textit{FBN1}; yet, identical mutations in this region have resulted in early onset MFS as well as classic or atypical MFS. These observations have led some to argue against the existence of specific genotype -phenotype correlations.

We report on the detailed clinical findings in three cases of early onset MFS and review three case reports from the literature, all with an amino acid substitution of isoleucine for threonine at codon 1048 (I1048T). One of our three cases has been briefly mentioned in the literature\textsuperscript{1}. All six cases had findings of polyvalvular disease, arachnodactyly and characteristic facies consistent with early onset MFS. The similar presentation and clinical course provide evidence that this recurrent amino acid substitution confers a severe early onset phenotype.

The pathogenesis of the I1048T mutation is incompletely understood. Lonneqvist et al. (1996) demonstrated that the I1048T mutation forms a novel N-glycosylation site, which may contribute to the severe phenotype. However, deletion of codon 1048 also resulted in the same phenotype, suggesting increased glycosylation may not be the only mechanism involved\textsuperscript{2}. As with many mutations in early onset MFS, the I1048T mutation lies in within a conserved calcium binding-EGF-like domain. Yet, this specific codon itself is not highly conserved. Molecular models showing amino acid 1048 to be exposed on the protein surface suggest this region may be essential to inter- and intra-molecular relations\textsuperscript{3}.

In conclusion, our findings support the existence of a specific genotype-phenotype correlation in early onset MFS, implying a consistently malignant effect of the I1048T substitution on fibrillin function. Current models of fibrillin-1 do not fully explain this association. Identifying the effects of the I1048T substitution on fibrillin-1 structure and function may lead to better understanding of the pathophysiology of MFS.

\textsuperscript{1}Faivre et al. \textit{European Journal of Human Genetics}, 2009
\textsuperscript{2}Putnam et al. \textit{American Journal of Medical Genetics}, 1996.