Mutation and Polymorphism Report

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Title : A novel complex mutation of the OTC (ornithine transcarbamylase) gene in a Malaysian pedigree

Keywords:
ornithine transcarbamylase, OTC, indel mutation, urea cycle, infant, newborn

Species: Human

Change is: mutation

Gene/Locus

Name:	ornithine carbamoyltransferase (ornithine transcarbamylase)
Symbol:	OTC
Genbank accession number:	K02100
OMIM accession number:	311250
Locus specific database:	http://www.peds.umn.edu/otc
Chromosomal location:	Xp21.1
Inheritance:	X-linked

Mutation / polymorphism name

Nucleotide change–Systematic name:	c.813 indel AG>C
Amino acid change–Trivial name:	stop 288
Mutation / polymorphism type:	indel mutation, frameshift
Polymorphism frequency:	
Detection method:	Direct DNA Sequencing
Detection conditions:	Primers: 5'-ttactgtcccatgaagttatttaacc-3' 5'-ggaattaatgaacctgagagagcat-3'

Standard 30 cycle PCR, annealing temperature 55 C

Diagnosis method developed: Mutation disrupts normal MnlI restriction site

Evidence for existence and effect of mutation:

	Yes	No	Don't know
1. Base change found on repeat PCR sample	X		
2. Base change segregates or appears with trait	X		
3. Base change affects conserved residue	X		
4. Expression analysis supports hypothesis for causation			X
5. Normals tested (50 required)		X	

Ancillary data

1. **Haplotype association :**
2. **Ethnic background/Population association :** Malay
3. **Geographic association :** Malaysia
4. **Frequency** (of mutation) **in population:**
5. **Clinical phenotype of proband :** Severe neonatal hyperammonemia
6. **Homologous allele** (if recessive trait)**:**
7. **PIC:** (if microsatellite)
8. **Other:**
9. **Present in HGMD listing:** Yes: No: X
   (http://www.cf.ac.uk/uwcm/mg/hgmd0.html)

Comments

The propositus, presented with clinical symptoms at day 2 of life and had a strong family history of multiple early neonatal deaths in males. PCR and direct sequencing using primer sequences of Matsuura et al. (1993) revealed an innocent polymorphism (L101F) (Tuchman and Plante, 1995) and a complex mutation consisting of deletions of A and G of nucleotides 813 and 814 respectively in exon 8 (the third nucleotide of codon 271 and the first nucleotide of codon 272) which were replaced by an insertion of C (c.813 indel AG > C). The indel mutation caused a frame shift which resulted in a stop codon (TGA) occurring 17 amino acids downstream the first mutant codon. The frameshift also resulted in the 17 amino acid (DRRRKSGSRLSKVTRLQ) sequence being different from corresponding wild type sequence of the human OTC (EEEKKKRLQAFQGYQVT) (Hata et al., 1988). The predicted amino acid sequence would result in a truncated protein of 287 amino acid (the wild type being 355 aa). (The mutation was named based on the cDNA sequence of the OTC precursor protein (Horwich et al., 1984) beginning from position 136 of the mRNA sequence Gen Bank Acc No. K02100 ie. the same numbering system used in HGMD).

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References

Hata A, Tsuzuki T, Shimada K, Takiguchi M, Mori M, Matsuda I (1988) Structure of the human ornithine transcarbamylase gene. J Biochem 103: 302-308

Horwich AL, Fenton WA, Williams KR, Kalousek F, Krau JP, Doolittle RF. Konigsberg W, Rosenberg LE (1984) Structure and expression of a complementary DNA for the nuclear coded precursor of human mitochondrial ornithine transcarbamylase. Science 224: 1068-1074

Matsuura T, Hoshide R, Setoyama C, Shimada K, Hase Y, Yanagawa T, Kajita M, Matsuda I (1993) Four novel gene mutations in five Japanese male patients with neonatal or late onset OTC deficiency: application of PCR- single-strand- conformation polymorphisms for all exons and adjacent introns. Hum Genet 92: 49-56

Tuchman M; and Plante,RJ; (1995) Mutations & polymorphisms in the human ornithine transcarbamylase gene: Mutation update addendum. Hum Mutat. 5(4):293-295.