

AB098. Genotype-phenotype association studies in patients with Beta-thalassemia: a systematic review

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Background: It is known that type of β -globin (*HBB*) gene mutation primarily affects the severity of beta-thalassemia disease. This study aimed to determine the association of different types of *HBB* mutation and genetic modifiers with disease manifestations (phenotypes) in β -thalassemia.

Methods: A systematic review was conducted through literature search using MEDLINE covering the period, 1996–May 2017. The following (Mesh) terms were used: (I) genotypes/mutations: beta-thalassemia; beta-globins; genotype; DNA mutational analysis; phenotype; (II) clinical manifestation: age of presentation; age of first transfusion; transfusion dependence; spleen size; liver size; growth and development; ferritin level; steady-state hemoglobin; hematologic profile; response to treatment; survival. The searched articles were screened on the basis of titles and abstracts. Our inclusion criteria were studies containing the following information: (I) β -globin gene mutations and/or β -thalassemia modifier genes; (II) phenotype in terms of age at disease presentation, age at receiving first blood transfusion, requirement for transfusion, spleen size, liver size, growth and development, ferritin level, steady state hemoglobin level, response to drug treatment, and/or survival; phenotype described as β -thalassemia major,

β -thalassemia intermedia or β -thalassemia minor; (III) genotype-phenotype correlation.

Results: A total of 39 studies containing genotype-phenotype correlation were included. Ten studies investigated mutations on *HBB* gene and *HBB* pseudogene and related clinical phenotypes and disease severity. The IVS1-5 (G>C) mutation was found common in India and Thailand and associated with moderate-to-severe phenotypes. Majority of the *HBB* genotypes were single nucleotide substitutions in intervening sequences and specific codons, they were found correlated with moderate-to-severe phenotypes. Nineteen studies investigated the effect of *HBB* mutations and co-inheritance of alpha-thalassemia and HbF enhancer genes. Co-inheritance of α -thalassemia in β -thalassemia (7/7 studies) and the presence of XmnI polymorphism (8/8 studies) were associated with less severe phenotypes in terms of age of onset, age of first transfusion, and transfusion dependence. Five studies analyzed the effect of co-inheritance with alpha triplicated genes on the presentation and disease severity of beta-thalassemia. It (3/4 studies) was shown that co-inheritance with alpha gene triplication were correlated with more severe disease.

Conclusions: β -thalassemia disease presentation is influenced primarily by type of β -globin mutation but modifier genes also play roles in disease phenotype by affecting globin chain imbalance.

Keywords: Beta-thalassemia; genotype-phenotype correlation; systematic review

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