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Concomitant Variants Associated to Hereditary Persistence of Fetal Hemoglobin (HPFH) in a Non Transfusion Dependent Homozygous Beta(O)39 Background.

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Beta thalassemias are characterized by reduced (beta+) or absent (beta0) beta globin chain production due to homozygous or double heterozygous mutations in beta globin gene. Beta(0) 39 (C>T) mutation, which converts the normal CAG codon for glutamine in a TAG stop codon, causes premature termination of beta chain synthesis. Individuals homozygous for this mutation are forced since childhood to regular blood transfusions and clinically classified as Thalassemia Major (TM). However, this homozygosity is sometime masked by other mutations or deletions in the beta globin gene cluster leading to an asymptomatic condition called hereditary persistence of fetal hemoglobin (HPFH). Here we report four cases of beta thalassemia intermedia (TI): two patients were episodically transfused, one became transfusion dependent at the age of 37 after pregnancy and the last was never transfused. They all carry homozygous beta(0) 39 mutation, two of them have heterozygous mutation in G-gamma globin gene -158 C>T and the four bases -225 to -222(-AGCA) deletion in A-gamma globin gene, while the other two had this deletion in homozygous state. These globin genes mutations are combined with haplotypes in the modifier genes associated to HPFH such as BCL11A and HBS1L-MYB intergenic region. These data suggest that the high level of fetal hemoglobin (Hb F) could be due to the synergistic effect of all these variants, although the contribution of other unknown genetic factors could not be completely ruled out.