A de novo splice donor mutation in the thrombopoietin gene causes hereditary thrombocythemia in a Polish family

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BACKGROUND: Hereditary thrombocythemia is an autosomal dominant disorder with clinical features resembling sporadic essential thrombocythemia. Germline mutations in families with hereditary thrombocythemia have been identified in the gene for thrombopoietin (TPHO) and its receptor, MPL. DESIGN AND METHODS: Here we characterized a THPO mutation in a hereditary thrombocythemia pedigree with 11 affected family members. RESULTS: Affected family members carry a G –> C transversion in the splice donor of intron 3 of THPO that co-segregated with thrombocytosis within the pedigree. We previously described the identical mutation in a Dutch family with hereditary thrombocythemia. Haplotype analysis using single nucleotide polymorphisms surrounding the mutation indicated that the mutations arose independently in the two families. MPL protein levels, but not mRNA levels, were low in platelets from affected family members. Bone marrow histology showed features compatible with those of essential thrombocythemia, but the megakaryocytes were unusually compact, as assessed by planimetric analysis. Impaired microcirculation resulting in brief episodes of fainting and dizziness that responded well to aspirin were the predominant clinical features in a total of 23 affected family members studied. Disease onset is earlier in patients with hereditary thrombocythemia than in those with essential thrombocythemia, but the frequencies of thrombotic, vascular and hemorrhagic events are similar in the two groups. CONCLUSIONS: A mutation in THPO occurred de novo in the same position as in a previously described family with hereditary thrombocythemia. Patients with this mutation have elevated serum levels of thrombopoietin and a phenotype that responds to aspirin and does not require cytoreductive treatment.
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