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Case Report

Cerebrotendinous xanthomatosis: Possibility of founder mutation in CYP27A1 gene (c.526delG) in Eastern Indian and Surinamese population

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ABSTRACT

Cerebrotendinous xanthomatosis is a lipid storage disease characterized by diarrhea, cataract, tendon xanthoma and neurological regression if untreated. CYP27A1 is the only gene in which mutations are known to cause Cerebrotendinous xanthomatosis. We report two Indian families from different regions of India who underwent molecular testing of *CYP27A1*. The first family from Eastern India consisting of two affected individuals was found to have the c.526delG homozygous mutation in exon 3, previously reported from our laboratory, also in a patient from Eastern India. However the second affected individual from Southern India that we studied and two previously reported cases from Northern India have different mutations. Interestingly the only previous report of c.526delG mutation was in a Surinamese individual from the Netherlands. To date most of the pathogenic mutations for Cerebrotendinous xanthomatosis have been confined to single population except for R362C mutation which was reported from the Netherlands and the USA (Black). To our knowledge this is the second causal mutation for Cerebrotendinous xanthomatosis which has been reported in two different populations. As human trading was prevalent from Eastern India to Surinam by the Dutch settlers this mutation might suggest a common founder mutation in these populations.

1. Introduction

Cerebrotendinous xanthomatosis is a lipid storage disease characterized by diarrhea, cataract, tendon xanthoma and neurological dysfunction. The onset of these features follows a chronological order. *CYP27A1* is the only gene in which mutations are known to cause Cerebrotendinous xanthomatosis. *CYP27A1* gene is located in chromosome 2q33 and contains nine exons. This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. This mitochondrial protein oxidizes cholesterol intermediates as part of the bile synthesis pathway. Since the conversion of cholesterol to bile acids is the major route for removing cholesterol from the body, this protein is important for overall cholesterol homeostasis. Early diagnosis by biochemical testing or molecular genetic testing if the two disease-causing mutations in the family are known allows for early treatment that may prevent or limit disease manifestations. Cerebrotendinous xanthomatosis is inherited in an autosomal recessive manner. To date around 90% of cases of Cerebrotendinous xanthomatosis have been ascribed to point mutations and another 8% to deletions or duplications [1].

2. Material and methods

Two Indian families (family 1 and family 2) with a clinical diagnosis of Cerebrotendinous xanthomatosis were recruited for CYP27A1 gene analysis after obtaining informed consent. The clinical, laboratory and radiological characteristics are summarized in Table 1.

The study was funded by Christian Medical College, Vellore fluid research grant (IRB No. 8491/9-10-13). The study was approved by the Institutional Review Board and the Ethics Committee and 5 ml of blood was collected aseptically from the affected patients, parents, (father of affected family 1 was unavailable) and unaffected siblings. DNA was extracted with QIAamp DNA Minikit from Qiagen as per standard protocol. DNA purity was checked in a Nanodrop instrument. PCR of all exons and intron–exon boundaries was done using a published protocol [2]. PCR products were visualized by electrophoresis in 2% agarose gel. PCR

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Table 1
Clinical details of the probands in two families studied.

Patient		Family I-A	Family II-C
Ethnicity		Eastern India	Southern India
Consanguinity		No	Yes (3rd degree)
Age (in years)/sex		26/male	33/male
Age at onset of first symptom (years)		4 (diarrhea)	7 (prolonged cholestatic jaundice)
Age at diagnosis (years)		25	32
Age at onset of symptoms (years)	Diarrhea	04	08
	Xanthomas	10	30
	Cataract	14	27
	Neurological symptoms	24	30
Seizures		−	+
Jaundice		−	+
Intellectual disability		+	+
Palatal myoclonus		−	+
Pes cavus		+	+
Spasticity		+	+
Cerebellar signs		+	+
Bulbar involvement		−	+
Gall stones		−	−
Infertility		−	+
Cholesterol levels (mg/dl)		129	133
MRI brain		Periventricular white matter hyperintensity, mild cerebellar atrophy	Symmetric hyperintensity along CST with marked cerebellar and cerebral atrophic changes, dentate nucleus hyperintensity
Nerve conduction study		Motor demyelinating polyneuropathy	Motor demyelinating polyneuropathy
Somatosensory evoked potential		ND	Cortical potentials not obtained
Visual evoked potential		ND	Bilateral anterior optic pathway dysfunction
Cardiac workup		Left ventricular hypertrophy	Normal

(ND — not done, + present, − absent, CST — corticospinal tract).

Table 2
CYP27A1 gene analysis results.

Family	Case	Mutation	Exon/intron	Position	Consequences	Result	Previous reports
1	A, B	Homozygous deletion of G	Exon 3	c.526delG	Frame shift	Pathogenic	Verrips et al. 1996; Shah et al., 2012
2	C	Homozygous G to A substitution	Intron 2 splice donor site	c.446 + 1 G to A	Splice donor site variation	Pathogenic	Verrips et al. 2000 (in compound heterozygous state)

products were purified using Exosap kit from Qiagen. PCR products were sequenced by Sanger sequencing in ABI 3500 genetic analyzer. Sequences were analyzed in Ensemble database and pathogenic mutations were checked in Human Genome Mutation Database (public version) for previous reports on 02.09.2014.

3. Results

The genotyping results are summarized in Table 2. Two affected individuals from the first family had a homozygous c.526delG mutation and the mother is a heterozygote — Fig. 1.

This is a known pathogenic mutation which leads to frame shift. The single affected individual from the second family had a homozygous c.446 + 1G-A mutation. This is also a known splice donor site mutation. Parents are heterozygotes — Fig. 2.

4. Discussion

We describe two different mutations in the CTX patients belonging to two different regions of India. The first familial case from Eastern India has homozygous c.526delG.mutation, the affected sister is homozygous while the mother who is unaffected is heterozygous for this known mutation. The father was unavailable for testing and is presumed to be a carrier. The second case and the first one to be reported from South India have homozygous c.446 + 1G-A mutation which is already reported in heterozygous state in a Spanish patient [3]. The parents are heterozygous for the mutation. Previously our laboratory has reported the first Indian case with the same homozygous c.526delG mutation also from Eastern India [4]. Another report from the Northern part of the Country described a patient with compound heterozygous (c. 1151C > T p. P384L and c. 2T > C p.M1T) [5]. Patients from all three

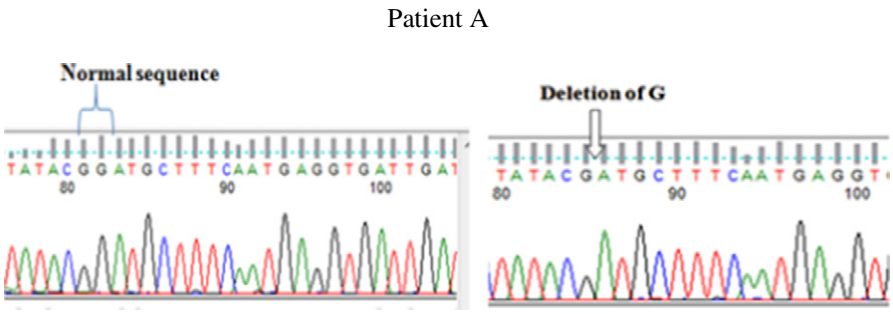

Fig. 1. Patient A.

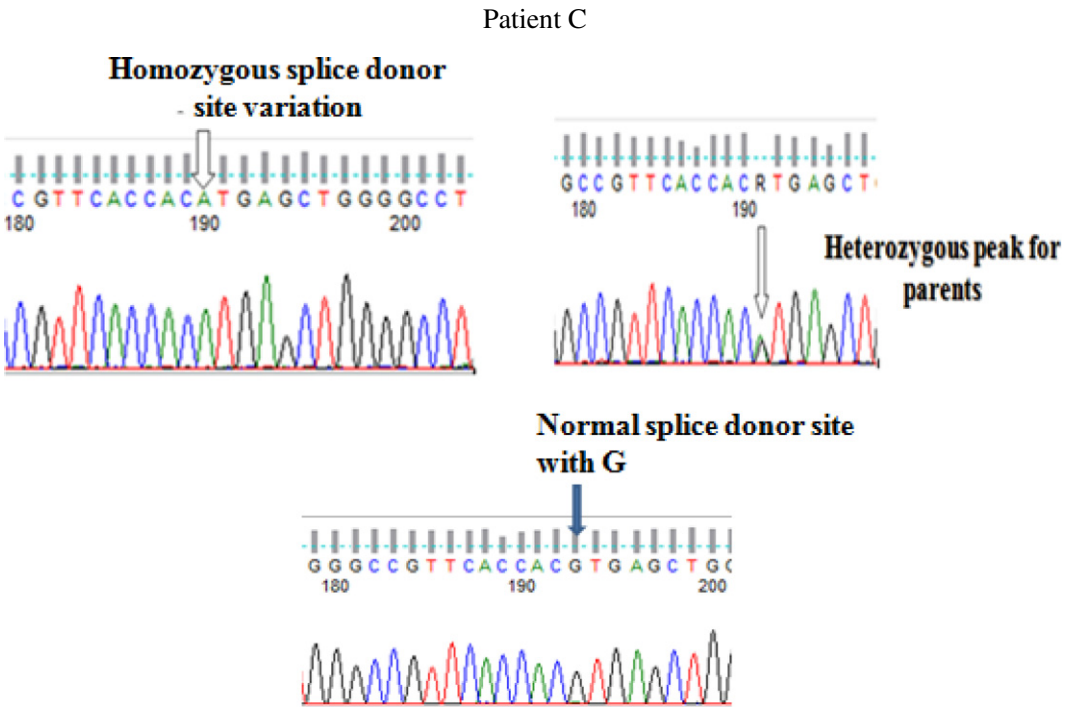

Fig. 2. Patient C.

regions have separate mutations. However to date two unrelated Eastern Indian families have the same homozygous c.526delG mutation. The only documented report of the same mutation was from the Netherlands in a Surinamese patient [6]. The pathogenic mutations in Cerebrotendinous xanthomatosis are usually restricted to specific populations except for R362C mutation which has been reported from the Netherlands and the USA (Black) [7]. The present reported mutation is the second of its kind to be reported from two different populations. As human trading between Eastern India and Surinam was prevalent in the ninetieth century this mutation might represent a common founder mutation [8].

Compliance with ethics guidelines

Conflict of interest — Atanu Kumar Dutta, Sumita Danda, Karthik M, Mathew Alexander, Sniya Valsa Sudhakar, Samuel Hansdak, Rini Bandyopadhyay, G B Bakhya Shree and L Rekha declare that they have no conflict of interest.

Patient consent statement — All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Each participant or his/her legally authorized representative, provided written informed consent before entering the study in compliance with the applicable local regulations.

Contributions of individual authors — Atanu Kumar Dutta — Recruiting participants, designing primers, standardizing PCR conditions, interpretation of sequencing data, literature search, preparation of manuscript. Sumita Danda — Conceptualizing the study, mentoring Atanu Kumar Dutta, supervising the study, reviewing the manuscript, corresponding the manuscript. Karthik M, Mathew Alexander, Samuel Hansdak and Rini Bandyopadhyay — Diagnosing clinical cases. Sniya Valsa Sudhakar — Reporting brain MRI images. G B Bakhya Shree and L Rekha — Carrying out DNA extraction, PCR and sequencing experiments.

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