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LETTER TO THE EDITOR

Absence of CYCS mutations in a large Italian cohort of patients with inherited thrombocytopenias of unknown origin

ANNA SAVOIA[1], PATRIZIA NORIS[2], SILVERIO PERROTTA[3], FRANCESCA PUNZO[3,4], DANIELA DE ROCCO[1], BEN A. OOSTRA[4], & CARLO L. BALDUINI[2]

[1]*Medical Genetics, Department of Reproductive and Developmental Sciences, Institute for Maternal and Child Health, IRCCS "Burlo Garofolo", University of Trieste, Trieste, Italy,* [2]*Clinica Medica III, IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy,* [3]*Department of Pediatrics, Second University of Naples, Naples, Italy, and* [4]*Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, Netherlands*

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Inherited thrombocytopenias comprise a variety of rare disorders that result from defects of platelet production or shortened platelet survival. Although many forms have been characterized and a diagnostic algorithm has been proposed and validated to facilitate their diagnosis, many patients with familial thrombocytopenia do not fall into the category of any defined disease [1]. At least in Italy, approximately 50% of patients remain without a definite diagnosis, which suggests that they are affected with novel forms of these disorders [2]. Most of these affected individuals manifest a non-syndromic, isolated thrombocytopenia without any apparent abnormality of platelet morphology or function. Therefore, distinguishing them from subjects with idiopathic thrombocytopenic purpura may be very difficult or even impossible whenever no other family members are affected and no previous blood count demonstrates that their thrombocytopenia was present since birth. Thus, patients with indefinite genetic thrombocytopenias are at risk of misdiagnosis and unnecessary therapies [3].

The clinical and molecular characterization of any new forms of inherited thrombocytopenia is an important achievement since it reduces the number of patients with unclassified forms and facilitates differential diagnosis between inherited and acquired forms. In this regards, a missense mutation (Gly41Ser substitution in the amino acid sequence lacking the initiating methionine) in the cytochrome c (CYCS) gene has recently been identified as the cause for an autosomal dominant form of non-syndromic thrombocytopenia (THC4, OMIM 612004) in a New Zealand family of English origin [4]. Affected individuals had a mean platelet count of 109×10^9/l, normal platelet morphology and volume, and mild or no bleeding tendency. The mutation yielded a CYCS variant with enhanced activity of the intrinsic apoptosis pathway which is finely regulated during megakaryopoiesis [4]. Indeed, patients showed a reduction of platelets due to a dysregulated megakaryopoiesis with premature release of platelets into bone marrow space rather than into sinusoids.

In order to define any potential role of cytochrome c in our thrombocytopenic population, the CYCS gene was screened for mutations in 77 patients, who were accurately selected among the 202 unrelated individuals refereed to our centers in the last 10 years and diagnosed to have an inherited thrombocytopenia. In 94 patients of these cases a certain diagnosis was made according to the algorithm proposed by the Italian Platelet Study Group [1]. The more frequent disorders were biallelic (no. 10) and monoallelic forms of Bernard-Soulier syndrome (no. 44, 25 of them with the Ala156Val in the gene for GPIbα), MYH9-related disease (no. 22), gray-platelet syndrome (no. 5) and congenital amegakaryocytic thrombocytopenia (no. 4). In the remaining

Correspondence: A. Savoia, Medical Genetics, Department of Reproductive and Developmental Science, IRCCS Burlo Garofolo Hospital, University of Trieste, Via dell'Istria 65/1, 34137 Trieste, Italy. Tel: +39 040 3785275-538. Fax: +39 040 3785540. E-mail: savoia@burlo.trieste.it

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108 affected individuals, we failed to reach a diagnosis. Seventy-seven of them had clinical and laboratory features similar to those of patients with the CYCS mutation [4]. Their mean age was 34 years, and the male/female ratio was 33/44. They had a moderate thrombocytopenia (mean platelet count: $89 \pm 39 \times 10^9$/l) with normal platelet volume (patients 10.6 ± 1.3 fL, controls 10.7 ± 0.9 fL) and normal platelet morphology. In these 77 patients, mutational screening of the CYCS gene (coding exons and their flanking intronic regions) did not identify any alterations of the open reading frame. Only one single nucleotide polymorphism, rs11267038, within the 5′ untranslated region was detected in two unrelated individuals.

Due to the large cohort of patients, who were from different geographic areas and accurately selected to match the phenotypic characteristics of those described in the New Zealand family, we concluded that mutational screening of CYCS should not be included in the front line diagnostic tests in Italy. We are aware that further investigation is required to characterize the unknown disorders that affect more than half the patients referred to our centers.

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