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ORIGINAL COMMUNICATION

The identification of a transthyretin variant p.D38G in a Chinese family with early-onset leptomeningeal amyloidosis

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Abstract

Familial amyloid polyneuropathies (FAPs) are life-threatening, autosomal dominant diseases resulting, in most instances, from transthyretin gene (*TTR*) variants. A small number of *TTR* variants lead to leptomeningeal amyloidosis (LA), which is a rare FAP subtype with late-onset central nervous system (CNS) impairment symptoms. Previous studies suggest that LA's CNS selectivity was due to complete endoplasmic reticulum-associated degradation of highly destabilized mutants in peripheral tissues. LA's later age at onset (AAO) was due to lower choroid plexus secretory efficacy. This study reports on a family with LA, including six symptomatic and three presymptomatic members. The LA diagnosis was confirmed by leptomeningeal enhancement on contrast MRI, elevated cerebrospinal fluid protein levels, and positive Congo red staining. The predominant symptoms included headaches, dizziness, vomiting, hallucinations, and cognitive impairments which associated with obstructive hydrocephalus. The *TTR* p.D38G variant with the lowest secretory efficacy was identified as the genetic cause by whole exome sequencing. The family had a statistically significantly earlier mean AAO of 31.3 ± 7.4 ($p = 0.001$). These uncommon phenotypes indicate unknown factors influencing the progress of CNS impairment via TTR mutants. Medical imaging examinations suggest the potential early diagnosis value of contrast MRI and the importance of ependyma involvement in LA. LA genetic and clinical data were reviewed and summarized. These findings expand the FAPs' phenotypic spectrum and are valuable in FAP diagnosis, treatment, and further research.

Keywords Genetics · Transthyretin · Familial amyloid polyneuropathy · Transthyretin-related amyloidosis · Leptomeningeal amyloidosis

Introduction

Familial amyloid polyneuropathies (FAPs, OMIM 105210) are a genetically and clinically heterogeneous group of life-threatening multisystem diseases having autosomal dominant inheritance [1]. They are characterized by the extracellular deposition of insoluble amyloid fibrils on peripheral nerves and other organs [2, 3]. FAPs can be caused by variants in the following four genes: the transthyretin gene (*TTR*), the apolipoprotein A1 gene, the gelsolin gene, and the beta-2-microglobulin gene [4]. *TTR*-related amyloidosis (ATTR) is the most common genetic subtype [1]. The *TTR* gene, located on 18q12.1, encodes a 20-amino acid signal peptide and a 127-amino acid mature protein [5]. The mature protein is a β-sheet-rich protein and assembles to a tetrameric carrier for thyroid hormones and retinol transport in plasma and cerebrospinal fluid (CSF) [1, 2]. TTR mutants destabilize the native tetramer into monomer resulting in an aggregation of the predominantly mutant TTR protein [1, 6].

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This typically leads to death within 10 years after onset [1]. As of this writing (2018), more than 112 *TTR* gene variants have been identified and considered as the genetic causes for FAPs. The p.V50M (c.148G > A, formerly labeled as "V30M" based on the sequence of mature protein) variant accounts for 50% of the variants in ATTR patients [1, 4, 7]. ATTR prevalence is less than 1/100,000 in European populations and approximately 1/1,000,000 in the Japanese population [8]. The wide variety of clinical phenotypes frequently leads to misdiagnosis, a considerable time before correct diagnosis and poorer patient outcomes [2, 9].

Most ATTR patients present with progressive length-dependent sensory-motor polyneuropathy, autonomic dysfunction, gastrointestinal impairments, cardiomyopathy, nephropathy, and/or ocular deposition before age 40 [1, 8, 9]. Ninety-five percent of all TTR protein in plasma is of hepatic origin. The common ATTR therapeutic strategy is an orthotopic liver transplant (OLT) which can slow the progression of peripheral and autonomic neuropathy [2, 6]. Leptomeningeal amyloidosis (LA) is a rare ATTR subtype, mainly causing strokes and/or hydrocephalus [1]. It presents with central nervous system (CNS) symptoms, including headaches, vomiting, ataxia, hearing loss, seizures, hemiplegic paralysis, and dementia [2, 10]. These CNS pathological changes are caused by the deposition of mutant TTR protein secreted from choroid plexus and cannot be blocked by OLT [8, 11]. LA diagnosis hallmarks include extensive leptomeningeal enhancement on contrast MRI and increased CSF protein levels [10, 12].

This study reports on a family with early-onset LA and identifies a p.D38G (c.113A > G, formerly labeled as "D18G") variant as the genetic cause using whole exome sequencing. These unusual findings expand the ATTR phenotypic spectrum and have potential value in the diagnosis, treatment, and elucidation of its pathogenic mechanisms.

Materials and methods

Subjects and clinical evaluations

A four-generation Han-Chinese family with LA was enrolled in this study. An autosomal dominant inheritance pattern was proposed based on the family history. Written informed consent was obtained from ten family members. Detailed medical histories were collected from all participants. Enrolled family members had a complete physical examination performed by two neurologists. Peripheral blood samples were obtained. Auxiliary examinations included: routine blood, urine, and CSF examinations; ophthalmic examinations; audiometric tests; abdomen ultrasound; electrocardiograph (ECG); ultrasonic cardiogram (UCG); electromyography (EMG); CT scans; multiple MRI scans; and cerebral angiography. The protocol of this study was approved by the Institutional Review Board of the Third Xiangya Hospital, Central South University, Changsha, Hunan, China.

Genetic analysis

A standard phenol–chloroform extraction method, as previously described, was used to refine genomic DNA (gDNA) from all participants [13]. gDNA samples were randomly fragmented by a Covaris sonicator. They were end-repaired, enriched, and circularized into DNA nanoballs. Subsequently, whole exome sequencing was performed to comprehensively search for the disease-causing variant using a BGISEQ-500 platform (BGI, Shenzhen, China). After data filtering, the clean data were mapped to the human reference genome (GRCh37/hg19) using Burrows–Wheeler Aligner (v0.7.15). Picard tools (v2.5.0, http://broadinstitute.github.io/picard/) were used to remove duplicate reads. Insertion and deletion (InDel) realignment and base recalibration were conducted by Genome Analysis Toolkit (GATK, v3.3.0). All variants, including single nucleotide polymorphisms (SNPs) and InDels, were detected and filtered by GATK HaplotypeCaller. SnpEff tool (http://snpeff.sourceforge.net/SnpEff_manual.html) annotated and filtered variants using the SNP database (v141) and the 1000 Genomes Project. The in-house BGI exome database with 2,375 ethnically matched Chinese controls was used to further sift out remaining variants. Sorting Intolerant from Tolerant (SIFT, http://sift.jcvi.org/), Polymorphism Phenotyping version 2 (PolyPhen-2, http://genetics.bwh.harvard.edu/pph2/), and MutationTaster (http://www.mutationtaster.org/) evaluated the potential pathogenic effects of amino acid changes. The Basic Local Alignment Search Tool (https://blast.ncbi.nlm.nih.gov/Blast.cgi) was applied to analyze the conservation of amid acid sequence. Using an ABI3500 sequencer (Applied Biosystems Inc., Foster City, CA, USA), candidate variant was detected in all enrolled family members via Sanger sequencing. The primer sequences for detecting *TTR* c.113A > G variant were as follows: 5′-TCTTGTTTC GCTCCAGATTTC-3′ and 5′-TTTGGCAACTTACCCAGA GG-3′. All variants in this study are described based upon the transcript NM_000371.3.

Searches and statistical analysis

A search of PubMed was conducted to find LA cases in reports published between 1 January 1980 and 31 July 2018 using the following query: (leptomeningeal amyloidosis) OR oculoleptomeningeal amyloidosis. ATTR patients whose CNS symptoms presented before OLT were included. LA was defined as ATTR with CNS symptoms as the initial symptoms. Age at onset (AAO) of disease was established as the age at which certain ATTR-related symptoms appeared.

Quantitative data were described as mean ± standard deviation to single decimal place. Statistical analysis was performed by SPSS (v17.0) to test significance of differences using Kolmogorov–Smirnov test and Student's *t* test. The level of statistical significance was set to 0.05.

Results

Clinical features

This family had three presymptomatic individuals and six symptomatic patients with a mean AAO of 31.3 ± 7.4 (Table 1). All symptomatic individuals had periodic headaches and/or dizziness accompanied by vomiting as their initial symptoms. Hallucinations were present in four patients (I:1, II:3, II:6, and II:8). Fluctuating cognitive impairment presented in three patients (I:1, II:3, and II:8). These symptoms worsened over time. Patient III:1 had limb numbness, and patient II:8 had visual decline, but EMG and ophthalmic examinations excluded peripheral neuropathy and vitreous opacity in both patients. No patient had obvious hearing loss symptom. Audiometric tests found bilateral, mild mixed hearing loss in patient II:8 and normal hearing function in patient III:1, respectively. Physical examinations were normal for all participants. CT and MRI scans revealed obstructive hydrocephalus in three older symptomatic patients (II:1, II:3, and II:8; Fig. 1a–c). There was a positive correlation between symptom severity and the extent of interstitial cerebral edema (Fig. 1a, b). Contrast MRI revealed extensive enhancement of leptomeninges and ependyma in two symptomatic individuals (II:8 and III:1; Fig. 2a, b). Partial enhancement was discovered in three presymptomatic individuals (III:2, III:3, and III:6), primarily on the lateral ventricle, the fourth ventricle, and the brainstem surfaces (Fig. 2c, d). Earlier cranial MRI susceptibility-weighted imaging (SWI) sequences and cerebral artery angiographies (CT angiography or catheter angiography) showed a lack of either micro-bleeding or subarachnoid hemorrhage (SAH) in two symptomatic patients (II:8 and III:1). However, the latest gradient recalled echo-T2* (GRE-T2*) and SWI sequence found superficial siderosis on patient II:8 cerebellar vermis and lateral fissure surfaces. This patient had longer disease course and more severe clinical symptoms including three stroke-like episodes in the 6 months prior to the latest MRI scans. Lumbar punctures found slightly elevated CSF pressures (163.3 ± 58.9 mmH_2O) in patient II:8 and slightly lower CSF pressures (80 ± 18.0 mm H_2O) in patient III:1. Patients II:8 and III:1 CSFs were both xanthochromic and had significantly higher protein levels (282.3 ± 63.7 mg/dL) along with normal or mildly increased white blood cell counts (10.3 ± 6.1/mm^3). Routine blood and urine examinations, abdominal ultrasounds, ECGs, and UCGs were all normal. Contrast enhancement abnormalities were not found in a cardiac contrast MRI examination of patient II:8. An operation resected an intraspinal mass and partially lessened Patient III:1 lower limb numbness (Fig. 1d). Thickened arachnoid membrane and yellow caseous tissues wrapping nerve roots were observed. Amyloidosis was confirmed by positive Congo red staining on histological examination. Patient II:3 underwent a resection of mass in the fourth ventricle. Diffuse granular depositions were discovered in the subarachnoid space and the ependyma surface. She died of postoperative complications. Tissue blocks of these patients were unavailable for immunohistochemical staining. Two other patients (I:1 and II:1) died of severe hydrocephalus and one (II:6) from a cognitive impairment-caused accident. The mean age at death was 39.0 ± 5.7. Detailed clinical presentations for all patients appear in Table 1.

Genetic findings

Taking into account the absence of immunohistochemical staining and unusual clinical phenotypes, whole exome sequencing was performed on patients (III:1 and III:6; Fig. 3a). Average exome sequencing depths of 219.41× (III:1) and 215.41× (III:6) provided sufficient accuracies to call variants in 99.92% and 99.93% of the target regions, respectively. After filtering known variants and performing functional predictions, a known pathological heterozygous missense variant, c.113A > G (p.D38G) in the *TTR* gene, was identified in both subjects and suspected as the candidate disease-causing variant in this family. No other potential pathogenic variants in genes known to cause CNS amyloidosis were found. This variant was subsequently confirmed by Sanger sequencing (Fig. 3b). Further analysis discovered this variant in all symptomatic and presymptomatic patients and an asymptomatic 6-year male (IV:1). The 6-year-old individual did not undergo a contrast MRI scan. This variant was absent from other unaffected family members (I:2, II:5, II:9, and III:5; Fig. 3c). It was also absent from Exome Aggregation Consortium, Genome Aggregation Database and 2,375 ethnically matched controls in the in-house BGI exome database. Multiple sequence alignments revealed that the aspartic acid at position 38 is phylogenetically conserved among various species from zebrafish to human, suggesting its importance to the TTR protein structure and function (Fig. 3d). The variant was predicted to be "damaging", "probably damaging" and "disease causing" by SIFT, PolyPhen-2, and MutationTaster, respectively. Combined with the previous reports and functional researches, this results support classifying the p.D38G variant as a pathogenic variant applying the American College of Medical Genetics and Genomics standards and guidelines for variant interpretation [10, 14–18].

Table 1 Clinical presentations and genotypes of the individuals with the p.D38G variant of *TTR* gene [10, 17, 18]

Subject	China										Hungary [10]				Japan [17]		USA case [18]
	I:1	II:1	II:3	II:6	II:8	III:1	III:2	III:3	III:6	IV:1	II:6	II:7	III:14	III:16	Patient 1	Patient 2	
Sex (M = Male, F = Female)	M	M	F	F	M	M	F	F	M	M	M	M	F	F	M	M	F
Age at last examination (years)	/	/	/	/	44	27	26	30	18	6	/	/	/	51	41	46	47
Age at onset (years)	36	39	26	25	39	23	/	/	/	/	36	37	53	46	40	40	47
Age at death (years)	42	39	44	31	/	/	/	/	/	/	58	53	60	/	/	/	/
Genotype[a]	/	/	/	/	N/V	N/V	N/V	N/V	N/V	N/V	/	N/V	N/V	N/V	N/V	N/V	N/V
Dizziness	/	/	/	/	+	+	−	−	−	−	+	+	/	/	+	+	/
Headache	+	+	+	+	+	−	−	−	−	−	+	/	+	/	+	+	+
Vomiting	+	+	+	+	+	+	−	−	−	−	+	+	+	/	/	+	+
Ataxia	/	−	−	−	−	−	−	−	−	−	+	+	+	+	+	+	/
Seizure	/	−	−	−	−	−	−	−	−	−	/	/	/	/	/	/	/
Stroke or SLE	/	−	−	−	+	−	−	−	−	−	+	+	/	/	+	+	+
Psychiatric symptoms	+	−	+	+	+	−	−	−	−	−	/	+	+	/	/	/	/
Cognitive impairment	+	−	+	/	+	−	−	−	−	−	/	+	+	+	/	/	/
Numbness in limbs	/	/	−	−	−	+	−	−	−	−	/	/	/	/	/	+	/
Electromyography	/	/	/	/	−	−	/	/	−	/	/	/	/	−	/	/	/
Autonomic dysfunction	/	/	/	/	−	−	−	−	−	/	+	+	/	/	+	+	/
Hearing loss	/	/	/	/	±	−	/	/	/	/	+	+	+	+	±	±	/
Cardiac impairment	/	/	−	/	−	−	/	/	−	/	/	/	/	/	+	/	/
Vitreous opacity	/	/	/	/	−	−	/	/	−	/	−	−	/	−	+	/	/
Hydrocephalus	/	+	+	/	+	−	−	−	−	/	+	+	−	−	−	+	+
Leptormeningeal enhancement	/	/	/	/	+	+	+	+	+	/	+	+	+	+	+	+	+
Subarachnoid hemorrhage	/	/	−	/	−	−	−	−	−	/	−	−	−	−	+	+	+
CSF protein (mg/dL)	/	/	/	/	220–322	274–423	/	/	/	/	103–330	920	340–440	820	115–145	53	/

− normal, + abnormal, ± mild, / not available, *TTR* transthyretin, *SLE* stroke-like episode, *CSF* cerebrospinal fluid

[a]N: normal allele; V: allele with *TTR* c.113A > G (p.D38G) variant

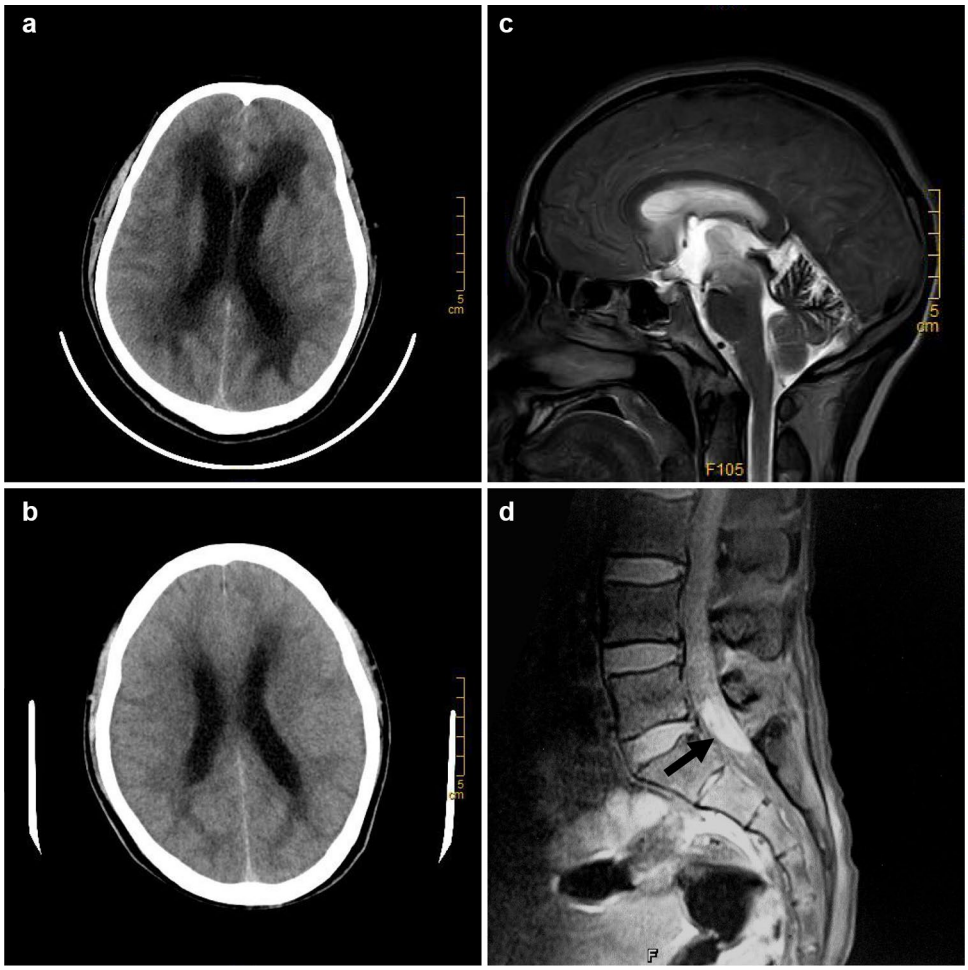

Fig. 1 **a, b** CT scans of patient II:8, showing the hydrocephalus and interstitial cerebral edema when his clinical symptoms got worse (**a**) and improved (**b**). **c** T2-weighted MRI sequence of patient II:8, showing the hydrocephalus and aqueductal stenosis. **d** T1-weighted MRI sequence of patient III:1, showing the intraspinal mass (arrow)

Statistical analysis

This family's unusual AAO led us to search LA patients reported in the PubMed database for genetic and clinical information of LA and to verify the significance of this difference. Two hundred and thirteen articles were screened and 60 cases with 15 different *TTR* variants were extracted from 32 reports (Supplementary Fig. 1). This includes 47 LA patients and 13 other ATTR patients with CNS symptoms [10, 12, 17–46]. The mean AAO was 45.1 ± 8.9 in 44 LA cases with detailed information (Table 2). Statistical analyses show that the affected patients in this family have a significantly earlier AAO than other LA patients ($p = 0.001$) or other p.D38G variant-associated patients ($p = 0.012$).

Discussion

As of this writing (2018), nine *TTR* gene variants have been reported to be associated with LA (Table 2) [47, 48]. The genotype–phenotype correlation for LA was reported, while its underlying pathogenic mechanism is still somewhat unclear. A proposed mechanism which may explain CNS selectivity is that highly destabilized TTR proteins encoded by these variants were completely degraded through the endoplasmic reticulum-associated degradation mechanism in peripheral tissues [16]. They could cause later CNS impairment, because these mutants were secreted with lower efficacy from choroid plexus due to a stabilizing effect of thyroxine chaperoning, which is highly concentrated in choroid plexus cells [16]. The prior study suggests that the p.D38G variant caused LA with later AAO, because it encoded the most unstable TTR protein which had the lowest concentration in CSF [16]. In this study, identifying the p.D38G variant in an early-onset LA family may indicate another pathogenic mechanism or the presence of another unknown regulating factor for this disorder. The hydrocephalus-associated clinical symptoms and the absence of peripheral neuropathy, vitreous opacity, and cardiac impairment further support the high CNS selectivity of the p.D38G variant. Only mild hearing loss was found in a patient with severe hydrocephalus, indicating that hearing loss is not a frequent or early symptom in this family, unlike a Hungarian family reported [10]. The clinical features of patients

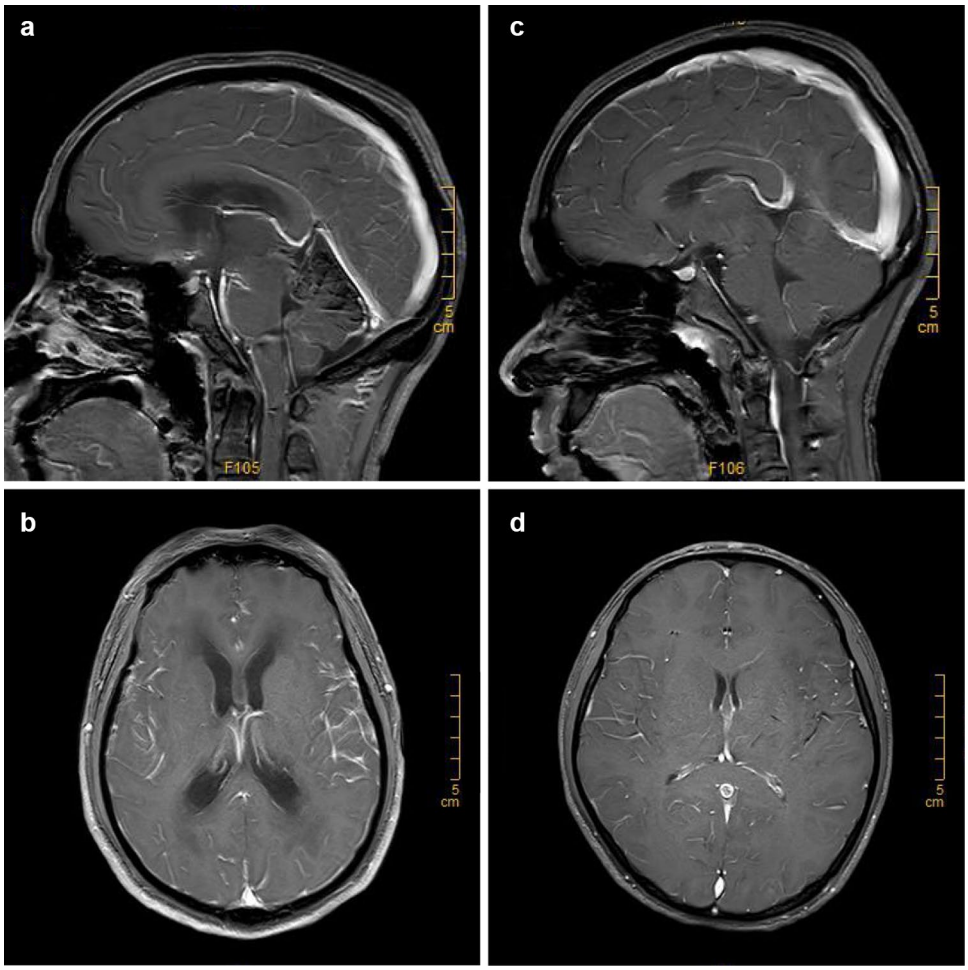

Fig. 2 T1-weighted MRI sequence shows extensive enhancement of the administered contrast medium at the leptomeninges and ependyma in symptomatic patient II:8 (**a, b**), and partial enhancement in presymptomatic patient III:3 (**c, d**)

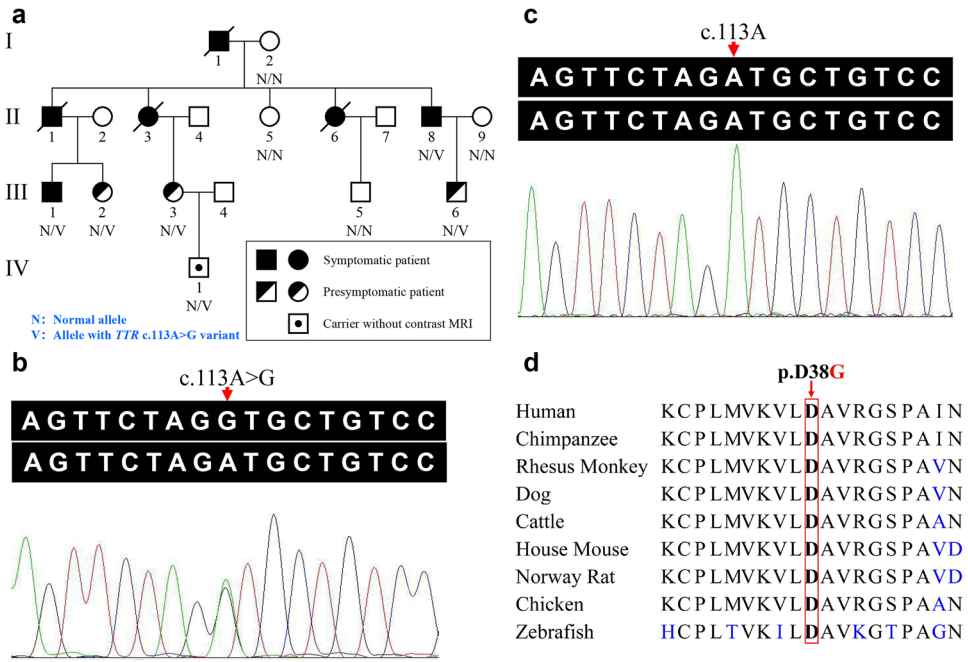

Fig. 3 **a** Pedigree of the family with leptomeningeal amyloidosis. **b** Chromatogram (genomic DNA) of heterozygous *TTR* c.113A > G variant in symptomatic patient (III:1). **c** DNA sequencing of wild-type *TTR* gene in normal member (I:2). **d** Conservation analysis of TTR p.D38 amino acid residue

Table 2 Variants previously reported to be associated with leptomeningeal amyloidosis and the main clinical phenotypes [10, 12, 17–47]

Amino acid change	Nucleotide change	Mature protein change	References	Cases	Country	AAO (years)	Survival time (years)	Headache	Ataxia	Seizures	CI	Hearing loss	Hydrocephalus	Stroke or SLE	SAH	PN	AN	Vitreous opacity	Cardiac involvement
Leptomeningeal amyloidosis-associated variants																			
p.L32P	c.95T > C	L12P	[19–21]	4	UK, Nigeria, Germany	36.1 ± 6.0	15	+	+	+	+	+	+	+	+	+	+	/	+
p.D38G[a]	c.113A > G	D18G	[10, 17, 18]	7	Hungary, Japan, US, China	42.7 ± 6.2	15 ± 7.5	+	+	/	+	+	+	+	+	/	+	/	/
p.A45T	c.133G > A	A25T	[22–24]	3	Japan, Spain	46.0 ± 4.4	7.5 ± 4.9	/	+	+	+	+	/	+	+	+	/	/	/
p.V50G	c.148G > A	V30G	[26–31]	11	US	46.1 ± 8.9	5.6 ± 3.6	+	+	+	+	+	+	+	/	/	/	+	/
p.G73R	c.217G > A	G53R	[37]	2	US	51.0 ± 7.1	17	/	/	+	+	/	+	+	/	/	/	/	/
p.G73E	c.218G > A	G53E	[35]	3	France	38.3 ± 3.2	4.5 ± 3.5	+	+	/	+	/	/	/	+	/	+	/	+
p.G73A	c.218G > C	G53A	[36]	1	UK	40	/	+	+	/	+	/	/	+	/	+	/	/	+
p.F84S	c.251T > C	F64S	[38, 39]	3	Canada	28	12	+	+	+	+	+	+	+	/	+	+	+	+
p.Y89H	c.265T > C	Y69H	[40–45]	13	US, Sweden, Canada	50.4 ± 9.2	7.7 ± 3.1	+	+	+	+	+	/	+	+	+	/	+	/
Combined				47		45.1 ± 8.9[b]	8.6 ± 5.3[b]												
Other ATTR-associated variants cause CNS symptoms																			
p.V50M	c.148G > A	V30M	[25, 47]	1	US	63	/	+	/	/	+	/	+	/	/	+	+	+	+
p.A56P	c.166G > C	A36P	[32]	3	Italy	38 ± 1.7	17.5 ± 20.5	/	+	/	+	+	+	+	+	+	/	+	/
p.F64S	c.191T > C	F44S	[33]	1	US	26	/	+	/	/	+	+	/	/	/	+	+	/	+
p.T69P	c.205A > C	T49P	[34, 47]	1	US	50	/	+	/	+	+	+	/	+	/	+	/	/	+
p.I127M	c.381T > C	I107M	[46, 47]	1	Canada	51	/	/	+	/	/	/	/	/	/	+	+	+	+
p.Y134C	c.401A > G	Y114C	[12, 47]	6	Japan	–	/	/	/	/	+	/	/	+	/	+	+	+	+
Combined (All)				60		44.8 ± 9.3[c]	9.3 ± 7.1[c]												

+ have symptom, / not reported, *TTR* transthyretin, *AAO* age at onset, *CI* cognitive impairment, *SLE* stroke-like episode, *SAH* subarachnoid hemorrhage, *PN* peripheral neuropathy, *AN* autonomic neuropathy

[a]Not including the patients reported in this study

[b]Calculated from 44 cases with definite age at onset and 23 cases with definite survival time

[c]Calculated from 51 cases with definite age at onset and 25 cases with definite survival time

with the p.D38G variant were homogeneous in the same family, but heterogeneous between different families, such as ataxia and hearing loss in the Hungarian family, SAH in a Japanese family, and hydrocephalus in sufferers of this family (Table 1) [10, 17]. These findings indicate the presence of unknown genetic and/or environment factors that modify the manifestations of LA.

Previous studies focused on LA blood vessel impairment. Superficial siderosis was suggested as a possibly useful hallmark of this disease [17]. GRE-T2* and SWI sequences found superficial siderosis on patient with longer disease course in this study, indicating that it is a later marker of this disease as reported elsewhere [49, 50]. The positive correlation between clinical symptom severity and hydrocephalus suggests the importance of ependyma involvement in this family. The frequent periodic headaches and vomiting symptoms in LA patients suggest that hydrocephalus is probably more frequent than recorded. The different extents and degrees of leptomeninges and ependyma enhancement on contrast MRI in the three presymptomatic patients indicate the slow progress of CNS impairment, as well as the potential early diagnosis value of contrast MRI in the presymptomatic stage.

CNS symptoms are rare in ATTR patients before OLT. Due to the longer survival time provided by OLT, CNS symptoms were observed in at least 31% of ATTR patients with the p.V50M variant [11]. CNS impairment should be considered as an important pathogenic mechanism and treatment target for ATTR patients with the longer survival time. Future studies in TTR animal models with different genetic backgrounds which mimic LA phenotype may lead to new target therapies for CNS impairment of ATTR.

Conclusions

We identified a p.D38G (c.113A > G) variant as the genetic cause in a Chinese family with LA. The uncommonly early AAO and the hydrocephalus-associated symptoms indicate unknown factors influencing CNS impairment progression in its sufferers. The important role of ependyma involvement and the potential early diagnosis value of contrast MRI were suggested. These findings expand the phenotypic spectrum of *TTR* gene and have implications for the diagnosis, treatment, and systematic study of ATTR.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards The study received approval from the Ethics Committee of the Third Xiangya Hospital and was performed in accordance with the ethical standards stated in the 1964 Declaration of Helsinki.

Informed consent Informed consent was obtained from the individuals.

References

1. Planté-Bordeneuve V, Said G (2011) Familial amyloid polyneuropathy. Lancet Neurol 10(12):1086–1097. https://doi.org/10.1016/S1474-4422(11)70246-0
2. Sekijima Y (2015) Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry 86(9):1036–1043. https://doi.org/10.1136/jnnp-2014-308724
3. Hund E, Linke RP, Willig F, Grau A (2001) Transthyretin-associated neuropathic amyloidosis. Pathogenesis and treatment. Neurology 56(4):431–435. https://doi.org/10.1212/WNL.56.4.431
4. Chen Q, Yuan L, Deng X, Yang Z, Zhang S, Deng S, Lu H, Deng H (2018) A missense variant p.Ala117Ser in the transthyretin gene of a Han Chinese family with familial amyloid polyneuropathy. Mol Neurobiol 55(6):4911–4917. https://doi.org/10.1007/s12035-017-0694-0
5. Sekijima Y, Yoshida K, Tokuda T, Ikeda S (1993) Familial transthyretin amyloidosis. In: Adam MP, Ardinger HH, Pagon RA et al (eds) GeneReviews. Seattle (WA). http://www.ncbi.nlm.nih.gov/pubmed/20301373
6. Eisele YS, Monteiro C, Fearns C, Encalada SE, Wiseman RL, Powers ET, Kelly JW (2015) Targeting protein aggregation for the treatment of degenerative diseases. Nat Rev Drug Discov 14(11):759–780. https://doi.org/10.1038/nrd4593
7. Tawara S, Nakazato M, Kangawa K, Matsuo H, Araki S (1983) Identification of amyloid prealbumin variant in familial amyloidotic polyneuropathy (Japanese type). Biochem Biophys Res Commun 116(3):880–888. https://doi.org/10.1016/S0006-291X(83)80224-1
8. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L et al (2013) Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 8:31. https://doi.org/10.1186/1750-1172-8-31
9. Parman Y, Adams D, Obici L, Galán L, Guergueltcheva V, Suhr OB, Coelho T (2016) Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol 29(Suppl 1):S3–S13. https://doi.org/10.1097/WCO.0000000000000288
10. Garzuly F, Vidal R, Wisniewski T, Brittig F, Budka H (1996) Familial meningocerebrovascular amyloidosis, Hungarian type, with mutant transthyretin (TTR Asp18Gly). Neurology 47(6):1562–1567. https://doi.org/10.1212/WNL.47.6.1562

11. Maia LF, Magalhães R, Freitas J, Taipa R, Pires MM, Osório H, Dias D, Pessegueiro H et al (2015) CNS involvement in V30M transthyretin amyloidosis: clinical, neuropathological and biochemical findings. J Neurol Neurosurg Psychiatry 86(2):159–167. https://doi.org/10.1136/jnnp-2014-308107
12. Nakamura M, Yamashita T, Ueda M, Obayashi K, Sato T, Ikeda T, Washimi Y, Hirai T et al (2005) Neuroradiologic and clinicopathologic features of oculoleptomeningeal type amyloidosis. Neurology 65(7):1051–1056. https://doi.org/10.1212/01.wnl.0000178983.20975.af
13. Yuan L, Deng X, Song Z, Yang Z, Ni B, Chen Y, Deng H (2015) Genetic analysis of the RAB39B gene in Chinese Han patients with Parkinson's disease. Neurobiol Aging 36(10):2907.e11–2907.e12. https://doi.org/10.1016/j.neurobiolaging.2015.06.019
14. Mitsuhashi S, Yazaki M, Tokuda T, Sekijima Y, Washimi Y, Shimizu Y, Ando Y, Benson MD et al (2005) Biochemical characteristics of variant transthyretins causing hereditary leptomeningeal amyloidosis. Amyloid 12(4):216–225. https://doi.org/10.1080/13506120500352404
15. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M et al (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17(5):405–424. https://doi.org/10.1038/gim.2015.30
16. Sekijima Y, Wiseman RL, Matteson J, Hammarström P, Miller SR, Sawkar AR, Balch WE, Kelly JW (2005) The biological and chemical basis for tissue-selective amyloid disease. Cell 121(1):73–85. https://doi.org/10.1016/j.cell.2005.01.018
17. Jin K, Sato S, Takahashi T, Nakazaki H, Date Y, Nakazato M, Tominaga T, Itoyama Y et al (2004) Familial leptomeningeal amyloidosis with a transthyretin variant Asp18Gly representing repeated subarachnoid haemorrhages with superficial siderosis. J Neurol Neurosurg Psychiatry 75(10):1463–1466. https://doi.org/10.1136/jnnp.2003.029942
18. Bevers MB, McGuone D, Jerath NU, Musolino PL (2016) Leptomeningeal transthyretin-type amyloidosis presenting as acute hydrocephalus and subarachnoid hemorrhage. J Clin Neurosci 29:203–205. https://doi.org/10.1016/j.jocn.2015.12.017
19. Brett M, Persey MR, Reilly MM, Revesz T, Booth DR, Booth SE, Hawkins PN, Pepys MB et al (1999) Transthyretin Leu-12Pro is associated with systemic, neuropathic and leptomeningeal amyloidosis. Brain 122(Pt2):183–190. https://doi.org/10.1093/brain/122.2.183
20. Barreiros AP, Post F, Hoppe-Lotichius M, Linke RP, Vahl CF, Schäfers HJ, Galle PR, Otto G (2010) Liver transplantation and combined liver-heart transplantation in patients with familial amyloid polyneuropathy: a single-center experience. Liver Transpl 16(3):314–323. https://doi.org/10.1002/lt.21996
21. McColgan P, Viegas S, Gandhi S, Bull K, Tudor R, Sheikh F, Pinney J, Fontana M et al (2015) Oculoleptomeningeal amyloidosis associated with transthyretin Leu12Pro in an African patient. J Neurol 262(1):228–234. https://doi.org/10.1007/s00415-014-7594-2
22. Shimizu Y, Takeuchi M, Matsumura M, Tokuda T, Iwata M (2006) A case of biopsy-proven leptomeningeal amyloidosis and intravenous Ig-responsive polyneuropathy associated with the Ala25Thr transthyretin gene mutation. Amyloid 13(1):37–41. https://doi.org/10.1080/13506120600551814
23. Hagiwara K, Ochi H, Suzuki S, Shimizu Y, Tokuda T, Murai H, Shigeto H, Ohyagi Y et al (2009) Highly selective leptomeningeal amyloidosis with transthyretin variant Ala25Thr. Neurology 72(15):1358–1360. https://doi.org/10.1212/WNL.0b013e3181a0fe74
24. Llull L, Berenguer J, Yagüe J, Graus F (2014) Leptomeningeal amyloidosis due to A25T TTR mutation: a case report. Neurologia 29(6):382–384. https://doi.org/10.1016/j.nrl.2012.12.006
25. Herrick MK, DeBruyne K, Horoupian DS, Skare J, Vanefsky MA, Ong T (1996) Massive leptomeningeal amyloidosis associated with a Val30Met transthyretin gene. Neurology 47(4):988–992. https://doi.org/10.1212/WNL.47.4.988
26. Dowell JD, Fleck JD, Vakili ST, Benson MD (2007) Familial oculoleptomeningeal amyloidosis associated with primary angiitis of the CNS. Neurology 68(1):77–78. https://doi.org/10.1212/01.wnl.0000250343.34110.79
27. Goren H, Steinberg MC, Farboody GH (1980) Familial oculoleptomeningeal amyloidosis. Brain 103(3):473–495. https://doi.org/10.1093/brain/103.3.473
28. Petersen RB, Goren H, Cohen M, Richardson SL, Tresser N, Lynn A, Gali M, Estes M et al (1997) Transthyretin amyloidosis: a new mutation associated with dementia. Ann Neurol 41(3):307–313. https://doi.org/10.1002/ana.410410305
29. Roe RH, Fisher Y, Eagle RC, Fine HF, Cunningham ET (2007) Oculoleptomeningeal amyloidosis in a patient with a TTR Val30Gly mutation in the transthyretin gene. Ophthalmology 114(11):e33–e37. https://doi.org/10.1016/j.ophtha.2007.07.007
30. Liu JK, Turner RD, Luciano MG, Krishnaney AA (2015) Circumferential intrathecal ossification in oculoleptomeningeal amyloidosis. J Clin Neurosci 22(4):769–771. https://doi.org/10.1016/j.jocn.2014.10.021
31. Martin SE, Benson MD, Hattab EM (2014) The pathologic spectrum of oculoleptomeningeal amyloidosis with Val30Gly transthyretin gene mutation in a postmortem case. Hum Pathol 45(5):1105–1108. https://doi.org/10.1016/j.humpath.2013.10.037
32. Mascalchi M, Salvi F, Pirini MG, D'Errico A, Ferlini A, Lolli F, Plasmati R, Tessa C et al (1999) Transthyretin amyloidosis and superficial siderosis of the CNS. Neurology 53(7):1498–1503. https://doi.org/10.1212/WNL.53.7.1498
33. Klein CJ, Nakumura M, Jacobson DR, Lacy MQ, Benson MD, Petersen RC (1998) Transthyretin amyloidosis (serine 44) with headache, hearing loss, and peripheral neuropathy. Neurology 51(5):1462–1464. https://doi.org/10.1212/WNL.51.5.1462
34. Nakagawa K, Sheikh SI, Snuderl M, Frosch MP, Greenberg SM (2008) A new Thr49Pro transthyretin gene mutation associated with leptomeningeal amyloidosis. J Neurol Sci 272(1–2):186–190. https://doi.org/10.1016/j.jns.2008.05.014
35. Ellie E, Camou F, Vital A, Rummens C, Grateau G, Delpech M, Valleix S (2001) Recurrent subarachnoid hemorrhage associated with a new transthyretin variant (Gly53Glu). Neurology 57(1):135–137. https://doi.org/10.1212/WNL.57.1.135
36. Douglass C, Suvarna K, Reilly MM, Hawkins PN, Hadjivassiliou M (2007) A novel amyloidogenic transthyretin variant, Gly-53Ala, associated with intermittent headaches and ataxia. J Neurol Neurosurg Psychiatry 78(2):193–195. https://doi.org/10.1136/jnnp.2006.093500
37. Liepnieks JJ, Dickson DW, Benson MD (2011) A new transthyretin mutation associated with leptomeningeal amyloidosis. Amyloid 18(Suppl 1):160–162. https://doi.org/10.3109/13506129.2011.574354060
38. Uitti RJ, Donat JR, Rozdilsky B, Schneider RJ, Koeppen AH (1988) Familial oculoleptomeningeal amyloidosis. Report of a new family with unusual features. Arch Neurol 45(10):1118–1122. https://doi.org/10.1001/archneur.1988.00520340072015
39. Uemichi T, Uitti RJ, Koeppen AH, Donat JR, Benson MD (1999) Oculoleptomeningeal amyloidosis associated with a new transthyretin variant Ser64. Arch Neurol 56(9):1152–1155. https://doi.org/10.1001/archneur.56.9.1152
40. Blevins G, Macaulay R, Harder S, Fladeland D, Yamashita T, Yazaki M, Hamidi Asl K, Benson MD et al (2003) Oculoleptomeningeal amyloidosis in a large kindred with a new transthyretin

variant Tyr69His. Neurology 60(10):1625–1630. https://doi.org/10.1212/01.WNL.0000065901.18353.AB
41. Schweitzer K, Ehmann D, Garcia R, Alport E (2009) Oculoleptomeningeal amyloidosis in 3 individuals with the transthyretin variant Tyr69His. Can J Ophthalmol 44(3):317–319. https://doi.org/10.3129/i09-023
42. Suhr OB, Andersen O, Aronsson T, Jonasson J, Kalimo H, Lundahl C, Lundgren HE, Melberg A et al (2009) Report of five rare or previously unknown amyloidogenic transthyretin mutations disclosed in Sweden. Amyloid 16(4):208–214. https://doi.org/10.3109/13506120903421587
43. Ziskin JL, Greicius MD, Zhu W, Okumu AN, Adams CM, Plowey ED (2015) Neuropathologic analysis of Tyr69His TTR variant meningovascular amyloidosis with dementia. Acta Neuropathol Commun 3:43. https://doi.org/10.1186/s40478-015-0216-0
44. Zeldenrust SR, Skinner M, Share J, Benson MD (1994) A new transthyretin variant (His 69) associated with vitreous amyloid in an FAP family. Amyloid 1(1):17–22. https://doi.org/10.3109/13506129409148620
45. Purrucker JC, Hund E, Hinderhofer K, Kollmer J, Schönland S, Hegenbart U (2013) Doxycycline in ATTRY69H (p.ATTRY89H) amyloidosis with predominant leptomeningeal manifestation. Amyloid 20(4):279–280. https://doi.org/10.3109/13506129.2013.829439
46. Mathieu F, Morgan E, So J, Munoz DG, Mason W, Kongkham P (2018) Oculoleptomeningeal amyloidosis secondary to the rare transthyretin c.381T> G (p.Ile127Met) mutation. World Neurosurg 111:190–193. https://doi.org/10.1016/j.wneu.2017.12.096
47. Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE (2003) Tabulation of human transthyretin (TTR) variants, 2003. Amyloid 10(3):160–184. https://doi.org/10.3109/13506120308998998
48. Benson MD, Kincaid JC (2007) The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve 36(4):411–423. https://doi.org/10.1002/mus.20821
49. Salvi F, Pastorelli F, Plasmati R, Bartolomei I, Dall'Osso D, Rapezzi C (2012) Genotypic and phenotypic correlation in an Italian population of hereditary amyloidosis TTR-related (HA-TTR): clinical and neurophysiological aids to diagnosis and some reflections on misdiagnosis. Amyloid 19(Suppl 1):58–60. https://doi.org/10.3109/13506129.2012.682187
50. Stabile A, Di Lazzaro V, Colosimo C, Piazza F, Ferrarese C, Di Francesco JC (2018) Idiopathic infratentorial superficial siderosis of the central nervous system: case report and review of literature. Neurol Neurochir Pol 52(1):102–106. https://doi.org/10.1016/j.pjnns.2017.10.006