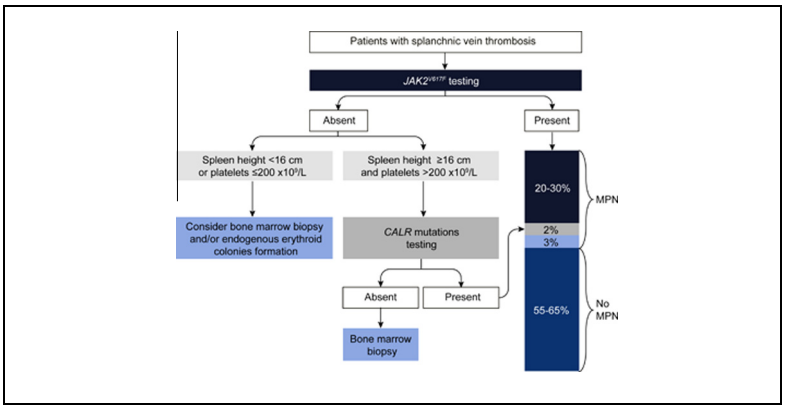
Research Article

JOURNAL OF HEPATOLOGY

Selective testing for calreticulin gene mutations in patients with splanchnic vein thrombosis: A prospective cohort study

Graphical Abstract



Highlights

- *CALR* mutations are detected in 2% of patients with splanchnic vein thrombosis.
- *CALR* mutations should not be tested in patients with *JAK2*^{V617F}.
- *CALR* mutations should be tested in patients with splenomegaly & platelets >200×10^9/L.
- This strategy avoids 96% of unnecessary *CALR* mutations testing.

Authors

Johanne Poisson, Aurélie Plessier, Jean-Jacques Kiladjian, ..., Dominique-Charles Valla, Pierre-Emmanuel Rautou, Christophe Marzac

Correspondence

pierre-emmanuel.rautou@inserm.fr (P.-E. Rautou)

Lay summary

Mutations of the *CALR* gene are detected in 0 to 2% of patients with SVT, thus the utility of systematic *CALR* mutation testing to diagnose MPN is questionable. This study demonstrates that *CALR* mutations testing can be restricted to patients with SVT, a spleen height ≥16 cm, a platelet count >200×10^9/L, and no *JAK2*^{V617F}. This strategy avoids 96% of unnecessary *CALR* mutations testing.

http://dx.doi.org/10.1016/j.jhep.2017.04.021
 J. Hepatol. 2017, 67, 501–507

Research Article

EASL JOURNAL OF HEPATOLOGY

Selective testing for calreticulin gene mutations in patients with splanchnic vein thrombosis: A prospective cohort study

Johanne Poisson[1], Aurélie Plessier[2], Jean-Jacques Kiladjian[3], Fanny Turon[4], Bruno Cassinat[3], Annalisa Andreoli[3], Emmanuelle De Raucourt[5], Odile Goria[6], Kamal Zekrini[3], Christophe Bureau[7], Florence Lorre[8,9], Francisco Cervantes[13], Dolors Colomer[14], François Durand[2,10,11], Juan-Carlos Garcia-Pagan[4,12], Nicole Casadevall[8,9], Dominique-Charles Valla[2,10,11], Pierre-Emmanuel Rautou[1,2,11,*,†], Christophe Marzac[8,9,†], for the French national network for vascular liver diseases

[1]*Inserm, U970, Paris Cardiovascular Research Center - PARCC, Université Paris Descartes, Sorbonne Paris Cité, Paris, France;* [2]*DHU Unity, Pôle des Maladies de l'Appareil Digestif, Service d'Hépatologie, Centre de Référence des Maladies Vasculaires du Foie, Hôpital Beaujon, AP-HP, Clichy, France;* [3]*Centre d'Investigations Cliniques, Hôpital St Louis, AP-HP, Clichy, France;* [4]*Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clínic, IDIBAPS, Barcelona, Spain;* [5]*Service d'Hématologie Biologique, Hôpital Beaujon, AP-HP, Clichy, France;* [6]*Service d'Hépato-gastroentérologie, CHU Rouen, Rouen, France;* [7]*Liver-Gastroenterology Department, University Hospital and Paul Sabatier University, Toulouse, France;* [8]*UPMC, Univ Paris 06, GRC n°7, Groupe de Recherche Clinique sur les Myéloprolifération Aiguës et Chroniques MYPAC, Paris, France;* [9]*Laboratoire d'Immunologie et Hématologie Biologique, Hôpital Saint-Antoine, AP-HP, Paris, France;* [10]*Inserm U1149, Centre de Recherche sur l'Inflammation (CRI), Paris, Université Paris 7-Denis-Diderot, Clichy, UFR de Médecine, Paris, France;* [11]*Université Paris Diderot, Sorbonne Paris cité, Paris, France;* [12]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain;* [13]*Hematology Department, Hospital Clínic, IDIBAPS, University of Barcelona, Spain;* [14]*Hematopathology Unit, Hospital Clínic, IDIBAPS, CIBERONC, Spain*

Background and Aims: Myeloproliferative neoplasms (MPN) are the leading cause of splanchnic vein thrombosis (SVT). Janus kinase 2 gene (*JAK2*)^{V617F} mutations are found in 80 to 90% of patients with SVT and MPN. Mutations of the calreticulin (*CALR*) gene have also been reported. However, as their prevalence ranges from 0 to 2%, the utility of routine testing is questionable. This study aimed to identify a group of patients with SVT at high risk of harboring *CALR* mutations and thus requiring this genetic testing.

Methods: *CALR*, *JAK2*^{V617F} and thrombopoietin receptor gene (*MPL*) mutations were analysed in a test cohort that included 312 patients with SVT. Criteria to identify patients at high risk of *CALR* mutations in this test cohort was used and evaluated in a validation cohort that included 209 patients with SVT.

Results: In the test cohort, 59 patients had *JAK2*^{V617F}, five had *CALR* and none had *MPL* mutations. Patients with *CALR* mutations had higher spleen height and platelet count than patients without these mutations. All patients with *CALR* mutations had a spleen height $\geqslant$16 cm and platelet count $>200\times10^9$/L. These criteria had a positive predictive value of 56% (5/9) and a negative predictive value of 100% (0/233) for the identification of *CALR* mutations. In the validation cohort, these criteria had a positive predictive value of 33% (2/6) and a negative predictive value of 99% (1/96).

Conclusion: *CALR* mutations should be tested in patients with SVT, a spleen height $\geqslant$16 cm, platelet count $>200\times10^9$/L, and no *JAK2*^{V617F}. This strategy avoids 96% of unnecessary *CALR* mutations testing.

Lay summary: Mutations of the *CALR* gene are detected in 0 to 2% of patients with SVT, thus the utility of systematic *CALR* mutation testing to diagnose MPN is questionable. This study demonstrates that *CALR* mutations testing can be restricted to patients with SVT, a spleen height $\geqslant$16 cm, a platelet count $>200\times10^9$/L, and no *JAK2*^{V617F}. This strategy avoids 96% of unnecessary *CALR* mutations testing.

Keywords: Myeloproliferative neoplasms; Budd-Chiari syndrome; Portal vein thrombosis; *JAK2*^{V617F}; *MPL* mutation; *CALR* mutations; Platelets count; Splenomegaly; DNA mutational analysis; Genetic testing.

Received 14 February 2017; received in revised form 19 April 2017; accepted 22 April 2017; available online 5 May 2017

* Corresponding author. Address: Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France. Tel.: +33 171114679; fax: +33 140875530.

E-mail address: pierre-emmanuel.rautou@inserm.fr (P.-E. Rautou).

† These authors contributed equally to this work.

Introduction

Splanchnic vein thrombosis (SVT) indicates Budd-Chiari syndrome (BCS) and portal venous system thrombosis (PVT). Primary BCS is a rare disorder defined as a blocked hepatic venous outflow tract at various levels from small hepatic veins to the terminal portion of the inferior vena cava.[1] Non-malignant non-cirrhotic extrahepatic PVT is characterized by thrombus development in the main portal