Novel splice site mutations in Iranian Phenylketonuria patients

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Introduction

- Phenylketonuria (PKU) as an autosomal recessive disease is one of the most common in born error of metabolism in our population.
- Untreated patients show different levels of mental and physical retardation, so early diagnosis is very crucial in patient management.
- In the present study, four splicing site mutations were observed which haven't been reported yet.
- PAH gene encodes phenylalanine hydroxylase enzyme which converts phenylalanine to tyrosine, the essential neurotransmitter precursor.
- Any malfunction may lead to disease state. This study aimed to identify the causative mutations in PKU patients referred to Dr.Zeinali Medical Genetics laboratory for mutation detection.

Materials and Methods

- After collecting blood samples and DNA extraction, mutation screening of PAH gen was performed using direct sequencing of all exons and exon-intron boundaries of the gene.

Results

- Different types of mutations were identified which include novel splice site mutations.
- The mutations were including two cases with c.169-1G>A in intron 2, four cases c.510-1G>A in intron 5, two c.970-1G>T in intron 9 and two c.1066-2A>G in intron10.
- Based on the autosomal recessive pattern of the disorder all parents were confirmed to be carrier using direct sequencing followed by linkage analysis using STR (Short tandem repeat) study as an indirect method.

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Discussion

- Any changes in invariant GT AT sequence in donor and acceptor splicing sites always will disturb recognition splice site by spliceosome. This phenomenon leads to skipping an exon or retaining intronic sequence in mature mRNA in most cases.
- The Human Splicing Finder website, confirmed their crucial effect of these changes on the final splicing of the protein; these alterations may lead to the enzyme dysfunction.
- So they are potentially pathogenic mutations and helpful in PGD (Preimplantation Genetic Diagnosis) and PND (Prenatal Diagnosis) purposes.

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