Essential Thrombocythemia: Current Molecular and Therapeutic Insights

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ABSTRACT

Essential thrombocythemia is one of the Philadelphia chromosome negative, clonal myeloproliferative disorders involving the hematopoietic stem cells and is characterized by elevated platelet counts and attendant thromboembolic phenomenon. A point mutation in the Janus-Activated Kinase 2 gene (JAK2V617F) accounts for nearly 50% of Essential thrombocythemia patients while about 10% have mutations in the thrombopoietin receptor (MPL) gene (MPLW515L/K). Several other genes are implicated, clearly indicating the existence of drivers both common and uncommon in the causation of Essential thrombocythemia. Genotyping for mutations will therefore be a useful diagnostic tool for detection of Janus-Activated Kinase 2 negative, MPL negative, Essential thrombocythemia patients. An integrated approach of systematic analysis leading to accurate diagnosis will enable risk stratification and institution of therapy following the World Health Organization guidelines. In addition to Janus-Activated Kinase inhibitors, a combination of agents that has anti-inflammatory properties could help prevention and/or reversal of fibrosis.

Keywords

Essential thrombocythemia; Myeloproliferative neoplasms; JAK2V617F mutation; MPLW515L/K mutation; Calreticulin mutation
INTRODUCTION

Essential thrombocythemia (ET) arises due to an acquired genetic defect in hematopoietic stem cells leading to clonal myeloproliferation. Hematopoietic stem cell (HSC) proliferation, differentiation and apoptotic effects mediated by epidermal growth factor, colony stimulating factor, platelet derived growth factor, interleukin 3 and erythropoietin are regulated via the Janus-Activated Kinase 2 (JAK2)/signal transducer and activator of transcription (STAT) signaling pathway.

ET is characterized by an increase in platelet numbers, which therefore can cause a predisposition to frequent thrombosis and hemorrhagic incidents. The prevalence in the general population is about 30/100000[1], having a slight female preponderance with a ratio of 2:1. Although the disease can occur at any age, the median age for ET is between 65 - 70 years. Due to occlusion of the microvessels (arteries/veins) vascular disturbances such as stroke, transient ischemic attacks, headache, lightheadedness and visual disabilities are frequently encountered[2]. Polycythemia vera (PV) and ET are commonly associated with microcirculatory disturbances leading to thrombotic/hemorrhagic incidents while primary myelofibrosis (PMF) has the propensity to undergo leukemic transformation[3,4]. Evidences indicate that angiogenesis or the process of new vessel formation occurs not only in solid tumors but also in hematological tumors, as noted by the increase in micro vessel density that was more predominant in PMF followed by PV and ET associated with vascular endothelial growth factor (VEGF) expression and in relation to JAK2 mutations[5,6].

Considerable overlap exists with myelodysplastic/myeloproliferative diseases such as chronic myelomonocytic leukemia and chronic myelogenous leukemia which are usually accompanied with dysplastic and ineffective erythropoiesis and hence it may be difficult to differentiate some cases of ET from reactive disorders[7]. Chronic inflammation is the underlying disorder in myeloproliferative neoplasms (MPNs), which eventually leads to cancerous transformation with poor prognosis and this transformation may be due to acquisition of additional genetic abnormalities[8]. Reticulin fibrosis is associated with increased risk of myeloproliferative changes in ET/PV and in general, MPNs transformed into acute promyelocytic leukemia have very poor prognosis. Precise diagnosis therefore needs to be established according to the World Health Organization (WHO) guidelines and appropriate therapy instituted. An international panel of experts in hematology and hematopathology have proposed a revised criteria for diagnosis in 2007 and this was adopted by the WHO in 2008[9,10]. An integrated approach, including the histomorphological changes, genetic abnormalities and clinical criteria, is essential in the differentiation and management of MPNs.

GENETIC MUTATIONS

JAK2 is widely distributed in the somatic cells and is also involved in the immune system regulation in addition to the hematopoietic signal transduction. The discovery of a point mutation in the JAK2 gene provided the initial molecular basis[9,10]. JAK2 is an important member of the JAK family which is located on chromosome 9p24. Mutation occurs at base position 1849 in exon 14 and the homozygous G to T transversion results in valine substitution to phenylalanine at residue 617 (V617F)[42]. JAK2V617F mutation is the most common genetic defect associated with ET. PV and PMF also carry JAK2V617F mutation and these disorders together with ET constitute the Philadelphia negative (BCR-ABL1 negative) chronic MPNs according to the WHO classification[5,10,11,14].

JAK2V617F mutation leads to constitutive activation of the thrombopoietin signaling mechanisms leading to ET. Importantly, the burden of JAK2V617F mutation is relatively low in ET and PMF compared to PV, in which the mutational load is high and is almost always present. Nearly 90% - 95% cases of PV have the JAK2V617F mutation while it is only present in about 60% of ET and PMF cases. A small fraction of JAK2 negative patients (about 3% to 7% of ET/PMF) are due to point mutations of the thrombopoietin receptor (MPL) MPLW515L/K[30]. Somatic mutation in the calreticulin (CALR) gene that encodes for CALR are also found in ET or PMF patients who do not harbor either JAK2 or MPL mutations[31,32]. CALR mutations occur in 20% to 25% of MPNs and nearly 40 CALR mutations are reported, with Type I (52 bp deletion) and Type II (5 bp insertion) being the most common[18,19].

The involvement of other genes indicates the existence of many drivers in MPNs all acting via the JAK-STAT signal transduction mechanism. Some of the other genes implicated are ASXL1, TET2, CBL, IDH2, IDH1, EZH2, IKZF1 and LNK[20-26]. High throughput single cell sequencing of cancer genome led to the identification of 8 candidate genes (viz. SESN2, DNAJC17, ST13, TOP1MT, NTRK1, ABCB5, FRG1, and ASNS) as possible drivers of JAK2/MPL negative cases of ET[27]. Screening of SESN2, DNAJC17, ST13, TOP1MT that exhibited the highest score in a cohort of 64 patients diagnosed with ET, found none of the proposed candidate drivers, but led to the identification of a novel mutation in exon 11 of TOP1MT, establishing that this mutation is involved in low frequency in the pathogenesis of JAK2/MPL negative ET (i.e., is recurrently mutated in ET)[28]. Another study, gene expression microarray studies of whole blood from 69 MPN patients, led to the identification of 5 upregulated genes, namely DEFA4, ELA2, OLFM4, CTSG, AZU1 in PMF. Interestingly, hierarchical clustering analysis showed most of these genes were also highly expressed in the transitional stages of ET and PV leading to PMF[29].

Inflammation leads to the production reactive oxygen species (ROS) and interestingly JAK2V617F mutation is associated with increased ROS production in the HSC niche. The Nrf2 gene, which is known to regulate stem cell function and has an anti-oxidant effect, is identified to be downregulated in MPNs[30,31]. All above studies clearly indicate that, apart from the common driver mutations
(JAK2/MPL/CALR), subclonal driver mutations in other genes, cytogenetic aberrations and epigenetic changes may influence disease progression in MPNs.

**EPIGENETIC MODIFICATIONS AND ESSENTIAL THROMBOCYTHEMIA**

In addition to the role of irreversible changes in the gene sequences viz. mutations, the reversible modifications which affect gene expression pattern, namely the epigenetic modifications viz DNA methylation/histone acetylation are well known to be associated with initiation and progression of various neoplasms. Epigenetic modifications, especially those of DNA methylation have been more identified with hematopoietic neoplasms such as acute leukemia and myelodysplastic syndromes.

Epigenetic modifications, especially the DNA methylation, is evident only during the transformation to acute leukemia, while differential methylation pattern is not prevalently found in PMF, ET or PCV. Minimal incidences of DNA methylation changes were evident in MPNs compared to control samples, but no differences were noted between ET, PCV or PMF. Apart from playing a role in causation, these epigenetic modifications may also affect the response of a drug leading to incomplete suppression or eradication of the altered HSC. This was clearly evident in a subset of patients who continued to have TET2 clones while JAK2 mutant clones were eradicated following therapy with pegylated interferon alpha 2a (PEG-IFN-2aa). A long term follow up of 40 ET patients on phase 2 clinical trial with PEG-IFN-2aa demonstrated complete molecular remission of JAK2V617F mutations in 17% and complete hematologic responses in 77%.[19] Interestingly, those patients who failed to have complete molecular response to PEG-IFN-2aa therapy had higher frequency of mutations outside the JAK2-STAT signaling pathways, thereby suggesting the role of alternative players in the causation and therapeutic outcome of ET.

**CLINICAL FEATURES**

Many patients may remain asymptomatic and thus never be diagnosed with ET unless seen by a physician for an unrelated illness. Patients with ET are at increased risk for arterial and venous thromboembolic events. Arterial thromboses are reported 3 times more often than venous thromboses. Arterial ischemic complications occur in about 35% (Table 1).

**CONCLUSIONS AND FUTURE PERSPECTIVES**

Recent research has identified involvement of many new genes either in the causation or transformation of Philadelphia negative MPNs. It is essential to consider reactive disorder and chronic myeloid disorders before making a diagnosis of ET. Powerful technologies have contributed to allow accurate diagnosis in a cost-effective manner. Agents that target the aberrant JAK-STAT signaling such as the small molecule ruxolitinib (FDA approved), momelotinib (CYT387) have demonstrated good clinical efficacy. However, resolution of marrow fibrosis or molecular remissions has not been successful, indicating clonal hematopoiesis may continue to persist due to alternative disease alleles. Therefore additional clinical and molecular testing will be necessary to enable detection of the sensitivity/resistance as well as to allow development of more targeted therapies.

**REFERENCES**

1. Johansson P. Epidemiology of the myeloproliferative disorders polycythemia vera and essential thrombocythemia. Semin Thromb Hemost. 2006; 32(3): 171–173.
2. Brière JB. Essential thrombocythemia. Orphanet J Rare Dis. 2007; 2: 3.
3. Landolf R, Cipriani MC, Novarese L. Thrombosis and bleeding in polycythemia vera and essential thrombocythemia: pathogenetic mechanisms and prevention. Best Pract Res Clin Haematol. 2006; 19(3): 617–633.
4. Vannucchi AM, Pieri L, Guglielmelli P. JAK2 allele burden in the myeloproliferative neoplasms: effects on phenotype, prognosis and change with treatment. Ther Adv Hematol. 2011; 2(1): 21–32.
5. Medinger M, Skoda R, Grathwohl A, Theocharides A, Buser A, Heim D, Dirnhofer S, Tichelli A, Tzankov A. Angiogenesis and vascular endothelial growth factor/receptor expression in myeloproliferative neoplasms: correlation with clinical parameters and JAK2-V617F mutational status. Br J Haematol. 2009; 146(2): 150–157.
6. Medinger M, Passweg J. Angiogenesis in myeloproliferative neoplasms, new markers and future directions. Memo. 2014; 7: 206–210.
7. Tefferi A, Gilliland DG. The JAK2V617F tyrosine kinase mutation in myeloproliferative disorders: status report and immediate implication for disease classification and diagnosis. Mayo Clin Proc. 2005; 80(7): 947–958.
8. Hasselbalch HC. Chronic inflammation as a promoter of mutagenesis in essential thrombocythemia, polycythemia vera and myelofibrosis. A human inflammation model for cancer development? Leuk Res. 2013; 37(2): 214–220.
9. Tefferi A, Thiele J, Orazi A, Kvasnicka HM, Barbui T, Hanson CA, Barosi G, Verstovsek S, Birgegard G,Mesa R, Reilly JT, Gisslinger H, Vannucchi AM, Cervantes F, Finazzi G, Hoffman R, Gilliland DG, Bloomfield CD, Vardiman JW. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood. 2007; 110(4): 1092–1097.
10. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM,Hellstrom-Lindberg E, Tefferi A, Bloomfield CD. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009; 114(5): 937–951.
11. Baxter EJ, Scott LM, Campbell PJ, East C, Foucarlas N, Swanton S, Vassiliou GS, Bench AJ, Boyd EM, Curtin N, Scott MA, Erber WN, Green AR. Cancer Genome Project. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005; 365(9464): 1054–1061.
12. Kralovics R, Passamonti F, Buser AS, Teo SS, Tiedt R, Passweg JR, Tichelli A, Cazzola M, Skoda RC. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005; 352(17): 1779-1790.

13. Spivak JL. The chronic myeloproliferative disorders: clonality and clinical heterogeneity. Semin Hematol. 2004; 41(2 Suppl 3): 1-5.

14. Campbell PJ, Green AR. The myeloproliferative disorders. N Engl J Med. 2006; 355(23): 2452-2466.

15. Vannuccih AM, Guglielmelli P. Molecular pathophysiology of Philadelphia-negative myeloproliferative disorders: beyond JAK2 and MPL mutations. Haematologica. 2008; 93(7): 972-976.

16. Tefferi A, Wasse EA, Guglielmelli P, Gangat N, Belachew AA, Lasho TL, Finke C, Ketterling RP, Hanson CA, Pardanani A, Wolansky AJ, MAffifioli M, Casalone R, Pacilli A, Vannuccii AM, Passamonti F. Type 1 versus Type 2 calreticulin mutations in essential thrombocythemia: a collaborative study of 1027 patients. Am J Hematol. 2014; 89(8): E121-E124.

17. Cazzola M, Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. Blood. 2014; 123(24): 3714-3719.

18. Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, Them NC, Berg T, Gisslinger B, Pietra D, Chen D, Vladimer GI, Bagienski K, Milanesi C, Casetti IC, Sant’Antonio E, Ferretti V, Elena C, Schischlik F, Cleary C, Six M, Schalling M, Schönegger A, Bock C, Malcovati L, Pascutto C, Superti-Furga G, Cazzola M, Kralovics R. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med. 2013; 369(25): 2379-2390.

19. Mondet J, Park JH, Menard A, Marzac C, Carillo S, Pourcelot E, Giroud F, Cabagnols X, Lodé L, Socoro N, Chauvet M, Bulabois CE, Cory-Mahkoul P, Corn S, Cahn JY, Mossuz P. Endogenous megakaryocytic colonies underlie an association between megakaryocytes and calreticulin mutations in Essential thrombocytopenia. Haematologica. 2015; 118927.

20. Carbuccion M, Murati A, Trouplin V, Brecqueville M, Adélaide J, Rey J, Vainchenker W, Bernard OA, Chaffanet M, Yen V, Birnbaum D, Mozizzonacci MJ. Mutations of ASXL1 gene in myeloproliferative neoplasms. Leukemia. 2009; 23(11): 2183-2186.

21. Delhommeau F, Dupont S, Della Valle V, James C, Trannoy S, Massé A, Kosimider O, Le Couedic JP, Robert F, Alberdi A, Lécluse Y, Pio I, Dreyfus FJ, Marzac C, Casadevall N, Lacombe C, Romana SP, Dessen P, Soulier J, Viguier F, Fontenay M, Vainchenker W, Bernard OA. Mutation in TET2 in myeloid cancers. N Eng J Med. 2009; 360(22): 2289-2301.

22. Grand FH, Hidalgo-Curtis CE, Ernst T, Zoi K, Zoi C, McGuire C, Kreil S, Jones A, Score J, Metzgeroth G, Osier D, Hall A, Brands C, Serve H, Reiter A, Chase AJ, Cross NC. Frequent CBL mutations associated with 11q acquired uniparental disomy in myeloproliferative neoplasms. Blood. 2009; 113(24): 6182-6192.

23. Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH1 and IKZF1. Leukemia. 2010; 24(6): 1128-1138.

24. Ernst T, Chase AJ, Score J, Hidalgo-Curtis CE, Bryant C, Jones AV, Waghourn K, Zoi K, Ross FM, Reiter A, Hochhaus A, Drexler HG, Duncombe A, Cervantes F, Osier D, Boulwood J, Grand FH, Cross NC. Inactivating mutations of the histone methyltransferase gene EZH2 in myeloid disorders. Nat Gen. 2010; 42(8): 722-726.

25. Jager R, Gisslinger H, Passamonti F, Rumi E, Berg T, Gisslinger B, Pietra D, Harutyunyan A, Klampfl T, Ocladyd A, Cazzola M, Kralovics R. Deletions of the transcription factor Ikaros in myeloproliferative neoplasms. Leukemia. 2010; 24(7): 1290-1298.

26. Oh ST, Simonds EF, Jones C, Hale MB, Goltsev Y, Gibbs KD Jr, Merker JD, Zehnder JL, Nolan GP, Golliff J. Novel mutations in the inhibitory adaptor protein LINK drive JAK-STAT signaling in patients with myeloproliferative neoplasms. Blood. 2010; 116(6): 988-992.

27. Hou Y, Song L, Zhu P, Zhang B, Tao Y, Xu X, Li F, Wu K, Liang J, Shao D, Wu H, Ye X, Ye C, Wu R, Jian M, Chen Y, Xie W, Zhang R, Chen L, Liu X, Yao X, Zheng H, Yu C, Li Q, Gong Z, Mao M, Yang X, Yang L, Li J, Wang W, Lu Z, Gu N, Laurie G, Boland L, Kristiansen K, Wang J, Yang H, Li Y, Zhang X, Wang J. Single-cell exome sequencing and monoclonal evolution of a JAK2-negative myeloproliferative neoplasm. Cell. 2012; 148(5): 873-885.

28. Al Assaf C, Cerrato E, Devos T, Billiet J, Graux C, Papadopoulos P, Vandenbergh P. Screening of JAK2 V617F and MPL W515 K/L negative essential thrombocytopenia patients formutations in SESN2, DNAJC17, ST13, TOP1MT1, and NTRK1. Br J Haematol. 2014; 165(5): 734-737.

29. Hasselbalch HC, Thomassen M, Riley CH, Bergen JD, Berg T, Gisslinger B, Friel PJ, Van Aelers J, Jensen MK, Bjerrum OW, Kruse TA, Skov V. Whole blood transcriptional profiling reveals deregulation of oxidative and antiapoptotic defence genes in myelofibrosis and related neoplasms. Potential implications of downregulation of Nrf2 for genomic instability and disease progression. PLoS One. 2014; 9(11): e112786.

30. Marty C, Lacout C, Droin N, Le Couedic JP, Ribrag V, Solary E, Vainchenker W, Villeval JL, Plou I. A role for reactive oxygen species in JAK2(V617F) myeloproliferative neoplasm progression. Leukemia. 2013; 27(11): 2187-2195.

31. Tsai JJ, Dudakov JA, Takahashi K, Shieh JH, Velardi E, Holland AM, Singer NV, West ML, Smith OM, Young LF, Shono Y, Ghosh A, Hanash AM, Tran HT, Moore MA, van den Brink MR. Nrf2 regulates haematopoietic stem cell function. Nat Cell Biol. 2013; 15(3): 309-316.

32. Martin-Subero Jl, Ammerpohl O, Bibikova M, Wickham-Garcia E, Agirre X, Alvarez S, Brüggemann M, Bug S, Calasanz MJ, Deckert M, Dreyling M, Du MQ, Dürig J, Dyer MJ, Fan JB, Gekk S, Hansmann ML, Harder L, Hartmann S, Karger W, Kuppers R, Montesinos-Rongen M, Nagel I, Pott C, Richter J, Román-Gómez J, Seifert M, Stein H, Suela J, Trümper L, Vater I, Prosper F, Haferlach C, Cruz Cigudosa J, Siebert R. A comprehensive microarray-based DNA methylation study of 367 hematological neoplasms. PloS One. 2009; 4(9): e6986.

33. Alvarez S, Suela J, Valencia A, Fernández A, Wunderlich M, Agirre X, Prósper F, Martin-Subero Jl, Maiques A, Acquafurdo F, Rodriguez Perales S, Calasanz MJ, Roman-Gómez J, Siebert R, Mullot JC, Cervera J, Sanz MA, Esteller M, Cigudosa JC. DNA methylation profiles and their relationship with cytogenetic status in adult acute myeloid leukemia. PloS One. 2010; 5(8): e12197.

34. Pérez C, Pascual M, Martin-Subero Jl, Bellosillo B, Segura V, Delabesse E, Alvarez S, Larrayoz M, Ríñon J, Cigudosa JC, Bessas C, Calasanz MJ, Cross NC, Prósper F, Agirre
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35. Nischal S, Bhattacharyya S, Christopeit M, Yu Y, Zhou L, Bhagat TD, Sohal D, Will B, Mo Y, Suzuki M, Pardanani A, McDevitt M, Maciejewski JP, Melnick AM, Greally JM, Steidl U, Moliterno A, Verma A. Methylome profiling reveals distinct alterations in phenotypic and mutational subgroups of myeloproliferative neoplasms. Cancer Res. 2013; 73(3): 1076-1085.

36. Moran-Crusio K, Reavie L, Shih A, Abdel-Wahab O, Ndiaye-Loby D, Loby C, Figueroa ME, Vasanthakumar A, Patel J, Zhao X, Perna F, Pandey S, Madzo J, Song C, Dai Q, He C, Ibrahim S, Beran M, Zavadil J, Nimer SD, Melnick A, Godley LA, Aifantis I, Levine RL. Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. Cancer Cell. 2011; 20(1): 11-24.

37. Challen GA, Sun D, Jeong M, Luo M, Jelinek J, Berg JS, Bock C, Vasanthakumar A, Gu H, Xi Y, Liang S, Lu Y, Darlington GJ, Meissner A, Issa JP, Godley LA, Li W, Goodell MA. Dnmt3a is essential for hematopoietic stem cell differentiation. Nat Genet. 2011; 44(1): 23-31.

38. Kiladjian JJ, Massé A, Cassinat B, Mokrani H, Teysyandier I, le Couédic JP, Cambier N, Almire C, Pronier E, Casadevall N, Vainchenker W, Chomienne C, Delhommeau F; French Intergroup of Myeloproliferative Neoplasms (FIM). Clonal analysis of erythroid progenitors suggests that pegylated interferon alpha-2a treatment targets JAK2V617F clones without affecting TET2 mutant cells. Leukemia. 2010; 24(8): 1519-1523.

39. Quintás-Cardama A, Abdel-Wahab O, Manshouri T, Kilpivaara O, Cortes J, Roupie AL, Zhang SJ, Harris D, Estrov Z, Kantarjian H, Levine RL, Verstovsek S. Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon α-2a. Blood. 2013; 122(6): 893-901.

40. Tefferi A, Barbui T. Personalized management of essential thrombocythemia-application of recent evidence to clinical practice. Leukemia. 2013; 27(8): 1617-1620.

41. Sonbol MB, Firwana B, Zarzour A, Morad M, Rana V, Tiu RV. Comprehensive review of JAK inhibitors in myeloproliferative neoplasms. Ther Adv Hematol. 2013; 4(1): 15-35.
كثرة الصفحات الدموية: دراسة للجزئيات والعلاج الحالي

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المستخلص

تعتبر زيادة عدد الصفحات الدموية واحدة من اضطرابات التكاثر النووي السلبي لكروموسوم فيلادلفيا وتطوري على الخلايا الجذعية المكونة للدم. تسبب هذه المشكلة ظاهرة الإنصمام الخثاري، والتي قد تؤثر على متوسط العمر المتوقع ولكلّ لوظائف الطفرة الجينية JAK2-2 في 20 في المائة من حالات زيادة عدد الصفحات الدموية، في حين حوالي 10 في المائة توجد لديهم طفرات جينية في JAK2V617F (MPLW515L/K) وبعض الجينات الأخرى مثل كالريتكيلن (CALR, AsxI1). وهذا يدل بوضوح على وجود أسباب جينية أكثر شيوعا وأقل حدوثاً. وتعتبر الطفرات الجينية مفيدة للكشف عن هذا المرض، كما أن وجود منهج متكامل لتشخيص يؤدي إلى النهاة في تشخيص هذا المرض ووضع خطة واضحة ومتميزة للعلاج. وإضافة لما سبق، فإن مزيجاً من مضادات الالتهاب قد تعكس أو تمنع التليف.

مفتاح الورقة العلمية:

زيادة عدد الصفحات الدموية JAK2V617F MPLW515L/K Calreticulin