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Role of the Xmn1- "G"γ polymorphism of γGglobin gene in the regulation of Hb F levels in β thalassemia intermedia patients: experience of a single Thalassemia Center.

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Background. β-Thalassemia intermedia (β-TI) represents a highly heterogeneous entity because the clinical picture ranges from non-symptomatic to severe transfusion-dependent forms. Wide-spectrum phenotypic appearance of β-TI can be partly attributed to its great genetics. Several studies have shown that the variation in the level of HbF is genetically controlled. About one third of the genetic variance is due to Xmn1- "G"γ polymorphism (RFLP) of γGglobin gene (HBG2). It is a prominent quantitative trait loci (QTL) in β-thalassemia intermedia (β-TI) and is due to a common genetic variant, C-T at position -158 of the "G"γ globin gene.

In our study, we evaluated the frequency of Xmn1- "G"γ RFLP and its association with Hb F level in a group of β-TI patients.

Patients and Methods. Thirty-one patients with diagnosis of β-TI registered in Thalassemia Center of University Hospital of Messina (Italy) were enrolled in the study. The diagnosis of β-TI was made according to clinical, laboratory and molecular criteria. Genomic DNA was obtained from peripheral blood using standard phenol chloroform extraction. The Xmn1- "G"γ RFLP was studied by amplification of a fragment containing the polymorphic size followed by digestion with the enzyme Xmn1. The product sizes obtained were labeled as (a) Xmn1- "G"γ -/- :666 bp, (b) Xmn1- "G"γ +/-:666, 458, and 208 bp, (c) Xmn1- "G"γ: 458 and 208 bp. Thus, the patients were classified according to status of their Xmn1- "G"γ RFLP as Xmn1- "G"γ +/+, heterozygous Xmn1- "G"γ +/-, and Xmn1- "G"γ -/-.

Results: The study participants consisted of 16 (51.6 %) males and 15 (48.4%) females. Mean age of the patients was 35±3.1 years old. The median age at onset of symptoms and diagnosis were 4.3 years (range: 2-10 years) and 5.0 years (range: 2-13 years), respectively. Four patients (12.9%) were ≤4 years old. Xmn1- "G"γ RFLP was observed in 20 (64.5%) patients. Homozygous (TT) and heterozygous (CT) genotypes of the RFLP represented with frequencies of 8 (25.8%) and 11 (35%), respectively.

Non-zero (β+) alleles of HBB gene constituted 12.9 % (2 patients with heterozygous β+ and 2 with homozygous β+ genotype). Hb F level was significantly higher in patients with at least one Xmn1 allele (53.9±6.9%) than those without the polymorphism (22.5±10.3%, P<0.001). Also, patients with homozygous genotype demonstrated significantly higher Hb F compared to heterozygous (CT) cases (respective percentages of 71±3.8 and 53.9±6.9%, p<0.001).

Conclusion: Our preliminary data highlighted that Xmn1- "G"γ +/+ RFLP is very frequent in β-TI patients, and that it may play a role as regulator of Hb F levels in β-TI. Further studies are needed to clarify the interaction of Xmn1- "G"γ RFLP with other genetic factors.