Mutation and Polymorphism Report

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Title : Two novel mutations in the MPZ gene coding region in Charcot-Marie-Tooth type 1 patients of Turkish origin: S54P, [I30del; GVYI29ins]

Keywords: Two Charcot-Marie-Tooth type 1B, CMT1B, myelin protein zero, MPZ, Turkey

Species: Homo sapiens

Change is: One point mutation, and one deletion/insertion

Gene/Locus

Name:	Myelin Protein Zero
Symbol:	MPZ
Genbank accession number:	D14584
OMIM accession number:	118200
Locus specific database:	
Chromosomal location:	1q22-q23
Inheritance:	Somatic- Autosomal Dominant

Mutation / polymorphism name

Nucleotide change–Systematic name:	1) g161T>C
	2) g89-91delATC, g88-92ins GGGGTTTACACC
Amino acid change–Trivial name:	1) S54P
	2) I30del; GVYI29ins
Mutation / polymorphism type:	Missense, Deletion-Insertion
Polymorphism frequency:	
Detection method:	SSCP and DNA Sequencing
Detection conditions:	As described by Nelis et al. 1994.
Diagnosis method developed:	1) Hae III restriction analysis for S54P; 2) I30del; GVYI29ins mutation cloning and sequencing were performed

Evidence for existence and effect of mutation:

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

Ancillary data

1. **Haplotype association :**
2. **Ethnic background/Population association :** Turkish population
3. **Geographic association :**
4. **Frequency** (of mutation) **in population:**
5. **Clinical phenotype of proband :**

Patient 1: distal weakness, abolished deep tendon reflexes, and diminished vibratory sensation in the lower extremities, pes cavus and hammer toes. Absence of sensory action potential, median motor NCV was 22m/s.

Patient 2: distal weakness and wasting of the extremities, areflexia, glove and stocking type of hypoesthesia with diminished vibratory sensation of the four limbs, and pes cavus. Absence of sensory action potentials, NCV of median nerve was 17m/s.

Both patients: severe reduction in density of myelinated fibers with onion bulbs on sural nerve biopsy.

6. **Homologous allele** (if recessive trait)**:**
7. **PIC:** (if microsatellite)
8. **Other:**
9. **Present in HGMD listing:** (http://www.cf.ac.uk/uwcm/mg/hgmd0.html)

Yes: No: xx

Comments

Charcot-Marie-Tooth type 1B (CMT1B) cosegregates with mutations in the Myelin Protein Zero (MPZ) gene (Pham-Dinh et al, 1993). MPZ functions as a double adhesion molecule to hold together the myelin sheath through extracellular and cytoplasmic interactions (Fiblin et al, 1990). In this study, we report MPZ gene mutations in exon 2 of two unrelated CMT1B patients from Turkey. Both patients were clinically diagnosed as CMT1 with NCV values of 22 and 17m/s. Patient 1 is a 26-year old female with no family history of neurological disorders. The patient was found to be heterozygous for a T>C transition resulting in a S54P substitution. This mutation creates a *Hae* III restriction site which was detected in the patient but not in her parents and 50 normal controls. Introduction of Proline by this substitution might result in an extra α helix in the amino acid chain, and therefore alter the capacity of the extracellular domain to interact correctly. Patient 2 is a 57-year old diabetic male. His mother and maternal grandmother had complained of unstable walking prior to their death. In patient 2, sequencing of the cloned exon 2 fragment revealed the deletion of codon 30 and an insertion of 12 nucleotides which seems to be an imperfect (GTG -> GGG at codon 31) tandem duplication of the following 12 nucleotides. While Isoleucine at codon 30 has been deleted, Glycine, Valine, Tyrosine, and Threonine have been

inserted in its place. This mutation will lengthen the beta strand between Isoleucine 30 and the following 5 amino acids (Kirschner et al, 1994), and may hinder normal homophilic interactions. The two novel mutations reported here, in addition to others, will help unravel underlying molecular mechanisms that lead to CMT1.

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