Neurogenetics (2011) 12:93–95
DOI 10.1007/s10048-010-0258-1

LETTER TO THE EDITORS

A novel *CLN2/TPP1* mutation in a Chinese patient with late infantile neuronal ceroid lipofuscinosis

Yu-Liang Wang · Zhi-Yong Zeng · Xing-Wang Song · Zhuo-Fang Hao · Yi-Wu Shi · Bin Tang · Sheng-Qiang Chen · Mei-Mei Gao · Wei Di · Yue-Sheng Long · Yong-Hong Yi · Wei-Ping Liao

Received: 29 June 2010 / Accepted: 26 August 2010 / Published online: 7 September 2010

The neuronal ceroid lipofuscinoses (NCLs) are a group of autosomal recessive hereditary disorders with progressive neuron degeneration. Traditionally, NCLs were classified into infantile NCL, classical late infantile NCL (LINCL), juvenile NCL, adult NCL, and several variant forms [1, 2]. Recent studies have advanced the classification of human NCLs into at least ten genetic forms (CLN1–CLN10), among which eight genes have been identified (*CLN1–3, CLN5–8*, *CLN10*; *CLN4* and *CLN9* to be defined). Mutations in two more genes, *CLCN6* and *SGSH*, have also been identified in unusual NCL cases (http://www.ucl.ac.uk/ncl). *CLN2* gene encodes tripeptidyl peptidase 1 (TPP1) [3]. Deficiency of TPP1 leads to the accumulation of autofluorescent lipopigments consisting of the subunit c of mitochondrial ATP synthase in lysosome, which results in typically clinical and pathomorphological features of LINCL [4]. Mutations in *CLN2/TPP1*, which are always homozygote or compound heterozygote, cause the majority cases of classical LINCL [1, 5]. Up to now, 72 mutations in *CLN2/TPP1* have been found. Here, we report a novel splice site mutation in *CLN2/TPP1* from a Chinese LINCL patient, which constitutes a compound heterozygous mutation in *CLN2/TPP1* with another missense mutation.

The patient and her parents were examined at the present hospital. Exons and exon/intron boundaries of the *CLN2/TPP1* (NM_000391.3) were PCR-amplified and sequenced.

Pedigree of the family is shown in Fig. 1a. The proband showed myoclonic seizures at 3.5 years as an initial symptom, which progressively aggravated and became intractable, with tonic–clonic seizures later. Progressive cognitive and neuromotor dysfunction, including prominent speech regression and ataxia, appeared gradually afterwards. Vision problems occurred recently (6 years). The video EEG revealed irregular and slow background activity with intermittent bursts of generalized, or occipital-dominant, spike-waves or poolyspike-waves. Synchronous myoclonic seizures occurred with the bursts of discharge on EEG. MRI demonstrated generalized encephalatrophy, remarkably in the cerebellum. Pathological examination of the biopsy tissue from right frontal lobe showed a typical pathological change of LINCL (Figs. 1b–e). The TPP1 activity measurement was not available. Based on the clinical and pathological findings, the patient was diagnosed as having LINCL.

DNA sequencing identified a novel compound heterozygous mutation consisting of *c.646G >A* (p.Val216Met)

Yu-Liang Wang and Zhi-Yong Zeng have contributed equally to this research.

Y.-L. Wang · X.-W. Song · Y.-W. Shi · B. Tang · S.-Q. Chen · M.-M. Gao · W. Di · Y.-S. Long · Y.-H. Yi (✉) · W.-P. Liao
Key Laboratory of Neurogenetics and Channelopathies of Guangdong Province and the Ministry of Education of China, The Second Affiliated Hospital of Guangzhou Medical University, Chang-gang-dong road 250, Guangzhou 510260, China
e-mail: yyh168@sina.com

Y.-L. Wang · X.-W. Song · Y.-W. Shi · B. Tang · S.-Q. Chen · M.-M. Gao · W. Di · Y.-S. Long · Y.-H. Yi · W.-P. Liao
Institute of Neuroscience, Guangzhou Medical University, Chang-gang-dong road 250, Guangzhou 510260, China

Z.-Y. Zeng
Pediatric Department, Buji People's Hospital, Shenzhen 518112, China

Z.-F. Hao
Department of Pathology, The Second Affiliated Hospital of Guangzhou Medical University, Chang-gang-dong road 250, Guangzhou 510260, China

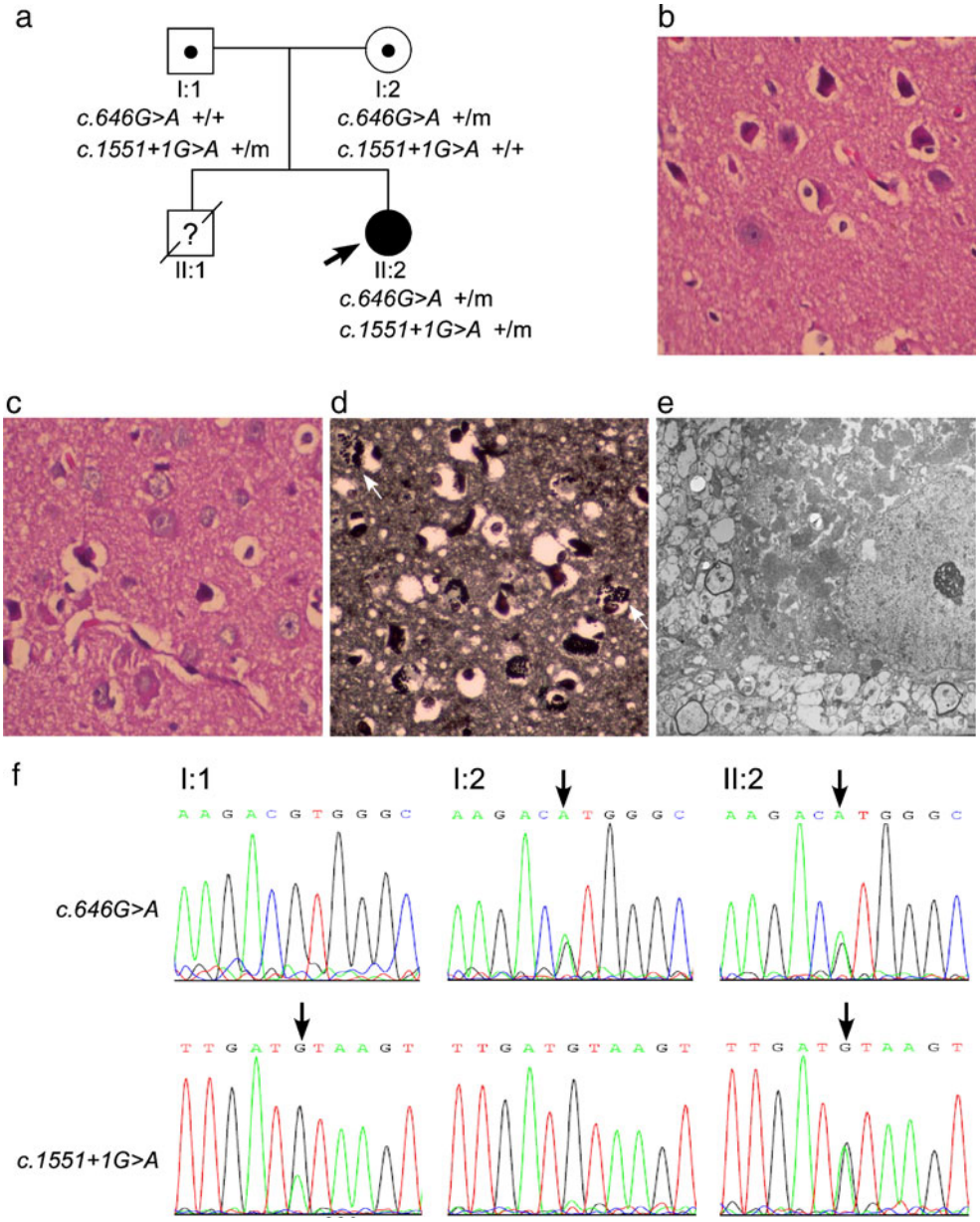

Fig. 1 Pedigree, pathological features, and mutation analysis of the family. **a** The pedigree of the family. II:2 is the proband. Her sibling showed similar symptoms and evolution from 2 years old, and died at 14 years (II:1). Her parents were asymptomatic. Written informed consent has been obtained from the family. **b** Degenerative and atrophic neurons in the cortex (light microscope, ×400). **c** Immature neurons mixed with other abnormal neurons in the cortex (light microscope, ×400). **d** Brown-black granules (*white arrows*) in neuron plasma shown by sliver staining (light microscope, ×400). **e** Numerous lipofuscinic pigments with curvilinear-like bodies in neurons (electron microscope, ×20,000). **f** Sequencing of *CLN2/TPP1*. *Arrows* indicate the heterozygous mutant nucleotides. Heterozygous mutations *g.646G >A* and *c.1551+1G >A* were detected in the mother and father, respectively, and both mutations appeared in the proband

and *c.1551+1(IVS12+1)G >A* in *CLN2/TPP1* in the patient; heterozygous *c.646G >A* and *c.1551+1G >A* in her asymptomatic mother and father, respectively (Fig. 1f). Missense mutation *c.646G >A* has been identified in a patient with LINCL (http://www.ucl.ac.uk/ncl) previously; whereas splice site mutation *c.1551+1G >A* is a novel finding, which changed the invariant splice junction residue.

Previous studies have shown that splice site mutations in *CLN2/TPP1* are common causes of LINCL [5]. It has been reported that patients with *CLN2/TPP1* mutations have relatively homogenous clinical pictures, although missense mutations p.Arg447His, p.Ser153Pro, and p. Arg127Gln were shown to be associated with later onset age and more protracted courses [5, 6]. The present patient has the classic clinical and pathological features of LINCL, suggesting that mutation *c.1551+1G >A* may be similar in causative of LINCL as most of the *CLN2/TPP1* mutations reported before. Although NCL cases were occasionally reported in China, there is no report showing its incidence or gene mutations. Further studies are required to know the frequency of *c.1551+1G >A* in Chinese LINCL patients.

Acknowledgements This work was supported in part by grants from the National Nature Science Foundation of China (no 30870876) and the Guangdong Natural Science Foundation (no 2008B030301250).

Conflict of interest statement None of the authors has any conflict of interest to disclose.

References

1. Haltia M (2003) The neuronal ceroid-lipofuscinoses. J Neuropathol Exp Neurol 62(1):1–13
2. Mole SE, Williams RE, Goebel HH (2005) Correlations between genotype, ultrastructural morphology and clinical phenotype in the neuronal ceroid lipofuscinoses. Neurogenetics 6:107–126
3. Sleat DE, Donnelly RJ, Lackland H et al (1997) Association of mutations in a lysosomal protein with classical late-infantile neuronal ceroid lipofuscinosis. Science 277:1802–1805
4. Rawlings ND, Barrett AJ (1999) Tripeptidyl-peptidase I is apparently the *CLN2* protein absent in classical late-infantile neuronal ceroid lipofuscinosis. Biochem Biophys Acta 1429:496–500
5. Sleat DE, Gin RM, Sohar I, Wisniewski K, Sklower-Brooks S, Pullarkat RK, Palmer DN, Lerner TJ, Boustany RM, Uldall P, Siakotos AN, Donnelly RJ, Lobel P (1999) Mutational analysis of the defective protease in classical late-infantile neuronal ceroid lipofuscinosis, a neurodegenerative lysosomal storage disorder. Am J Hum Genet 64:1511–1523
6. Steinfeld R, Heim P, Von Gregory H, Meyer K, Ullrich K, Goebel HH, Kohlschutter A (2002) Late infantile neuronal ceroid lipofuscinosis: quantitative description of the clinical course in patients with *CLN2* mutations. Am J Med Genet 112:347–354