

## Letter to the Editor

### High Frequency of IVS10nt546 Linked to VNTR8 in Iranian PKU Patients from Fars Province

#### Dear Editor;

Analysis of the phenylalanine hydroxylase (PAH; McKusick 261600) gene in different populations has revealed more than 320 different mutations associated with phenylketonuria (PKU). One of these mutations, IVS10nt546, results in severe PAH deficiency due to defective mRNA splicing. It accounts for about 40 percent of all mutant alleles in Turkish and between 10 to 20 percent of all mutant alleles in Spanish, Italian, Sicilian, and Bulgarian populations [1-6]. This allele is rare in Western Europe and is mostly absent in northern and eastern European populations [1, 7].

Analysis of variable number of tandem repeat (VNTR) polymorphism linked to the IVS10nt546 mutation in Turkey, Israel, Italy, Spain, Germany, Switzerland and Denmark showed that in these populations the IVS10nt546 mainly linked to allele VNTR with 7 repeat (based on 252 observed IVS10nt546) [1, 3-5]. However, only in 3 cases from Italy the mutant allele was linked with VNTR8 [1, 5]. Unfortunately, there is no information about the frequency of IVS10nt546 and its linkage(s) with VNTR alleles in Iranian populations.

We extracted genomic DNA from patient's leukocytes and used for PCR. Mutation analysis on 8 PKU patients, showed 5 alleles of IVS10nt546 in 3 patients (two patients were homozygous and one patient was heterozygous for the IVS10nt546 allele). Interestingly, all of these alleles were linked with 8 repeats of VNTR. Although the sample size was small, it is suggested that the IVS10nt546 allele linked to VNTR8 have high frequency in Iranian PKU patients.

In European populations from 252 observed IVS10nt546 alleles, only in 3 cases from Italy the mutant allele was linked with VNTR8 [1, 5]. Fisher's exact two-tailed test showed the statistically significant difference for the frequency of IVS10nt546-VNTR8 between Iranian and European PKU patients ( $P = 0.0000013$ ). Therefore, our results revealed that Iranian population has similarity with Turkish population for high frequency of IVS10nt546 allele, but there is a remarkable difference for linkage of VNTR alleles and IVS10nt546 between Iran and Turkey. The high difference of a PAH gene mutation linked with a

specific repeat of VNTR in an Iranian population compared with European populations, is probably a reflection of the complex demographic history of Iran at the crossroad of prehistoric and historical demographic in this area. However, more data are needed to discuss about the geographical distribution and origin of the IVS10nt546-VNTR8.

This study was supported by Shiraz University.

#### REFERENCES

1. Glotsov, A.A., Eisensmith, R.C., Konecki, D.S., Lichter-Konecki, U. and Woo, S.L.C. (1992) Association between mutations and a VNTR in the Human phenylalanine hydroxylase gene. *Am. J. Hum. Genet.* 51: 627-636.
2. Perez, B., Desviat, L.R., Die, M. and Ugarte, M. (1992) Mutation analysis of phenylketonuria in Spain: prevalence of two Mediterranean mutations. *Hum. Genet.* 89: 341-342.
3. Perez, B., Desviat, L.R., De Lucca, M. and Ugarte, M. (1994) Spectrum and origin of phenylketonuria mutations in Spain. *Acta. Paediatr. (Suppl)* 407: 34-36.
4. Romano, V., Cali, F., Guldberg, P., Guttler, F., Indelicato, A., Bosco, P. and Ceratto, N. (1994) Association between haplotypes, Hind III-VNTR alleles and mutations at the PAH locus in Sicily. *Acta. Paediatr. (Suppl)* 407: 39-40.
5. Cali, F., Dianzani, I., Desviat, L.R., Perez, B., Ugarte, M., Ozguc, M., Seyrantepe, V., Shiloh, Y., Giannattasio, S., Carducci, C., Bosco, P., De Leo, G., Piazza, A. and Romano, V. (1997) The STR252- IVS10nt546-VNTR7 phenylalanine hydroxylase minihaplotype in five Mediterranean samples. *Hum. Genet.* 100: 350-355.
6. Guzzetta, V., Bonapace, G., Dianzani, I., Parenti, G., Lecora, M., Giannattasio, S., Concolino, D., Strisciuglio, P., Sebastio, G. and Andria, G. (1997) Phenylketonuria in Italy: Distinct distribution pattern of three mutations of the phenylalanine hydroxylase gene. *J. Inher. Metab. Dis.* 20: 619-624.
7. Eisensmith, R.C. and Woo, S.L.C. (1994) Population genetics of phenylketonuria. *Acta. Paediatr. (Suppl)* 407: 19-2.

---

**Mostafa Saadat\*, Maryam Kamkar, Hassan Mohabatkar and Iraj Saadat**

*Dept. of Biology, College of Sciences, Shiraz University, Shiraz 71454, Iran*

\*Corresponding author; Fax; (98-711) 228 0926; Tel. (98-711) 228 2747; E-mail: saadat@susc.ac.ir