Molecular Characterisation and Frequency of TGFβ1 Gene Polymorphism and its Relation to Bone Complications in Egyptian β-thalassaemia Patients

Thesis

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Summary

β-thalassaemia syndromes are one of the most common autosomal recessive hereditary disorders worldwide, with high prevalence in the populations of the Mediterranean, Middle-East, Central Asia, Indian subcontinent and Far East.

Blood transfusions from infancy until adulthood in beta-thalassaemia major patients have substituted severe bone complications with less marked skeletal lesions such as osteoporosis that is characterized by low bone mineral density resulting in reduced bone strength and increased risk of fractures. Genetic factors play an important role in the pathogenesis of this disease.

Transforming growth factor β1 (TGFβ1) gene was one of the first suggested candidate genes to contribute to genetic risk for low BMD and osteoporosis.

Several polymorphisms have been identified in the TGFβ1 gene. Many ofthese polymorphisms are located in the promoter region and may influence transcription with subsequent change in TGFβ1factor level.

Previously, the TGFβ1gene promoter polymorphism C-509T (*C−1348T, rs1800469*) has been associated with changes in BMD and osteoporosis, although with different and contradictory results.

This study aimed to determine the frequency of TGFβ1 (C-

509T) gene polymorphism and its relation to bone complications in β-thalassaemia major patients in Egypt.

The present study included 100 children with β-thalassaemia major. They were selected among cases attending Fayoum University Hospitals and under regular blood transfusion and chelation therapy.

All patients were subjected to history taking, routine laboratory investigations and determination of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA). Genotyping was conducted for TGFβ1 gene polymorphism at C-509T using PCR/RFLP analysis.

The frequency of TGFβ1 gene polymorphism C-509T genotypes in all studied patients was 6% for homozygous CC, 85% for heterozygous CT and 9% for homozygous TT. The C allele frequency was 48.5% while T allele frequency was 51.5%.

Mean BMD Z-score was significantly higher in TT genotype compared to CC genotype with p-value <0.05.

According to DXA Z-score, patients were divided into two groups, 50 (51%) with BMD deficit (Z-score $\geq$ -1) and 49 (49%) with normal BMD (Z-score $<$ -1). The frequency of TGFβ1 gene polymorphism C-509T genotypes in patients with BMD deficit was 11.8%)6/51) for homozygous CC genotype, 84.3% (43/51) for heterozygous CT genotype and 3.9% (2/51) for homozygous TT. In patients with normal BMD, the frequency of TGFβ1 gene polymorphism homozygous CC genotype was 0 % (0/49), heterozygous CT genotype was 85.7% (42/49) and for homozygous

TT was 14.3 % (7/49).

TGFβ1 gene polymorphism C-509T genotypes were distributed differently among patients with BMD deficit and patients with normal BMD. The TT genotype was less common in patients with BMD deficit ($p < 0.05$).

TGFβ1 gene polymorphism C-509T was associated with bone mineral density (BMD) and genetic susceptibility to osteoporosis in the studied population and may play a role in the pathogenesis and modification of bone complications in β- thalassaemia major. However further studies with larger cohort are needed to confirm the findings of this study.