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Short Communication

Familial Myeloproliferative Disorders

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Abstract

Review on Familial Myeloproliferative Disorders, with data on clinics, and the genes involved.

Keywords

Familial; Myeloproliferative disorders; Hereditary erythrocytosis; Hereditary thrombocytosis; TERT; GSKIP; ATG2B; RBBP6

Identity

Other names

Familial myeloproliferative neoplasms
Hereditary erythrocytosis
Hereditary thrombocytosis

Note

Myeloproliferative neoplasms (MPN) are clonal and chronic hematological malignancies caused by genetic defects that result in overproduction of one or several myeloid lineages (erythroïd, megakaryocytic and granulocytic lineages). The classic MPN or Ph-chromosome-negative MPN include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

Familial MPN are estimated to 2 to 10% according to studies.

They are divided in two overlapping entities:

- True MPN disorders with germline predisposition that are familial clustering of MPN with autosomal dominant inheritance and incomplete penetrance. These familial cases are indistinguishable from the sporadic cases of MPN in terms of clinical features and acquired genetic abnormalities.

- Hereditary MPN-like disorders with clinical symptoms of MPN but affecting a single lineage involvement.

They include hereditary thrombocytosis (THPO, MPL, JAK2 genes), hereditary erythrocytosis (EPOR, VHL, EGLN1 and EPAS1 genes) and hereditary neutrophilia (CSF3R gene).

These hereditary disorders are non-malignant diseases and have distinct features: polyclonal hematopoiesis, absence of disease progression and autosomal dominant inheritance with complete penetrance.

Inheritance

Most of familial MPN are compatible with an autosomal dominant with incomplete penetrance. However, an autosomal recessive pattern has been suggested by some authors and could not be excluded.

Clinics

Phenotype and clinics

Familial MPN include the three classic MPN or Ph-chromosome-negative MPN: PV, ET, and PMF. Patients with familial MPN have the same clinical presentation at diagnosis as patients with sporadic MPN.

They develop the same type of complications (thrombosis and hemorrhage) and disease evolution (post-PV myelofibrosis, post-ET myelofibrosis, and acute myeloid leukemia). The distribution of MPN phenotypes within MPN families is homogeneous in half of cases (all affected family cases have the same MPN).

Neoplastic risk

RISK increased of transformation to acute myeloid leukemia (AML).

Treatment

The recommendations are those used for sporadic MPNS.
In low-risk patients, phlebotomy in PV patients and low-dose aspirin in ET patients are recommended. In the presence of risk factors for thrombosis, hydroxyurea is used as first-line treatment and busulfan or interferon-α as second-line.
Novel therapies based on JAK2 inhibitors have been developed and up to date, are restricted to patients with myelofibrosis.

Evolution

The main cause of death is the evolution to myelofibrosis and AML.
In familial cases, the incidence annual rate of AML has been estimated to 1.25% patients/year for PV and 0.68% patients/year for ET.

Prognosis

Familial PV: 83% of overall survival at 10 years; Familial ET: 84% to 100% of overall survival at 10 years; Familial PMF: 30% of overall survival at 10 years.

Cytogenetics

Cytogenetics of cancer

Chromosomal aberrations observed in familial MPN are similar to those reported in sporadic cases.
About two-third of MPN harbor at least one chromosomal aberration. Some of them are more specifically acquired with disease progression to secondary myelofibrosis such as uniparental disomy (UPD) of 9p, gain of 1q whereas others are more frequently associated with post-MPN acute myeloid leukemia such as gain of 1q, deletions of 7q, 5q, 6p, 7p, 3q and UPD of 19q and 22q.

Other findings

MPNs are driven by at least one somatic acquired mutation (V617F in JAK2 or mutations in MPL and CALR for ET and PMF) and mutations in epigenetic regulators such as TET2,
Several predisposing single-nucleotide polymorphism (SNP) such as the JAK2 haplotype 46/1 (also named GGCC) in JAK2, SNP rs2736100 in TERT, SNP rs2201862 in MECOM and SNP rs9376092 in HBS1L / MYB have been shown to play a role in the development of MPN in the general population by favoring the acquisition of driver mutations. However, except TERT (detailed below, none of them explain the familial clustering of MPN.

Genes involved and proteins

RBBP6 (RB binding protein 6, ubiquitin ligase)

Location
16p12.1

DNA/RNA

Description
Encoded in 18 exons spanning 33.2 Kb.

Transcription
NM_006910.4 encodes the longest transcript.

Protein

Description
Protein of 1792 amino acids.

Function
Possible link to P53 function.

Mutations

Germinal
All mutations located in the putative p53-binding region.

ATG2B (Autophagy-related 2B)

Location
14q32.2

Note
Cooperates with GSKIP, also located in 14q32.2 and included in the 700 kb duplication NC_000014.9:g.95696766_96390792dup (on Assembly GRCh38).

DNA/RNA

Description
Encoded in 42 exons spanning 82 Kb.

Transcription
Unique transcript NM_018036.

Protein

Description
Protein of 2078 amino acids.

Expression
Expressed in CD34+ hematopoietic progenitors and during erythroïd and megakaryocyte differentiation.

Function
Overexpression of ATG2B enhances hematopoietic progenitor differentiation, particularly in megacaryocytes and cooperates with classical driver mutations.

Mutations

Note
Founder defect in families originated from West-Indies.

Germinal
Head-to-tail 700 kb tandem duplication (g.95696766_96390792dup).

Somatic
Associated with classical driver mutations such as V617F in JAK2, W515L in MPL and 1099_1050del52 in CALR and with an increased frequency of mutations in TET2, IDH1 and IDH2.

GSKIP (GSK3-beta interaction protein)

Location
14q32.2

Note
Cooperates with ATG2B, also located in 14q32.2 and included in the 700 kb duplication NC_000014.9:g.95696766_96390792dup (on Assembly GRCh38).

DNA/RNA

Description
Encoded in 3 exons spanning 7 Kb.

Transcription
NM_001271904 encodes the longest transcript; 3 other transcripts encode the same protein with differences in the 5'UTR.

Protein

Description
Protein of 139 amino acids.

Expression
in CD34+ hematopoietic progenitors and during erythroïd and megakaryocyte differentiation.

Function
Overexpression of GSKIP enhances hematopoietic progenitor differentiation, particularly of megacaryocytes and cooperates with classical driver mutations.

Mutations

Note
Founder defect in families originated from West-Indies.

Germinal
Head-to-tail 700 kb tandem duplication (g.95696766_96390792dup).

Somatic
Associated with classical driver mutations such as V617F in JAK2, W515L in MPL and 1099_1050del52 in CALR and with an increased frequency of mutations in TET2, IDH1 and IDH2.

TERT (telomerase reverse transcriptase)

Location
5p15.33

DNA/RNA

Description
Encoded in 16 exons spanning 42 Kb.

Transcription
NM_198253.2 encodes the longest isoform (1); a shorter isoform lacking an alternate in-frame exon in the middle portion of the coding exon is also reported.

Protein

Description
Protein of 1132 amino acids.

Expression
Blood cells.

Function
Telomerase activity, essential for maintaining telomere length.

Mutations

Germinal
Allele C of SNP rs2736100, located in the second intron of the TERT gene, is associated with an increased risk for MPN (PV, ET and PMF).

To be noted

Germline duplication of ATG2B and GSKIP predispose with a high penetrance (above 80%) to several myeloid malignancies, particularly essential thrombocythemia frequently progressing to AML.
RBBP6 germline gain-of-function mutations mostly associated with primary myelofibrosis, observed in 5% of the familial and 0.6% of the sporadic MPN cases. TERT rs2736100_C risk allele is significantly associated with familial MPN, whatever the subtype (PV, ET and PMF

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