Early-onset severe hereditary sensory and autonomic neuropathy type 1 with S331F *SPTLC1* mutation

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Abstract. Hereditary sensory and autonomic neuropathy type I (HSAN I) is an autosomal dominant disease characterized by prominent sensory impairment, resulting in foot ulcers or amputations and has a juvenile to adult onset. The major underlying causes of HSAN I are mutations in *SPTLC1*, which encodes the first subunit of serine palmitoyltransferase (SPT). To date, there have been no reports with regard to an HSAN patient of Korean origin. In this report we discussed an HSAN I patient with a missense mutation in *SPTLC1* (c.992C>T: p.S331F). The patient had noticed frequent falls, lower leg weakness and hand tremors at age five. The patient also presented with foot ulcers, muscle hypotrophy, cataracts, hoarseness, vocal cord palsy and respiratory difficulties and succumbed to the condition at the age of 28 years. In accordance with previous reports, a mutation in Ser331 in the present patient was associated with early-onset and a severe phenotype. Therefore, Ser331 in SPTLC1 is a crucial amino acid, which characterizes the HSAN I phenotype.

Introduction

Hereditary sensory and autonomic neuropathy (HSAN), also known as hereditary sensory neuropathy, is a rare heterogeneous group of disorders with a wide range of clinical and genetic diversity (1). HSAN is traditionally classified into five subtypes (HSAN I-V) based on the age of the patient at onset, the pattern of inheritance and additional features such as degree of motor and sensory impairment, autonomic dysfunction, particularly anhidrosis, and mental retardation (2). HSAN type I (HSAN I; MIM: 162400) is the most frequent HSAN subtype with autosomal dominant inheritance characterized by marked distal sensory impairment leading to painless ulceration, soft tissue infection and osteomyelitis in the hands and feet (3). As the disease progresses, a variable degree of distal muscle weakness and wasting with lancinating pain may be observed.

Mutations in *SPTLC1* (MIM: 605712), which encodes the long-chain base subunit 1 of serine palmitoyltransferase (SPT), are the major underlying causes of HSAN I (1), and several mutations have been reported to be relevant in HSAN I: p.C133W, p.C133Y, p.C133R, p.V144D, p.S331F, pA310G, p.S331Y and p.A352V (2-13). SPT catalyzes serine and palmitoyl coenzyme A (CoA), which is the initial and rate-limiting step in the *de novo* biosynthesis of sphingolipids. The age of onset for HSAN I is usually in the second to fourth decades of life and motor involvement is variable and limited to the distal limbs. In contrast to typical HSAN I, three European cases of Ser331 mutations in *SPTLC1* (two with p.S331F and one with p.S331Y) demonstrated an early onset and a severe phenotype (2,4-6).

In this study we report on the first known Korean HSAN I patient to harbor a p.S331F mutation in *SPTLC1*, with early onset and a severe phenotype.

Patients and methods

Patients. A Korean family with one HSAN I patient and three healthy individuals (ID: FC142, Fig. 1A) were enrolled in this study. Healthy Korean controls with no familial history of neuromuscular disorders (n=300) were also recruited for this study. Paternity was confirmed by the genotyping of 15 microsatellites using a PowerPlex 16 system (Promega, Madison, WI, USA). Written informed consent was obtained from all participants according to the protocol approved by the Institutional Review Board for Ewha Womans University, Mokdong Hospital (ECT 11-58-37; B.O. Choi).

Clinical and electrophysiological assessments. The patient and the patient's sister and parents were examined for motor

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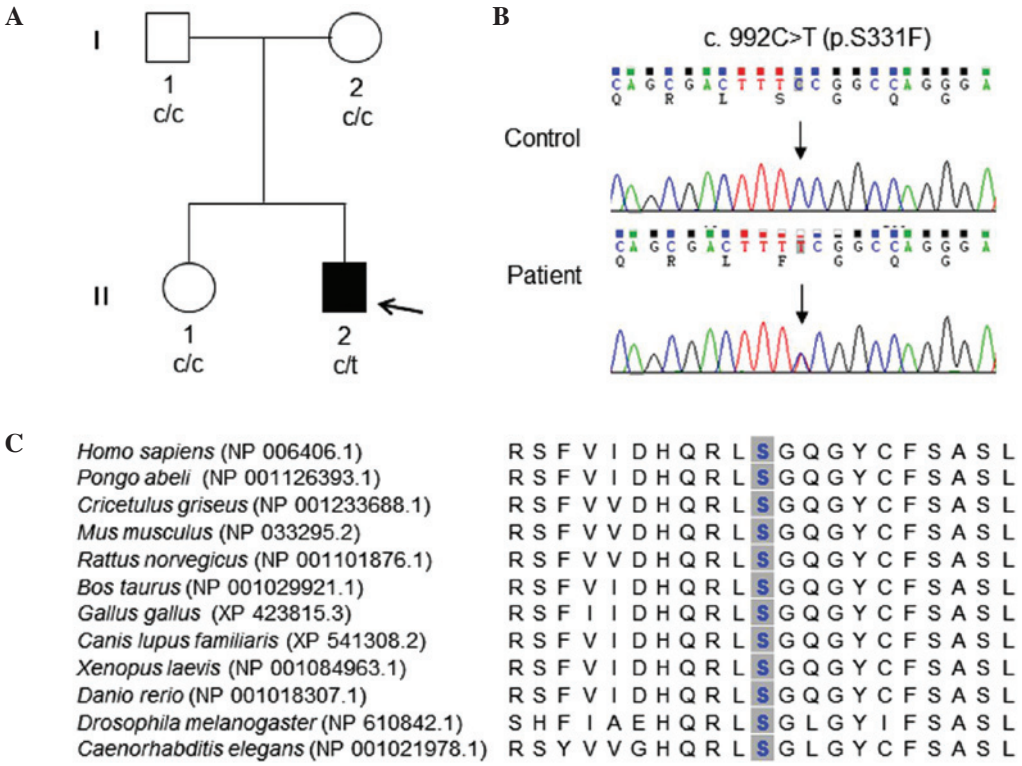

Figure 1. Pedigree, sequencing chromatogram of the *SPTLC1* gene mutation in the FC142 family. (A) The pedigree of the FC142 family. The open symbols represent unaffected individuals while the filled symbols represent affected individuals. The proband is indicated by an arrow. The genotypes of the *SPTLC1* mutation are indicated below each examined member. (B) Sequencing chromatograms. Vertical arrows indicate the mutation site. (C) Conservation analysis of the amino acid sequences between different species. The analysis was conducted using MEGA5 version 5.05. The mutation site and its neighboring sequences were well conserved among the different species.

and sensory impairments, deep tendon reflex abnormalities and muscle atrophy. The strength of the flexor and extensor muscles was assessed manually using the Medical Research Council scale (14). Physical disabilities were assessed using the functional disability scale (FDS) (15). Nerve conduction studies (NCS) were performed on all family members of FC142 with a surface electrode (Ambu, Ballerup, Denmark). Motor nerve conduction velocities (MNCVs) of the median and ulnar nerves were determined by providing stimulation at the elbow and wrist while recording the compound muscle action potentials (CMAPs) over the abductor pollicis brevis and adductor digiti quinti, respectively. In the same manner, the MNCVs and CMAPs of the fibular and tibial nerves were determined. Sensory nerve conduction velocities and sensory nerve action potentials (SNAPs) of the median, ulnar and sural nerves were obtained.

DNA preparation and pre-screening for Charcot-Marie-Tooth (CMT) disease genes. DNA was purified from blood samples using a QIAamp blood DNA purification kit (Qiagen, Hilden, Germany). The patient's DNA was pre-screened for a 1.4 Mbp length of 17p12 duplication/deletion, a major genetic cause of CMT, by using hexaplex microsatellite polymerase chain reaction (16).

Exome sequencing and identification of causative mutation. Exome sequencing was performed in the male patient (II-2) according to the previous report (17). Exome capturing was achieved using a SeqCap EZ, version 3.0 (Roche-NimbleGen, Madison, WI, USA), and next generation sequencing was performed using a HiSeq 2000 Genome analyzer (Illumina, San Diego, CA, USA). The UCSC assembly hg19 (NCBI build 37.1) was used as the reference sequence with BWA aligner software (http://bio-bwa.sourceforge.net/). Variant calling was achieved using a SAMtools program (http://samtools.sourceforge.net/). Single nucleotide polymorphisms (SNPs) with a quality value >20 were considered as candidates.

Table I. Summary of exome sequencing for the HSAN I patient (II-2).

Items	II-2
Total yields	6.14 Gbp
Mappable reads	93.1%
Target coverage (≥10x)	94.3%
Total observed SNP number	57705
Coding SNP number	19757
Total observed indel number	10450
Coding indel number	588
Functionally significant variants in CMT genes[a]	32

[a]Observed number of functionally significant variants (missense, nonsense, coding indels, and splicing site) in >60 CMT related genes. HSAN, hereditary sensory and autonomic neuropathy; SNP, single nucleotide polymorphisms; CMT, Charcot-Marie-Tooth disease.

Table II. Functionally significant variants observed in CMT genes for the FC142 family (II-2).

Gene	RefSeq[a]	Chr: position	Variants		dbSNP137	1000G[c]	Description
			Nt[b]	AA			
NGF	NM_002506.2	chr01:115829313	c.104C>T	A35V	rs6330	0.31	Polymorphism
OPA1	NM_130834.2	chr03:193334991	c.473G>A	S158N	rs7624750	0.46	Polymorphism
FIG4	NM_014845.5	chr06:110064928	c.1090A>T	M364L	rs2295837	0.10	Polymorphism
FIG4	-	chr06:110107517	c.1961T>C	V654A	rs9885672	0.37	Polymorphism
NEFL	NM_006158.4	chr08:24811071	c.1407_1408insC	P471fs	rs11300136	-	Polymorphism
SPTLC1	NM_006415.2	chr09:94809543	c.992C>T	S331F	-	-	Causative
IKBKAP	NM_003640.3	chr09:111659439	c.2490A>G	I830M	rs2230794	0.08	Polymorphism
IKBKAP	-	chr09:111659483	c.2446A>C	I816L	rs2230793	0.29	Polymorphism
IKBKAP	-	chr09:111660851	c.2294G>A	G765E	rs2230792	0.28	Polymorphism
IKBKAP	-	chr09:111665169	c.1804C>T	R602W	rs200397694	0.00	Non-cosegregation
LRSAM1	NM_138361.5	chr09:130242166	c.952A>G	N318D	rs1539567	0.74	Polymorphism
SETX	NM_015046.5	chr09:135139901	c.7759A>G	I2587V	rs1056899	0.51	Polymorphism
SETX	-	chr09:135173685	c.5563A>G	T1855A	rs2296871	0.41	Polymorphism
SETX	-	chr09:135203530	c.3455T>G	F1152C	rs3739922	0.10	Polymorphism
SETX	-	chr09:135205006	c.1979C>G	A660G	rs882709	0.21	Polymorphism
DHTKD1	NM_018706.6	chr10:12111090	c.58T>C	F20L	rs1279138	0.98	Polymorphism
DHTKD1	-	chr10:12131081	c.814T>G	Y272D	rs3740015	0.47	Polymorphism
DHTKD1	-	chr10:12143105	c.1821C>G	I607M	rs2062988	0.72	Polymorphism
SBF2	NM_030962.3	chr11:9853777	c.3646C>G	Q1216E	rs12574508	0.10	Polymorphism
IGHMBP2	NM_002180.2	chr11:68678962	c.602T>C	L201S	rs560096	0.70	Polymorphism
IGHMBP2	-	chr11:68705674	c.2636C>A	T879K	rs17612126	0.23	Polymorphism
WNK1	NM_213655.4	chr12:990912	c.3922A>C	T1308P	rs956868	0.85	Polymorphism
WNK1	-	chr12:994487	c.5273G>C	C1758S	rs7955371	0.99	Polymorphism
KARS	NM_005548.2	chr16:75669878	c.601T>C	Y201H	rs150529876	0.00	Polymorphism
SEPT9	NM_001113495.1	chr17:75494705	c.1390A>G	M464V	rs2627223	0.92	Polymorphism
CTDP1	NM_048368.3	chr18:77473127	c.1019C>T	T340M	rs2279103	0.11	Polymorphism
CTDP1	-	chr18:77474626	c.1166C>T	A389V	rs144647072	0.02	Polymorphism
DNMT1	NM_001379.2	chr19:10273372	c.931A>G	I311V	rs2228612	0.18	Polymorphism
PRX	NM_181882.2	chr19:40900865	c.3394G>A	G1132R	rs268674	0.96	Polymorphism
PRX	-	chr19:40902710	c.1549C>T	L517F	-	-	Non-cosegregation
DMPK	NM_001081563.1	chr19:46275976	c.1297C>G	L433V	rs527221	0.12	Polymorphism
ATP7A	NM_000052.5	chrX:77298857	c.4048G>A	E1350K	rs4826245	1.00	Polymorphism

[a]GenBank registration number of reference sequence. [b]cDNA numbering was achieved with +1, corresponding to the A of the ATG initiation codon. [c]Variant allele frequencies in 1000 genome (1000G) database. CMT, Charcot-Marie-Tooth disease; Chr, chromosome; Nt, nucleotide; AA, amino acid.

All variants occurring in CMT relevant genes (~60) were initially selected. The functionally significant variants (missense, nonsense, exonic indel (insertion and deletion) and splicing site variants) were selected while the remaining variants were filtered out. Sequencing variants were confirmed by the Sanger sequencing method using an automatic genetic analyzer ABI3130XL (Applied Biosystems, Foster City, CA, USA). A mutation was considered to be an underlying cause when a candidate mutation was only located in the affected member within the family, but was not located in >200 control samples. The mutation nomenclature recommendations of the Human Genome Variation Society (http://www.hgvs.org/mutnomen/) were used to describe the variants.

In silico analysis. The conservation pattern for the protein amino acid sequence was performed using MEGA5 software, version 5.05 (http://www.megasoftware.net/) (18). Prediction of protein function affection due to amino acid substitution was performed using the online tools SIFT (http://sift.jcvi.org/), PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/) and MuPro (http://mupro.proteomics.ics.uci.edu/).

Results

Identification of heterozygous missense mutation in SPTLC1. The summary of whole exome sequencing data is provided in Table I. The sequencing yield was ~6.14 Gbp. Mappable

Table III. Clinical features of HSAN patients with *SPTLC1* mutation with literature review.

AA change	Origin/ Inheritance	AAO (years)	NCS (PN)	Weakness/ muscle atrophy	Foot ulcer, amputation	Respiratory problem	Juvanile cataract age (years)	Others	Reference (Author, year, no.)
p.S331F	German/IC	Early childhood	SM	Yes	Yes	NM	Yes (9)	Joint contracture	Huehne *et al*, 2008 (6)
	French (Gypsy)/IC	Congenital	SM	Yes	Yes	Yes	Yes	Mental retardation, vocal cord palsy, joint hyperlaxity	Rotthier *et al*, 2009 (2)
	Korean/IC	5	SM	Yes walker (27)[a]	Yes	Yes	Yes (10)	Hoarseness, tremor, scoliosis	This study
p.S331Y	NM/IC	4	SM	Yes wheelchair (14)[a]	Yes	Yes	Yes (13)	Tremor, fasciculation, joint hypermobility	Auer-Grumbach *et al,* 2013 (4)
p.C133W	Australian English /NM	65	NM	Weakness in 4/38	Yes	NM	NM	NM	Dawkins *et al*, 2001 (8)
	Canadian/NM	20-40	NM	No	Yes	NM	NM	NM	Bejaoui *et al*, 2001 (9)
	Chinese/AD	20's	SM	No	Yes	NM	NM	NM	Bi *et al*, 2007 (10)
	Canadian/AD	12, 60's	S	Peroneal m. atrophy	Yes	NM	NM	NM	Klein *et al*, 2005 (11)
	English/AD, IC	12-29	SM	Yes	Yes	NM	NM	NM	Houlden *et al*, 2006 (3)
p.C133Y	German/NM	NM	NM	NM	NM	NM	NM	NM	Bejaoui *et al*, 2001 (9)
	Australian German /NM	NM	NM	NM	NM	NM	NM	NM	Dawkins *et al*, 2001 (8)
	Portuguese/AD	20's, 10	SM	No	No	NM	No	Foot pain, dry skin	Geraldes *et al*, 2004 (12)
p.C133R	German/AD	50	No	No	NM	NM	NM	NM	Rautenstrauss *et al*, 2009 (13)
p.V144D	Australian German /NM	NM	NM	NM	NM	NM	NM	NM	Dawkins *et al*, 2001 (8)
p.A310G	English/IC	50's	S	No	Yes	NM	NM	NM	Davidson *et al*, 2012 (1)
p.A352V	Austrian/IC	16	SM	Mild pes cavus, distal LL, peroneal atrophy	NM	NM	NM	NM	Rotthier *et al*, 2009 (2)

[a]Age (years) at which the patient had to start using the aid. AA, amino acid; AAO, age at onset; NCS, nerve conduction study; PN, polyneuropathy; IC, isolated case; SM, sensory motor polyneuropathy; NM, not mentioned; S, sensory polyneuropathy; m. atrophy, muscle atrophy; AD, autosomal dominant; LL, lower leg.

reads and target coverage (>10x reads) were 93.1 and 94.3%, respectively. Total observed numbers of SNP and indels were 57,705 and 10,450, respectively. Of these, coding SNPs and indels were 19,757 and 588, respectively.

In ~60 CMT relevant genes, 32 functionally significant variants were identified (Table II). Of these, a heterozygous missense mutation c.992C>T (p.S331F) was located in the *SPTLC1* gene, which was previously reported to cause HSAN I (2), and was also reported in the Inherited Peripheral Neuropathies Mutation Database (http://www.molgen.ua.ac.be/CMTMutations/). Capillary sequencing for this variant demonstrated concordant results (Fig. 1A and B). This mutation was located in neither the parents nor the sister. This result suggests that the *SPTLC1* mutation in the patient occurred by *de novo* mutation. Notably, this case and the case reported by Rotthier *et al* (2) are *de novo*. None of the 300 controls exhibited this mutation. The *SPTLC1* c.992C>T (p.S331F) variant is thus determined to be the causative mutation for II-2. The mutation lies in the aspartate aminotransferase superfamily (fold type I) domain of pyridoxal phosphate-dependent enzymes.

Appreciable *in silico* results were attained by using three tools: SIFT yielding a deleterious score of 0.02 (damaging score: ≤0.05), a PolyPhen score of 2.317 (damaging score: >1.0), and a MUpro protein instability score of -0.1034 (negative value: decreased stability). Analysis of multiple sequences for the conservation pattern of the STPLC1 protein demonstrated marked conservation throughout different species (Fig. 1C).

Except for *SPTLC1* c.992C>T, other variants in CMT relevant genes were not considered to be causative, as they were polymorphic (observed in the controls) or not cosegregated with the affected member within the pedigree. Despite the presence of several rare heterozygous variants in recessive genes, the possibility of an underlying cause was ruled out due the occurrence of the same mutation in either parent.

Clinical manifestations and electrophysiological features. The male proband (Fig. 1A, II-2) was the second child of non-consanguineous, healthy parents. Birth weight was 3.2 kg and motor milestones during the first year were normal. The patient noticed frequent falls, lower leg weakness and a hand tremor at age five. At seven years of age, the patient used an ankle-foot device due to a progressively impaired gait, and the diagnosis of hereditary motor and sensory neuropathy was made. Three years later, the patient had a cataract operation. Following adolescence, the voice of the patient became hoarse. Disease progression was rapid and the patient exhibited with respiratory problems and walker dependency at the age of 27 years. A neurological examination at 28 years of age revealed muscle weakness and atrophy of the proximal limb and trunk muscles (body mass index, 12.2 kg/m^2), and hypotonia with prominent weakness in the distal muscles of the upper and lower limbs (FDS 6, walking with a walker). The vibration and position senses were markedly more preserved compared with the pain and temperature senses. Marked reductions in pain and temperature sensation were noted. Bilateral hand tremors and severe scoliosis were observed. Deep tendon reflexes were absent in all extremities, but pathological reflexes were not identified.

NCS was performed at the ages of 12, 26 and 28 years. SNAPs of the median, ulnar and sural nerves were not evoked, and CMAPs of peroneal and tibial nerves were also absent. The median nerves revealed low CMAPs (range, 0.1-0.2 mV) and slow MNCVs (range, 12.2-25.9 m/s). CMAPs of the ulnar nerves were low and the range was similar to that of the median nerves (CMAP range, 0.1-0.4 mV; MNCV range, 17.5-27.0 m/s). However, when NCS was performed on the other family members (I-1, I-2, II-1), the results were completely normal.

Discussion

The present study reports on the early-onset of a severe phenotype of HSAN I with a missense mutation of c.992C>T (p.S331F) in *SPTLC1*. HSAN I is characterized by autosomal dominant inheritance, juvenile or adulthood disease onset, and marked distal pain and temperature sensory impairment leading to distal ulceration and mutilating arthropathy with relative preservation of motor and autonomic functions (19). Other subtypes of HSAN (HSAN types II-V) have autosomal recessive inheritance with an earlier onset of the disease and variable motor involvement. Therefore, the phenotype of this patient was different to the usual pattern of HSAN I, with the features of: i) A sporadic case rather than autosomal dominant inheritance; ii) earlier age of onset; iii) severe proximal and distal motor involvement with wasting; and iv) additional features including cataracts at a young age, hoarseness of the voice, tremor, scoliosis and respiratory insufficiency.

To date, numerous *SPTLC1* mutations have been identified at restricted amino acid positions (p.C133W, p.C133Y, p.C133R, p.V144D, p.S331F, p.S331Y, p.A310G, and p.A352V) (2-9). There have only been three previously reported cases with a mutation at the Ser331 position (2,4-6). Common findings of these three cases are a *de novo* mutation, symptom onset prior to 10 years of age, muscle hypotrophy due to prominent motor involvement in the polyneuropathy, foot ulcers, amputations and cataracts at a young age. Two of the cases also exhibited joint hypermobility, vocal cord paralysis and respiratory difficulties (2,4-6). Following a review of the literature with regard to the *SPTLC1* mutation, the present case and the aforementioned three cases carrying the Ser331 mutation resemble each other in terms of the inheritance pattern and the atypical clinical features (Table III).

It is hypothesized that reduced SPT activity with resultant accumulation of neurotoxic deoxysphingoid bases (DSB) may be the underlying pathomechanism of HSAN I with *SPTLC1* mutations. Rotthier *et al* (5) demonstrated that mutant proteins (C133W, S331F and A352V) are enzymatically defective; however, failed to demonstrate a positive correlation between DSB levels and phenotypic severity. These results imply that there may be an additional factor determining the severity of the disease, including genetic modifiers or other interacting proteins.

This is the first report of a Korean HSAN I patient with the p.S331F mutation in *SPTLC1*. The patient exhibited early onset and severe clinical manifestations, which are uncommon features of HSAN I but are an almost identical to those in patients with an Ser331 mutation. Therefore, HSAN I with a p.S331 mutation in *SPTLC1* may exhibit an early onset, severe

sensory motor deficits and various other features, including cataracts, vocal cord palsy and respiratory problems.

Acknowledgements

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