Identification of the Most Common Mutations in the Phenylalanine Hydroxylase (PAH) Gene in Jordanian Patients.


National Center for Diabetes, Endocrinology and Genetics (Amman), Institute of Medical Biology: Human Embryology (Singapore), Jordan PKU Clinic (Amman)

rgafaathalla@gmail.com

ABSTRACT:
Phenylketonuria (PKU) is an autosomal recessive metabolic disorder caused by mutations in the phenylalanine hydroxylase (PAH) gene. PKU is included in the National Jordanian Screening Program, with its incidence recorded at 1 in 4000. In spite of existence of such program, the spectrum of PAH gene mutations in Jordanian patients has not been examined yet. The current study was initiated by the National Centre for Diabetes, Endocrinology and Genetics (NCDEG) in collaboration with the Jordanian Ministry of Health, with the aim of establishing DNA diagnostic facilities, identifying the mutations and implementing prenatal and Pre-implantation Genetic Diagnosis (PGD) testing.

INTRODUCTION:
PKU is one of the most common inborn metabolic disorders, with an average incidence of 1 in 10000 in Caucasians and a variable frequency in other populations (6). It is an autosomal recessive disorder, caused by a genetic error in the hepatic enzyme PAH gene, located on chromosome 12q22-q24, 2, comprising 13 exons (5, 7).

Up to date, five hundred and sixty four mutations have been identified in the PAH gene with the majority of the mutations clustering in exons 6 and 7 (Fig. 1) (www.pahdb.mcgill.ca). According to the National Jordanian Screening Program (NJS), the average incidence of PKU in the Jordanian population is 1/4000. In association with the newly established newborn screening program, it is necessary to establish common mutational screening for the affected individuals and families.

RESULTS:
None of the forty seven PKU patients carried any of the mutations screened in this study (Fig. 3). Sequencing of the PAH gene in the five PKU index patients revealed that two were homozygous for the ES68C, IVS2+1G>A mutation in exon 2- intron 2 boundary (E2-12), which was previously reported in the Palestinian population (3). One patient was heterozygous for the L48S mutation in exon 2, which was detected in the Turkish population (4). And the remaining two mutations identified in our samples, the Y810-11G>A located in intron 10 and the F39del in exon 2 respectively, have been reported in the European populations (1, 2).

In order to confirm the obtained results, we sequenced exon 2 of the PAH gene in three of the patients, with the mutation also identified through our methodology (Fig. 4).

DISCUSSION AND CONCLUSION:
The molecular basis of the most common mutations within the Arab Jordanian population has not been extensively analyzed. Nevertheless, several studies have reported a PAH gene mutation pattern within the Mediterranean population (Fig. 2).

So far, the five mutations examined in our lab (common within Arab populations), were not present within the forty seven samples screened. Sequencing of the remaining patients presenting with PKU might reveal novel mutations that may be present only in the Jordanian population. Preliminary data indicates that common mutations within the Jordanian population might be clustered within exon 2 and not within exons 6 and 7 as predicated.

Furthermore, the current study of PKU may reveal a presence of novel, not yet identified, mutations in the Jordanian population. In the future, we hope that through mutual collaboration between the medical community, Jordan Charity Association for Phenylketonuria (JCA PKU) and molecular genetics laboratory, we will be able to identify PAH mutations present in Jordan, and provide better services related to diagnosis and prenatal testing of PKU.

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