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SHORT COMMENTARY

A patient with *PMP22*-related hereditary neuropathy and *DBH*-gene-related dysautonomia

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Abstract Recurrent focal neuropathy with liability to pressure palsies is a relatively frequent autosomal-dominant demyelinating neuropathy linked to peripheral myelin protein 22 (*PMP22*) gene deletions. The combination of *PMP22* gene mutations with other genetic variants is known to cause a more severe phenotype than expected. We present the case of a patient with severe orthostatic hypotension since 12 years of age, who inherited a *PMP22* gene deletion from his father. Genetic double trouble was suspected because of selective sympathetic autonomic disturbances. Through exome-sequencing analysis, we identified two novel mutations in the dopamine beta hydroxylase gene. Moreover, with interactome analysis, we excluded a further influence on the origin of the disease by variants in other genes. This case increases the number of unique patients presenting with dopamine-β-hydroxylase deficiency and of cases with genetically proven double trouble. Finding the right, complete diagnosis is crucial to obtain adequate medical care and appropriate genetic counseling.

Keywords Recurrent focal neuropathy with liability to pressure palsies · Dopamine-β-hydroxylase deficiency · Exome sequencing, dysautonomia

Introduction

Recurrent focal neuropathy with liability to pressure palsies, (hereditary neuropathy with liability to pressure palsies, HNPP) is an autosomal-dominant demyelinating neuropathy, caused in most patients by a 1.5-Mb deletion encompassing the peripheral myelin protein 22 (*PMP22*) gene on chromosome 17p11.2–12 [1]. HNPP manifests as a recurrent acute focal neuropathy with compression as a

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precipitating factor, affecting mainly the brachial plexus or common peroneal nerves in young patients, while sensory loss, weakness, and muscle atrophy in the hands and/or feet are often observed in the elderly [2].

Dopamine-β-hydroxylase (DβH) deficiency is a rare autosomal recessive disorder characterized by the congenital absence of the enzyme DβH, which is required for the conversion of dopamine (DA) to noradrenaline (NA), in sympathetic nerve terminals and adrenal medulla [3]. Accordingly, NA and adrenaline are undetectable in plasma, urine and cerebrospinal fluid with increased DA plasma levels [3, 4]. To our knowledge, 24 patients with DβH deficiency have been described worldwide (Table 1). The disease is clinically characterized by primary autonomic failure, mainly cardiovascular, with severe orthostatic hypotension [3]. We report a 37-year-old patient with tomacular neuropathy due to a deletion of the *PMP22* gene and neurogenic orthostatic hypotension secondary to DβH deficiency, caused by two novel mutations in the dopamine beta hydroxylase (*DBH*) gene.

Case report

The patient's history was remarkable for a left temporoparietal concussion at the age of three, with an occipital fracture and paroxysmal electroencephalogram (EEG) anomalies up to the age of nine. From age 12, the patient complained of fatigue, light-headedness, bilateral blurred vision and increased perspiration arising on assuming or keeping the upright position and ceasing with sitting or lying down. The patient complained monthly occasional diarrhea from the age of 20. The patient was started on midodrine and fludrocortisone, with symptoms' improvement. At age 28, episodic paraesthesias and tactile hypoaesthesias began, either spontaneously or after secondary compressions. These symptoms were limited to the extremities and had variable duration (from 1–2 days to 2 weeks), occurring 2–3 times per year. Three years later, motor impairment appeared, and the patient lost dorsiflexion of the tip of his right foot. Brain magnetic resonance imaging (MRI), performed at the age of 34 years, was normal. Electroneurography (ENG) studies at age 34 detected an increased distal motor latency in the right median and ulnar nerves, as well as a reduction in sensitive conduction at the elbow and an increase in F-wave mean latency. Right and left peroneal and posterior tibial nerve studies demonstrated an increase in distal motor latency and a reduction in distal motor conduction velocity, together with an increased F-wave mean latency. Overall, ENG showed a decrease in sensory-motor conduction velocity with preserved action potential amplitude.

The proband's father was diagnosed with hereditary neuropathy with liability to pressure palsies due to the deletion of the *PMP22* gene. After a specific genetic counseling, the presence of *PMP22* gene deletion was investigated also in the proband and his brother, and was identified only in the proband. The *PMP22* gene copy number was assessed by the Multiplex ligation-dependent probe amplification (MLPA) assay. The proband's mother was diagnosed with HLA-B27-positive rheumatoid arthritis when she was 27 years old and with type I diabetes mellitus at 32. The proband's brother had no relevant clinical history.

Neurological investigations

We performed an extended autonomic function test (AFT) aimed at measuring the cardiovascular autonomic responses to postural changes by means of head-up tilt (HUT) and standing tests, and determining the responsiveness of the autonomic nervous system (ANS) to stimuli in daily life. The sympathetic branch of the ANS was investigated by means of orthostatic challenges and pressor stimuli such as isometric exercise, cutaneous cold test, the Valsalva maneuver and mental arithmetic. Cardiac parasympathetic responsiveness was measured by means of deep breathing, the Valsalva maneuver, hyperventilation, and orthostatic challenges. In the proband, head-up tilt test was tolerated with a tilt angle of 65° for only 8′30″ and showed a severely symptomatic orthostatic hypotension [Δ systolic blood pressure (ΔSBP): −61 mmHg; Δ diastolic blood pressure (ΔDBP): −35 mmHg] with a compensatory heart rate (HR) increase (ΔHR: 30 bpm) (Supplementary Table S1). The expected BP overshoot during phase 4 of Valsalva Maneuver (VM) (post-release) was absent, and HR variability was reduced (Fig. 1). A modest respiratory arrhythmia was present during deep breathing (Δinspiratory − expiratory: 10 bpm). Isometric handgrip increased blood pressure (BP) (ΔSBP: 20 mmHg; ΔDBP: 15 mmHg; ΔHR: 14 bpm). The cold pressor stimulus failed to raise BP (ΔSBP: 4 mmHg; ΔDBP: 0 mmHg; ΔHR: −4 bpm). These results were compatible with a selective cardiovascular and skin noradrenergic failure with preserved cardiovagal function. Catecholamine titration in the proband demonstrated NA values of 6 pg/mL (normal values 182 ± 40 pg/ml) and DA values of 181 pg/mL (normal values up to 70 pg/ml) while lying flat as well as NA values of 16 pg/mL and DA values of 531 pg/mL while upright, and allowed the diagnosis of DβH deficiency (Supplementary Table S2). The proband's mother, father and brother showed no signs of orthostatic hypotension during HUT (Supplementary Table S1). Catecholamine titration performed on the proband's family showed no

Table 1 Review of clinical and genetic features of patients with DβH deficiency

Study	Sex	Age	BP (mmHg)		HR (bpm)		Clinical aspects	AFT	Plasma catecholamines (pg/mL)			MIBG scintigraphy	Pathogenic Mutations
			Supine	Upright	Supine	Upright			NA	A	DA		
Man in 't Veld et al. [5]	F	20	105/65	60/…	72–80	>96	OH, occasional syncope, weakness of facial musculature, recurrent hypoglycemic coma, sluggish deep tendon reflexes	Selective adrenergic sympathetic failure Intact cardiac vagal efferents Intact sympathetic cholinergic innervation	n.d.	n.d.	507		
Man in 't Veld et al. [6]	F	20					OH, occasional syncope, weakness of facial musculature, recurrent epileptiform symptoms, sluggish deep tendon reflexes	Selective adrenergic sympathetic failure Intact cardiac vagal efferents Intact sympathetic cholinergic innervation	n.d.	n.d.			
Biaggioni et al. [7]	M	42	102/56	56/34	56	62	Severe OH, ptosis, nasal stuffiness, impotence due to retrograde ejaculation, bouts of unexplained diarrhea, tonic–clonic seizures when upright, JHS	OH No response to pressor stimuli No Valsalva phase IV overshoot. Sweating intact. Selective noradrenergic failure	<5	<5	320		
Mathias et al. [8]	M	35	122/77	83/46	48	83	Severe OH, especially in the morning, heat and after exercise. Nocturia. Prolonged or absent ejaculation	Sympathetic adrenergic failure with spared sympathetic cholinergic and intact parasympathetic function	n.d.	n.d.	203		
	F	30	121/60	82/40	60	83	Severe OH, especially in the morning, heat and after exercise. Nocturia	Sympathetic adrenergic failure with spared sympathetic cholinergic and intact parasympathetic function	n.d.	n.d.	401		
Gentric et al. [9]	F	60					Severe orthostatic hypotension		n.d.	n.d.			
Thompson et al. [10]	F	14		100/60	70	44	Dizziness Lethargy after rising in the morning associated with diplopia and retro-orbital headaches	Sympathetic nervous system dysfunction No Valsalva maneuver (Phase IV) overshoot Parasympathetic function appears to be intact	20	n.d.	203		
Scurrah et al. [11]	F	22	95/60	80/40			OH, syncope, exercise intolerance						
Kim et al. [12]	M	55					Lifelong history of fainting spells, ptosis, nasal stiffness, and retrograde ejaculation		<10	n.d.	172		Intron 1: c.339 + 2T>C* Exon 2: p.Asp114Glu
	F	48					Lifelong history of orthostatic hypotension, ptosis, nasal stiffness, and a neonatal history of delayed eye opening		<10	n.d.	141		Intron 1: c.339 + 2T>C* Exon 1: p.Val101Met Exon 6: p.Asp345Asn

Table 1 continued

Study	Sex	Age	BP (mmHg)		HR (bpm)		Clinical aspects	AFT	Plasma catecholamines (pg/mL)			MIBG scintigraphy	Pathogenic Mutations
			Supine	Upright	Supine	Upright			NA	A	DA		
Garland et al. [13]	F	22					Orthostatic intolerance, inability to stand upright for more than 2 min without fainting		n.d.	n.d.	169		
Deinum et al. [14]							Orthostatic syndrome with sympathetic failure		0	0	480		Intron 1: c.339 + 2T>C* (homozygosity)
							Orthostatic syndrome with sympathetic failure		0	0	250		Intron 1: c.339 + 2T>C* Exon 3: p.Glu206Glyfs*82
							Unexplained mild anemia and postural dizziness, propensity to diarrhea and exercise intolerance during childhood		0	7	77		Exon 4: p.Cys269Phe (homozygosity)
							No spontaneous complaints, severe decrease in blood pressure during orthostatic challenge		20	72	205		Intron 1: c.339 + 2T>C* Exon 11: p.Tyr556Cys
							Orthostatic syndrome with sympathetic failure		0	10	51		Intron 1: c.339 + 2T>C* Exon 11: p.Tyr556Cys
							No spontaneous complaints, severe decrease in blood pressure during orthostatic challenge		5	0	114		Intron 1: c.339 + 2T>C* Exon 11: p.Tyr556Cys
Cheshire et al. [15]	M	28	170/104	55/30	62	87	Partial ptosis, Brachydactyly, decreased development of the central face, high palate, micrognathia, hypotonia, ataxia	Severe cardio- vascular adrenergic failure Preserved cardiovagal and postganglionic sudomotor responses	<10	<10	125		
Erez et al.[16]	F	16					Bilateral coloboma, short hands, and high-arched feet						Double trouble: *DBH* mutations: Exon 1: p.Val101Met Exon 6: p.Asp345Asn 46, XX, del(11)(p12p14)/46, XX
Despas et al. [17]	M	73						Isolated neurogenic OH without abnormal responses to deep breathing 30/15 ratio and handgrip	n.d.	n.d.	67	Elevated early (3.0) and delayed (3.7) H/M ratio (normal laboratory value 1.2)	
Kim et al. [18]	M	20	98/69	60/47	72	117	Severe OH and passing out beginning in early childhood		n.d.	n.d.	115		Intron 1: c.339 + 2T>C* Exon 6: p.Ala362Glu

Table 1 continued

Study	Sex	Age	BP (mmHg)		HR (bpm)		Clinical aspects	AFT	Plasma catecholamines (pg/mL)			MIBG scintigraphy	Pathogenic Mutations
			Supine	Upright	Supine	Upright			NA	A	DA		
Phillips et al. [19]	F	19	103/52	46/34	50	88	Episodes of syncope at 3 years old, diagnosed with DBHD at 16 years old; ptosis						Exon 1: p.Val101Met Exon 6: p.Asp345Asn (homozygosity)
	M	17	139/86	55/33	54	88	Muscle weakness and fatigue; nasal stuffiness; ptosis						Intron 1: c.339 + 2T>C* Exon 6: p.Asp345Asn
	M	23	133/80	73/49	61	91	Type I diabetes mellitus, fatigue; ptosis						Intron 1: c.339 + 2T>C* Exon 6: p.Asp345Asn
This work	M	38	137/81	76/46	54	84	Paroxysmal EEG abnormalities up to age 9 following temporo-parietal concussion. Orthostatic symptoms from age 12. Left retinoic vein subocclusion, ANA +, PMP22-related hereditary neuropathy	OH, no Valsalva phase IV overshoot, normal response to isometric exercise. Parasympathetic functions appears to be intact	16	17	531	Normal early (1.79) and late (2.07) H/M ratio	Double trouble: *DBH* mutations: Exon/Intron 8: c.1374_1374 + 18del Exon 9: p.Thr470Met *PMP22* deletion

The search strategy sought only studies published in English. The principal search terms were Dopamine AND Beta AND Hydroxylase, and/or DBH. We searched MEDLINE (National Library of Medicine) for relevant literature from 1986 to June 2015. Data from the review article Robertson D et al., "Dopamine beta-hydroxylase deficiency". Genereviews. Seattle, WA: University of Washington, Seattle. Initial Posting: September 4, 2003; Last Update: January 24, 201, were also included [4]

BP blood pressure, *HR* heart rate, *AFT* autonomic function testing, *MIBG* ^{131}I/^{123}I-metaiodobenzylguanidine, *Ref.* reference, *n.d.* non-detectable, *OH* orthostatic hypotension, *JHS* joint hypermobility syndrome, *DBHD* dopamine beta hydroxylase deficiency, *EEG* electroencephalography, *ANA* anti-nucleus antibodies, *PMP22* peripheral myelin protein 22

* Before described as c.348 + 2T>C [4]

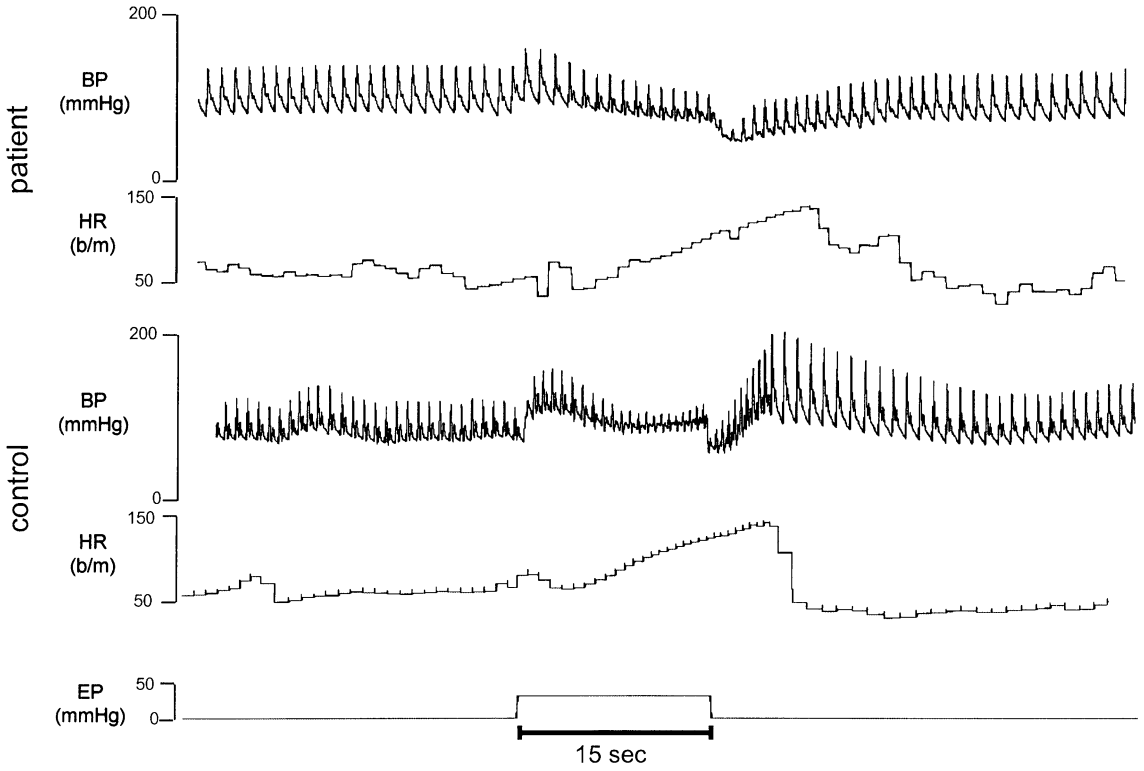

Fig. 1 Valsalva maneuver curve, proband vs. healthy control. Valsalva maneuver (VM) of the patient (*curve above*) vs. a healthy control (*curve below*). Note the absence of expected blood pressure overshoot during phase IV and the reduction in HR variability compared to a healthy control's response to the test

signs of reduced catecholamine synthesis or spillover (Supplementary Table S2). Autonomic nervous system screening tests and catecholamine titration were performed on the patient and his family, as previously described by Guaraldi et al. [20].

Whole exome sequencing

Due to the complex phenotype, whole exome sequencing (WES) analysis was performed on the proband, his parents and brother to identify a genetic cause for the complex clinical presentation (full WES protocol and data analysis are provided in the Supplementary Information). WES identified three candidate causative variants, two in the *DBH* gene and one in the phenylalanine hydroxylase (*PAH)* gene (Table 2; Supplementary Fig. S1). Direct sequencing of *DBH* exon 8/intron 8 boundary confirmed the deletion of 19 bases, including the last nucleotide of exon 8 and the first 18 nucleotides of intron 8 (c.1374_1374 + 18del) associated with the polymorphic variant c.1374 + 24T>G (intron 8) in the proband and in his father (Fig. 2). Two splice prediction tools [21, 22] foresaw that the deletion would lead to the loss of a canonical splice donor site in intron 8 (Supplementary Table S3), and that could be pathogenic. The maternally inherited variant c.1409C>T in the *DBH* exon 9, upstream of the SNP c.1410A>G (rs77905) (Fig. 2; Supplementary Fig. S1), causes the replacement of a threonine with a methionine at codon 470, and was defined as pathogenic by four out of five in silico tools (Supplementary Table S4) [23–27]. Among the genes coding for enzymes involved in NA synthesis and release pathways (*TH*, *DCC*, *VAMP2*, *SLC6A3*, *PAH*) [28], a rare point mutation (c.734T>C, p.Val245Ala) in the *PAH* gene, designated as damaging by four out of five in silico tools (Supplementary Table S4), was present in the affected patient, his brother and mother (Table 2). PAH complete absence, due to mutations in both alleles causes Phenylketonuria. The presence of a single mutation is associated with the condition of asymptomatic carrier (OMIM-261600).

To test whether other variants identified by WES analysis could affect the NA synthetic pathway in the affected proband, we performed a network-based approach (or interactome) analysis (the full protocol is provided in the Supplementary Information). This analysis failed to demonstrate any evidence of interaction between genes involved in NA synthesis and release and genes carrying *de novo* mutations or pathogenic variants identified through WES analysis (Supplementary Table S5–S7).

Table 2 Variants identified through WES analysis

Gene	Position	1.1	1.2	2.1	2.2	Classification	Name
DBH	136518096	C_C	C_T	C_T	C_C	Coding	
DBH	136517406	del	G_G	del	G_G	Deletion	
PAH	103246701	T_T	T_C	T_C	T_C	Coding	rs76212747

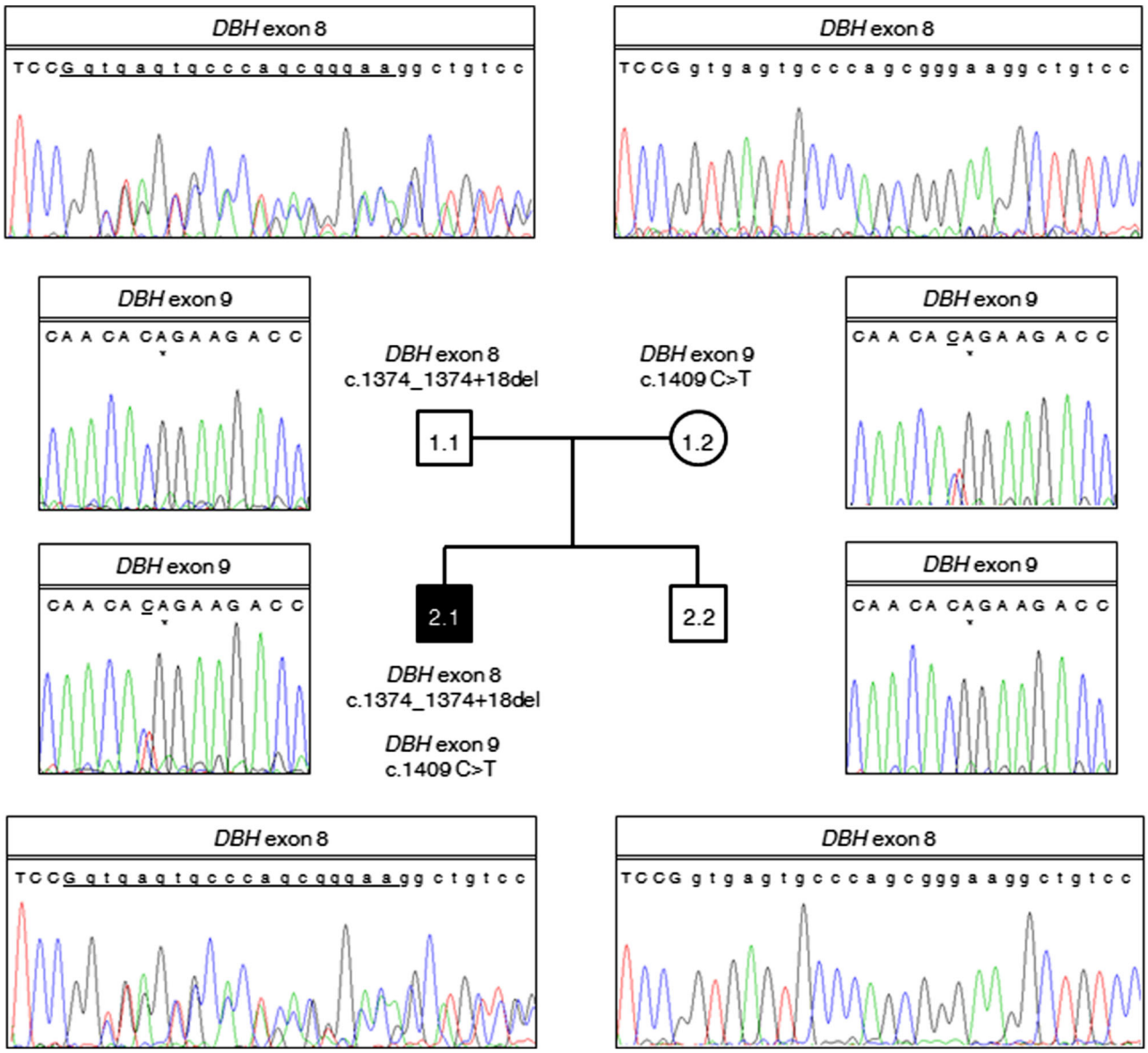

Fig. 2 *DBH* mutation identified through WES analysis. Family tree of patient with DβH deficiency and relative *DBH* mutations validated through Sanger sequencing. The *underlined* nucleotides in the reference sequence are those mutated/deleted. *Asterisk* SNP rs77905

Catecholamine titrations demonstrated the functional effect of the two newly reported *DBH* mutations (Supplementary Table S2). Moreover, the normal levels of NA and adrenaline in the proband's mother and brother proved that the mutation c.734T>C (p.Val245Ala) in *PAH* gene does not have a significant influence on the synthesis of NA and adrenaline.

Discussion

We present a patient with severe orthostatic hypotension since 12 years of age, an acute, recurring mononeuropathy and a *PMP22* gene deletion. Autonomic nervous system screening tests (HUT, VM, deep breathing, isometric handgrip, cold pressor stimulus) revealed sympathetic

selective autonomic disturbances and catecholamine titration confirmed very low NA and adrenaline with increased DA levels in plasma. The patient was put on L-*threo*-dihydroxyphenylserine (Droxidopa) 600 mg t.i.d. following in-ward titration and his orthostatic intolerance has very much improved ever since. However, it was unclear how *PMP22* gene deletion specifically contributed to the disease. To address these questions, through exome-sequencing analysis, we identified two novel mutations in the *DBH* gene and ~50 variants defined as pathogenic by in silico analysis. With a network-based approach, we excluded the contribution of these variants to the disease, highlighting the role of the two *DBH* mutations in the pathogenesis of our patient's dysautonomia.

So far, nine pathogenic combinations of eight known mutations *DBH* gene mutations have been reported in patients with the autosomal recessive DβH deficiency (Table 1). DβH deficiency is mainly due to a combination of one mutation causing an abnormal processing of the *DBH* mRNA (splice sites) and one causing its defective protein's trafficking (missense mutations) [18]. Likewise, in our newly identified variants, one is a missense mutation in exon 9 and the second one a deletion that impaired the splice donor site in intron 8.

The full clinical spectrum of DβH deficiency is not known, because of the limited number of reported cases. Clinical features in childhood include reduced exercise capacity, due to hypotension stimulated by physical exertion, with syncope often misinterpreted as seizures. Mental and physical development is normal. Symptoms worsen in late adolescence. By early adulthood, affected individuals have profound orthostatic hypotension, significantly reduced exercise tolerance, ptosis and nasal stuffiness, with normal mental status. Males experience retrograde or prolonged ejaculation [3]. In addition, single patients displayed other findings: atrial fibrillation developed in one individual, bilateral colobomas, short hands, and high-arched feet in a patient who also carried a mosaic deletion on chromosome 11p13, which includes the gene *PAX6* [16]. Because so few individuals have been diagnosed with DβH deficiency, it is not known what the relationship with the less frequent signs and the absence of the enzyme might be.

Mutations of the *PMP22* gene in combination with other genetic variants, such as missense mutations in *GJB1*, *ABCD1*, *FSHD* genes, CTG expansion in the *DMPK* gene have been previously reported to cause a more severe phenotype than the one expected by *PMP22* deletion alone [29].

This case adds to the increasing number of patients with DβH deficiency and of patients presenting with genetically proven double trouble. Even if a mutation in one disease gene has been found, further genetic testing might be warranted in cases with unusual clinical presentation to ensure a better medical care and genetic counseling.

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Compliance with ethical standards

Conflicts of interest The authors report no conflict of interests.

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