Screening for c-mpl mutations in patients with congenital amegakaryocytic thrombocytopenia identifies a polymorphism [letter]

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Screening for c-mpl mutations in patients with congenital amegakaryocytic thrombocytopenia identifies a polymorphism

Congenital amegakaryocytic thrombocytopenia (CAMT) is an uncommon disorder, characterized by an isolated thrombocytopenia and the almost complete absence of megakaryocytes in the bone marrow. Several studies have indicated that the origin of CAMT is an intrinsic stem cell defect.1-3 Recently, we and others have demonstrated the presence of mutations in the thrombopoietin-receptor gene, c-mpl, as a possible cause of CAMT.4-7 Although some mutations directly predict loss of Mpl function, it has not been established that others, notably those that lead to an amino acid substitution, also directly predict this loss.

To exclude that the mutations we found in our patients represent non-disease-related polymorphisms, we screened 50 healthy donors (100 alleles) for the presence of the different mutations by either sequence analysis or allele-specific restriction analysis.4 None of the healthy donors were carriers of our reported CAMT-associated mutations. In one new CAMT patient, 3 heterozygous mutations were observed: a G-to-C substitution at nucleotide 305 in exon 3, predicting an arginine-to-proline substitution at codon 102; a G-to-A transition at position 340, also in exon 3, leading to valine-to-methionine replacement at codon 114 (Mpl-114V/M); and a G-to-C substitution in the fifth nucleotide of intron 3, which leads to loss of the splice site 3′ of exon 3. Screening of 50 healthy donors revealed that 4 were heterozygous carriers of the G340A mutation. The other mutations were not observed in this population. The c-mpl-114V/M gene thus seems to have a frequency of 0.04

Propose that the first mutation plays a role in the development of CAMT in this patient. The G340A may not be involved in CAMT, and its presence in 2 CAMT patients may be incidental. To conclude, mutations that predict amino-acid substitutions found by genetic screening of patients with CAMT can be due to polymorphisms of the c-mpl gene. The relation of such mutations to disease should be proven by functional studies with the mutated protein.

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