Case Report

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

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1. Introduction

Cerebrotendinous xanthomatosis is a lipid storage disease characterized by diarrhea, cataract, tendon xanthoma and neurological dysfunctions. The onset of these features follows a chronological order. 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.

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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 Qiajen 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
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

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 | 08 |
| | Xanthomas | 10 |
| | Cataract | 14 |
| | Neurological symptoms | 24 |
| | | |
| 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 |

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 splice donor site | 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 + 1G to A | Splice donor site variation | Pathogenic | Verrips et al. 2000 (in compound heterozygous state) |

(ND — not done, + present, — absent, CST — corticospinal tract).
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 nineteenth 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 — Diagnosing clinical cases. Sniya Valsa Sudhakar — Reporting brain MRI images. G B Bakhy Shree and I Rekha — Carrying out DNA extraction, PCR and sequencing experiments.

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