Mutational analysis in TSC1 and TSC2 genes in patients with tuberous sclerosis complex

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INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the development of multiple hamartomas in many organs, with an incidence of 1 in 6,000 to 1 in 10,000 live births. TSC is caused by mutations in tumor suppressor genes *TSC1* and *TSC2*. Mutations in *TSC2* are about five times more common than mutations in *TSC1* in sporadic cases, whereas the ratio is 1:1 in large families with multiple generations affected. Mutations in *TSC1* and *TSC2* are very heterogeneous and no hotspots have been reported, making the molecular diagnosis of the disease extremely difficult.

AIM OF THE STUDY

The aim of this study was to analyze Macedonian patients with tuberous sclerosis for mutation in both *TSC1* and *TSC2* genes.

MATERIALS AND METHODS

Mutational analysis of *TSC1* and *TSC2* genes was performed in eight Macedonian patients with a clinical diagnosis of TSC using MLPA analysis for the detection of large gene rearrangements and sequencing analysis of all exons and exon/intron boundaries of the *TSC1* and *TSC2* genes.

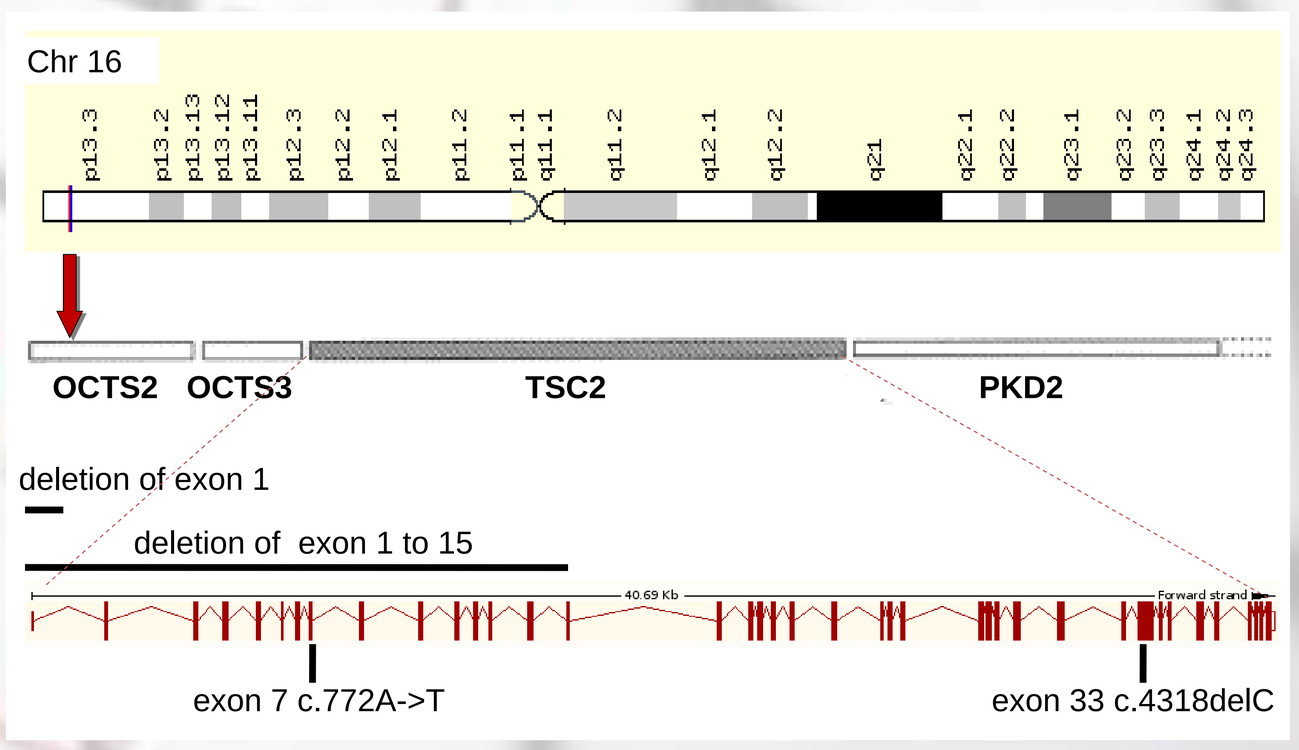

Figure 1. Diagram representing the locations of mutations in the *TSC2 gene.*

RESULTS

We have detected five mutations, of which four in *TSC2* (Figure 1) and one in *TSC1* gene. The *TSC2* defects included two large deletions (deletion of exon 1 and upstream sequence and deletion of exons 1-15 (Figure 2)), one frameshift mutation (c.4318delC) and one missense mutation (c.772A->T) (Figure 3). One frameshift mutation was detected in *TSC1* (c.1431_1434del|AGAA). All mutations were *de novo* events and have been previously reported.

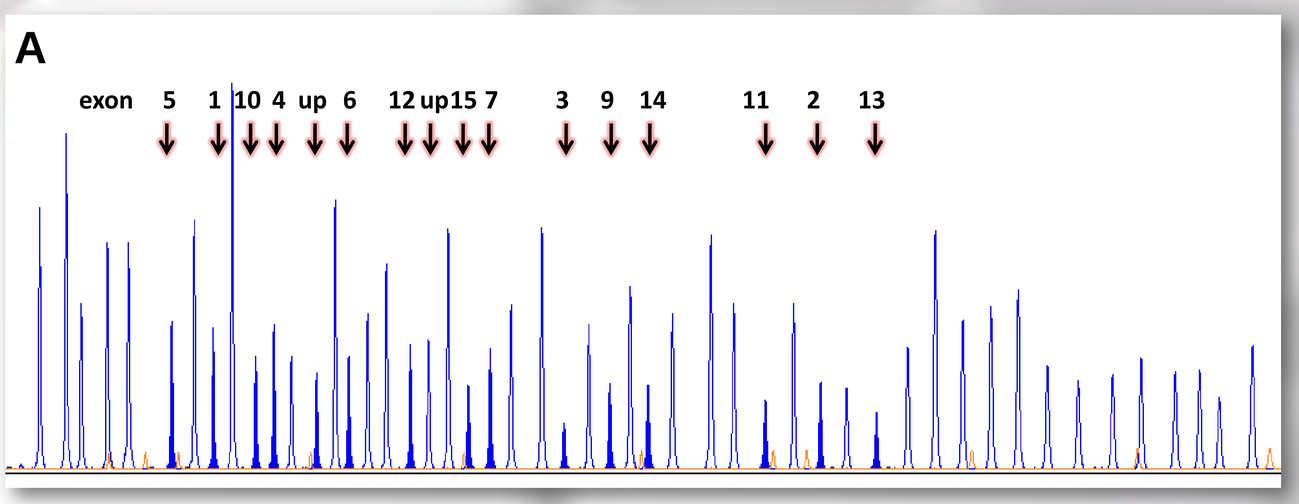

Figure 2. Electropherogram of MLPA analysis of *TSC2* gene showing presence of deletion of exons 1 to 15 in patient (A) and normal individual (B). Probe amplification products within the deletion are indicated with arrows.

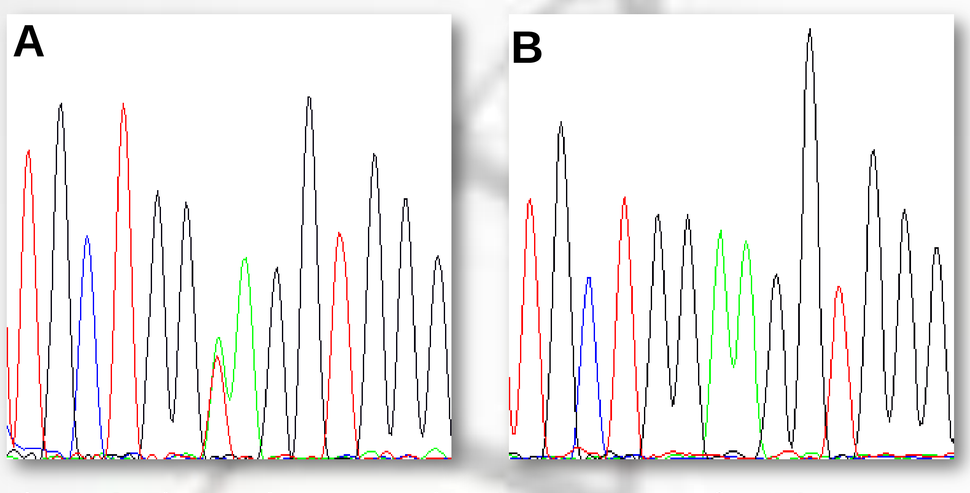

Figure 3. Electropherogram showing presence of c.772A->T mutation in *TSC2* gene in patient (A) and normal individual (B).

CONCLUSION

The mutational spectrum among our patients suggests that the best approach for detection of mutations in TSC patients would be MLPA analysis of TSC genes for the detection of large rearrangements, followed by sequencing analysis for the detection of point mutations first in *TSC2* than in *TSC1*.

ACKNOWLEDGMENTS

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