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Hereditary myeloproliferative disorders

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Hereditary forms of myeloproliferative disorders (MPD) can be divided into two broad categories. First, inherited syndromes that affect a single lineage with Mendelian inheritance, high penetrance and polyclonal hematopoiesis, and second, inherited predisposition to true MPD, characterized by low penetrance, clonal hematopoiesis and presence of somatic mutations, e.g. *JAK2*-V617F.[1,2] Relatively little is known about the clinical course and complications of inherited MPD-like syndromes. This short review will focus on recent reports that examined familial thrombocytosis caused by mutations in the genes for thrombopoietin (*THPO*) or its receptor "myeloproliferative leukemia" (*MPL*)

The prototypes for the first category are mutations in the erythropoietin receptor (*EPOR*) which truncate the intracellular domain of the erythropoietin receptor protein and render erythroid progenitors hypersensitive to erythropoietin. Patients with these mutations have an elevated hematocrit and low levels of erythropoietin in the serum,[3,4] but lack additional somatic mutations or the propensity to leukemic transformation, unless inappropriately treated with chemotherapy.[5] Mutations in genes which regulate the response to hypoxia, such as *VHL* and *PHD2* and *HIF-2α* have recently been found in a number of familial polycythemia syndromes with high serum erythropoietin levels.[6,7] Familial thrombocytosis without involvement of other lineages can be caused by mutations in *THPO* or *MPL*. Some families with elevated serum thrombopoietin levels carry activating mutations in the *THPO* gene which cause overproduction of the thrombopoietin protein by a mechanism of increased translational efficiency for the mutant *THPO* mRNA.[8,9] A mutation altering the transmembrane domain of Mpl protein (*MPL*-S505N) was discovered in a family with autosomal dominant thrombocytosis.[10] Interestingly, the identical mutation was also found in a mutational screen using retroviruses in mice,[11] and recently also as a somatic mutation in cases of sporadic essential thrombocythemia.[12]

In contrast, the primary defect that underlies the second category of hereditary MPD, i.e. the inherited predisposition to MPD that frequently comes with a somatic *JAK2*-V617F mutation,[13] remains to be defined. Numerous families with such a predisposing phenotype have recently been described.[14] Mutations in the putative tumor suppressor gene *TET2* occur in patients with sporadic MPD and other hematologic malignancies,[15,16] but *TET2* mutations do not appear to be involved as the primary germline event in familial MPD. Rather they occur as somatic mutations restricted to the hematopoietic system.[17]

In terms of molecular mechanisms, inherited MPD-like syndromes with mutations in erythropoietin and thrombopoietin ligands and receptors are among the best studied hematologic diseases. However, relatively little is known about the clinical course of patients with these disorders, in particular in respect to overall survival and the risk of complications. This is because of the low incidence of most of these familial disorders and the fact that familial MPD-like syndromes have been reported from diverse parts of the world, which makes it difficult to collect data on sufficient numbers of affected family members. Regional clustering has been described for Chuvash polycythemia, which is endemic in the Chuvash Republic, part of the Russian Federation,[18] and for the *MPL*-S505N mutation, which was present in four out of five Italian families with thrombocytosis studied.[19] The fact that all of these families originated from the region around Rome suggests

that a founder effect could be responsible for the geographical clustering of the *MPL*-S505N mutation, i.e. that this mutation occurred only once and that the affected family members are distantly related. Indeed, a follow-up study demonstrated that eight families from Italy with the *MPL*-S505N mutation, including those initially reported by Teofili and colleagues,[19] shared microsatellite markers and single nucleotide polymorphisms that defined a common haplotype surrounding the *MPL*-S505N allele.[20] Thus, the recurrent *MP*L-S505N mutation found in the eight Italian families with hereditary thrombocythemia is likely due to a founder effect that may have originated 23 generations ago. The Japanese family, in which the *MPL*-S505N mutation was first described,[10] showed a very different pattern of microsatellites and single nucleotide polymorphisms, indicating that the mutation in this family arose independently.[20]

In this issue of the journal, Teofili and colleagues present a retrospective case control study of eight families with thrombocytosis caused by the *MPL*-S505N mutation.[21] Clinical and hematologic data were available for 41 affected members of seven families, including 21 patients with a proven *MPL*-S505N mutation and 20 relatives with thrombocytosis and an assumed *MPL*-S505N mutation. Detailed hematologic data were available for 21 patients. Twenty-three unaffected family members and 72 patients with essential thrombocythemia without a family history served as controls. Almost all family members with *MPL*-S505N older than 20 years had splenomegaly and some degree of bone marrow fibrosis. Neither hemorrhagic complications nor leukemic transformation were observed. Hydroxyurea was used as a cytoreductive treatment in four affected family members and two patients received interferon. The thrombosis-free survival was shorter in family members with the *MPL*-S505N mutation than in non-affected family members, as was the overall survival. Thus, family members with the *MPL*-S505N mutation appear to primarily suffer from thrombotic complications, which included major events and even one case of Budd-Chiari syndrome. Low dose aspirin was given at diagnosis or during the follow-up to 15 out of 21 affected family members, but most patients were not receiving aspirin at the time of thrombosis. A tendency to an increased risk of thrombosis was also noted in patients with hereditary thrombocytosis due to a mutation in the *THPO* gene.[22]

The study by Teofili *et al.* is interesting and should encourage future cooperative efforts to learn more about the natural history of MPD-like syndromes, in which the primary disease-initiating mutation is known. However, some caution must be applied when interpreting the results. The weaknesses of this study include the fact that patients with confirmed and suspected *MPL*-S505N mutations were pooled, data on pediatric and adult patients were not examined separately, the control population of unaffected family members was not precisely defined and the study plan was not described in detail. Despite these limitations a number of interesting aspects can be considered. Although bone marrow fibrosis and splenomegaly appeared to be invariantly present in family members with the *MPL*-S505N mutation who were over 20 years old, cytopenia or progression to acute myeloid leukemia was not reported.[21] For comparison, the sporadic *MPL*-W515K/L mutation was more frequent in patients with primary myelofibrosis than in those with essential thrombocythemia and three patients with acute myeloid leukemia secondary to MPD had *MPL* mutations.[23,24] No germline *MPL*-W515K/L mutations have been described to date. In two large studies, progression to myelofibrosis in patients with sporadic essential thrombocythemia and *MPL*-W515K/L mutations was observed in four of 60 cases studied.[12,25] However, no information on the severity of myelofibrosis was given and no leukemic transformation was observed. Retroviral mouse models that over-express *MPL*-W515L showed a more severe phenotype than that in patients carrying the same mutation,[23] but this difference likely reflects retrovirally directed expression in lineages in which *MPL* is normally not expressed. It remains to be determined whether the *MPL*-S505N and *MPL*-W515K/L mutations differ with respect to the severity of myelofibrosis and/or propensity towards leukemic transformation. The Jak2 protein has recently been shown to phosphorylate histone H3 on tyrosine 41 and to exclude heterochromatin protein 1α from chromatin,[26] suggesting that Jak2 activity may contribute to genomic instability and potentially to leukemic transformation. However, the absence of leukemic transformation in 41 family members with *MPL*-S505N, and also in patients with germline mutations in *THPO* suggest that life-long stimulation of wild-type Jak2 protein through elevated thrombopoietin levels or constitutively active Mpl alone does not provide a strong leukemogenic stimulus. A similar conclusion can be drawn from the familial *EPOR* mutations.

It is of great importance to learn more about the clinical features of inherited MPD-like syndromes and compare these with disease progression in cases with somatic mutations and clonal hematopoiesis. Other recently described mutations in MPL can be included in such comparisons, e.g. mutations in the N-terminal region of the extracellular domain of Mpl protein, *MP*L-K39N (also called *MPL*-Baltimore),[27] and *MPL*-P106L, which is associated with a co-dominant transmission of thrombocytosis with elevated serum thrombopoietin levels in families of Arabic descent.[28] The experience from the studies on *MPL* and *THPO* will undoubtedly help to design the case-control studies that can address the most interesting issues, such as severity of myelofibrosis, progression to leukemia, but also therapeutic decisions, such as which patients with inherited *MPL* and *THPO* mutations should receive low dose aspirin.

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Current treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia

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Philadelphia chromosome-positive (Ph$^+$) acute lymphoblastic leukemia (ALL) is a relatively uncommon disease. However, it accounts for about one quarter of adult cases of ALL. Due to the paucity of patients, randomized controlled trials of therapy are unusual. This, together with the fact that outcomes for patients with Ph$^+$ ALL treated with standard combination chemotherapy are poor, has led to novel therapies typically being adopted early, in some cases prior to their risks and benefits being completely understood. Indeed, our two front-running therapeutic additions to standard combination chemotherapy – myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) and tyrosine kinase inhibitors (TKI) (principally, at present, imatinib) have never been evaluated in randomized controlled trials. Early inclusion of unrelated donors as a source of stem cells for allogeniec HSCT has largely precluded future donor *versus* no donor analyses, such that the role of sibling donor allogeneic HSCT has only been evaluated formally in a limited fashion. In addition, the great success of imatinib in treating chronic myeloid leukemia was very quickly interpreted as being similarly relevant to Ph$^+$ ALL. Hence, studies in adult patients in which the drug imatinib was not included at all in any treatment arm became impossible to conduct. As a result, data indicating a benefit from imatinib have all been generated from historical comparisons, with not one randomized study of imatinib *versus* no imatinib having ever been conducted in *de novo* Ph$^+$ ALL. In this issue of *Haematologica*, another collaborative study of the role of imatinib in the therapy of Ph$^+$ ALL from the PETHMA and GETH groups is published.[1] This commentary gives a background to the current, standard management of Ph$^+$ ALL, to set the context for the new data from the CSTIBES02 study.

The role of allogeneic bone marrow transplantation

Ph$^+$ ALL responds to combination chemotherapy, although complete remission is significantly less likely after standard induction regimens than in Ph$^-$ ALL.[2] Combined with a short remission duration, there is a median event-free survival of 8 months; prognosis is poor. Five-year overall survival rates of between 10-20% are typical when treatment is chemotherapy alone.[3-8] For this reason, myeloablative allogeneic HSCT has been a promi-