CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2015
Printed in Singapore. All rights reserved

CLINICAL GENETICS
doi: 10.1111/cge.12649

Letter to the Editor

COX6A1 mutation causes axonal hereditary motor and sensory neuropathy – the confirmation of the primary report

To the Editor

In the September 2014 issue of the *American Journal of Human Genetics*, Tamiya et al. stated that a homozygous deletion c.247-10_247-6del CACTC in COX6A1 is a cause of axonal and intermediate autosomal recessive Charcot–Marie–Tooth disease in two families of Japanese origin (1).

We report a patient with the same homozygous deletion. Our work confirms the link between *COX6A1* mutations and hereditary neuropathy. We report a first patient with *COX6A1* mutations outside Japan. This letter describes the phenotype of the patient in detail to support the primary report in the presentation of the disease, but also provides additional clinical features that were observed. Moreover, our data confirms a mutational hotspot which has been proposed by Tamyia et al. Last but not least, in our opinion, the correct nomenclature for the deletion should be: c.247-7_247-3del (not c.247-10_247-6delCACTC), and this is discussed at the end of the letter.

The patient is of Czech origin, now 37 years old, presenting severe diffuse axonal neuropathy. The patient is a sporadic case in the family. The father of the patient is a heterozygous carrier of the mutation. The mother of the patient is deceased. She has four half-siblings, none of them was available for testing. However, a nephew from the maternal side was tested and is also a heterozygous carrier of the mutation (Fig. S1, Supplementary Information). She has no children. The two families from Japan were consanguineous. However, as far as the proband knows, her parents are not related and not endogamous and originate from different regions of the Czech Republic. The mother's father is of Roma origin, the father is Caucasian.

The first symptoms occurred at the age of 5, mainly frequent falls and instability. The diagnosis of hereditary

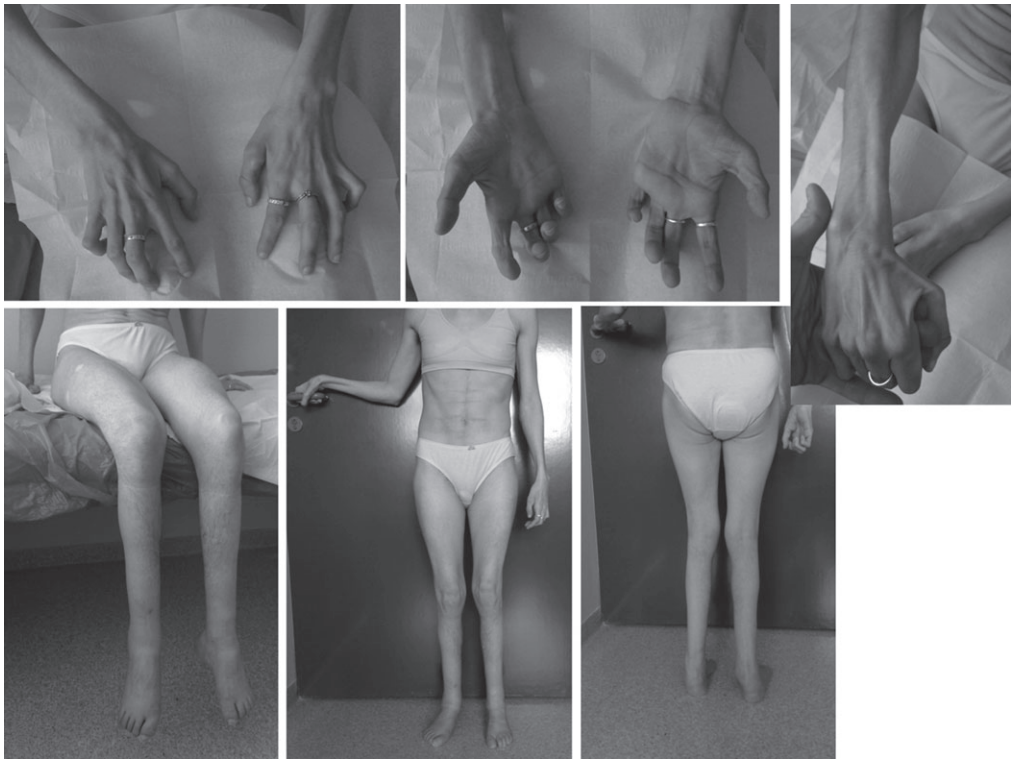

Fig. 1. Patient at the age of 37.

Table 1. Clinical examination

Presentation at 37 years	Test		Results	
Upper limbs	Muscle atrophies		Profound muscle atrophies of the forearm and hand muscles are present.	
	Contractures/deformities		Contractures of the fourth and fifth finger on both hands.	
	Reflexes		Reflexes C5-C8 are absent.	
	Muscle strength (MRC scale – Medical Research Council scale): grades 0–5		Muscle strength is normal proximally, with only a mild deficit distally (MRC 4).	
			Shoulder abduction, elbow flexion/extension 5	
			Wrist extension/flexion 5	
			Finger flexion 4-	
	Sensory testing		Glove deficit	
		Pin prick test	She was unable to distinguish sharp/blunt stimuli.	
		Vibration test	Vibration test at wrist was 4/8	
Lower limbs	Muscle atrophies		At lower limbs profound atrophies distally are present up to the mid-thigh.	
	Contractures/deformities		Foot deformity on both feet (pes cavus)	
	Reflexes		Knee reflex was increased (3+), ankle reflex absent (0)	
	Muscle strength (MRC scale – Medical Research Council scale): grades 0–5		Muscle strength proximally was preserved (MRC 4), but distally plegia.	
			Hip flexion/extension 4	
			Knee flexion/extension 4	
			Foot dorsiflexion/plantar flexion 0	
			Big toe extension/toes extension 0	
	Sensory testing		Sensory loss in stockings distribution	
		Pin prick test	She was unable to distinguish sharp/blunt stimuli.	
		Vibration test	At toe tips, metatarsal phalangeal joint and tibial tuberosity was 4/8.	
Additional clinical presentation			Bilateral hearing loss	
			Neuropathic pain – mainly nocturnal cramps	
Nerve conduction studies (examination at the age of 24)	Motor nerves:	Nerve	CMAP (mV)	CV (m/s)
		Ulnaris (Lt)	1.1	44
		Medianus (Lt)	1.2	46.4
		Tibialis (Lt)	Not evoked	
		Peroneus (Lt)	Not evoked	
	Sensory nerves	Nerve	SNAP (μV)	CV (m/s)
		Ulnaris (Lt)	4.0	22.5
		Radialis (Lt)	Not evoked	
		Suralis (Lt)	Not evoked	

CMAP, compound muscle action potential; CV, conduction velocity; Lt, left; SNAP, sensory nerve action potential.

motor and sensory neuropathy was stated at the age of 7. From the age of 10, she has used walking aids. She has undergone several foot surgeries, the first at the age of 13. The patient reports perceiving neuropathic pain in the last 6 years (from the age of 32). Treatment with a dose of Neurontin and Clonazepam daily is partially successful. The pain is mainly nocturnal cramps, seriously disrupting sleep. Additionally, the patient has bilateral hearing loss since the age of 35.

Recently, under clinical examination (at the age of 37), the patient presents with unstable gait. She is able to walk only with crutches and prefers to use a wheelchair in the near future due to overall weakness. Photographs of the patient are presented in a Fig. 1. Neurological examination is summarized in Table 1.

After single gene tests by Sanger sequencing of *GDAP1*, *MFN2*, *HK1*, *NDRG1* and *HINT1*, the patient was recently tested with massive parallel sequencing of a gene panel consisting of 78 genes currently associated with hereditary neuropathy. *COX6A1* gene was also included in the panel based on the new information from the primary article. Agilent HaloPlex was used for library preparation, data analysis was performed with SureCall (Agilent Technologies, Santa Clara, CA, USA) and in-house pipeline developed under local installation of Galaxy. Haplotype analysis was done with the same single-nucleotide polymorphism markers as in the primary report (seven markers were chosen). The testing showed different haplotypes around the mutation region for our family and Japanese families (Fig. S2). It is therefore highly probable that the mutation arose independently. Our work further supports the idea that the site of the deletion is a mutational hotspot.

In our opinion the correct designation of the mutation should be: 'GenBank: NM_004373.2:c.247-7_247-3del', on the genomic level: Chr12(GRCH37): g.120878250-120878254del. Our conclusion is based on recommendations from Human Genome Variation

Society (www.hgvs.com), which states that for deletions: 'for all descriptions the most 3′ position possible is arbitrarily assigned to have been changed' (2). We understand that this is not the most crucial point of our letter, however, we would like to clarify this in order to avoid ambiguities in the future.

We agree with Tamiya et al. that the mutation affects splicing. Brief explanation how this intronic mutation is expected to act as a pathogenic mutation is presented in Fig. S3. In summary, 122 patients – 244 alleles were tested for the presence of this mutation in the *COX6A1* gene, and mutation was detected in only one patient in homozygous state (2 alleles), thus allele frequency is maximum 0.0081%. This is in concordance with reported allele frequency in known databases, esp. Exome Aggregation Consortium (http://exac.broadinstitute.org/), where is stated frequency for this variant 0.004% for all populations, for European (Non-Finnish) population the observed frequency is 0.005%. Such a frequency is also in agreement with autosomal recessive inheritance – minor allele frequency in population in not zero, there is to be expected a small number of carriers in the population.

Our work confirms the link between *COX6A1* gene and hereditary neuropathy. Mutations in *COX6A1* might not be as rare as previously thought and we recommend including the *COX6A1* gene in a gene panel design for hereditary neuropathies. The study was approved by the ethics committee of University Hospital Motol, and the informed consent was obtained from the patient.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Acknowledgements

This work was supported by IGA MH CR NT 14348.

P. Laššuthová[a]
R. Beharka[b]
M. Krůtová[a]
J. Neupauerová[a]
P. Seeman[a]
[a]Department of Paediatric Neurology, DNA Laboratory, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic, and
[b]Department of Medical Genetics, The University Hospital Brno, Brno, Czech Republic

References

1. Tamiya G, Makino S, Hayashi M et al. A mutation of COX6A1 causes a recessive axonal or mixed form of Charcot-Marie-Tooth disease. Am J Hum Genet 2014: 95: 294–300.
2. den Dunnen JT, Antonarakis SE. Mutation nomenclature extensions and suggestions to describe complex mutations: a discussion. Hum Mutat 2000: 15: 7–12.

Correspondence:
Petra Laššuthová
Department of Paediatric Neurology
DNA Laboratory
2nd Faculty of Medicine
Charles University in Prague and University Hospital Motol
Prague
Czech Republic.
Tel.: +420 22443 6789;
fax: +420 22443 5820
e-mail: petra.lassuthova@gmail.com