Recurrent heterozygous missense mutation, p.Gly573Ser, in the TRPV3 gene in an Indian boy with sporadic Olmsted syndrome

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Summary

Olmsted syndrome (OS) is a rare genodermatosis that is often difficult to diagnose because of clinical overlap with other disorders and its uncertain mode of inheritance. The molecular basis of OS was investigated in an Indian boy using comparative exome sequencing and Sanger sequencing data. Sequencing identified a G-to-A transition at position c.573 in the TRPV3 gene, producing the missense mutation p.Gly573Ser in the proband. This mutation was not identified in the mother. This study supports the recent finding of TRPV3 as the gene implicated in OS and suggests that the mutation p.Gly573Ser may be a recurrent abnormality in this genodermatosis.

Case report

Our patient is a 12-year-old Indian boy born to nonconsanguineous parents (Fig. 1a). At birth, his skin was normal. From the age of 2 years, he started to develop progressive keratosis of the palms and soles resulting in profound functional impairment of his hands as well as difficulty weight-bearing and walking (Fig. 1b). At the age of 11 years, amputation of the right little toe was noted. He did not have other cutaneous and/or systemic involvement. His physical and mental milestones were appropriate for his age. Examination revealed severe bilateral and symmetrical mutilating palmo-plantar keratoderma with flexion deformities of the fingers. A keratotic plaque was noted in the natal cleft. Pruritus was also a significant symptom. His hair was dry and lusterless but there was no alopecia. He had dystrophy affecting all his toenails. He was started on oral isotretinoin (30 mg daily) along with topical keratolytics which improved the keratoderma. Hand and foot function, as well as quality of life, improved such that he was lost to follow-up.

Materials and methods

To identify the molecular basis of the OS, we made use of recent advances in next generation sequencing. Genomic DNA was extracted from a peripheral blood sample obtained from
Results

In the proband's DNA we identified 13 novel homozygous and 660 novel heterozygous variants but no clear candidate gene emerged. However, during our analysis, the genetic basis of OS became known with the discovery of pathogenic misense mutations in the TRPV3 gene – using an exome sequencing approach. In that study, the mode of inheritance was clarified and OS is now considered to be autosomal dominant. The TRPV3 gene encodes transient receptor potential vanilloid-3 cation channel (TRPV3), a transmembrane ion channel expressed in the skin, hair follicles, brain and spinal cord. Among the novel heterozygous variants detected in our patient's DNA by exome sequencing, we noted a G-to-A nucleotide substitution within TRPV3. This was confirmed by Sanger sequencing. Polymerase chain reaction (PCR) amplification was performed using the forward primer 5'-CGTGATTCTGGTCTCTTCAGC-3' and reverse primer 5'- CCTGGTTAAACCCCTCTTCC-3' that span the novel sequence variant. The PCR product was purified and sequenced on an automatic analyser (ABI 3730 Genetic Analyzer; Applied Biosystems, Warrington, Cheshire, U.K.). Bidirectional sequencing identified a heterozygous G-to-A transition at position c.573 converting a glycine residue to serine (Fig. 1c), thus confirming the exome sequencing data. Importantly, this mutation was not identified in the mother (Fig. 1c) or in 200 control chromosomes (data not shown).

Discussion

In the study by Lin et al. that identified TRPV3 as the gene for OS, six unrelated patients were investigated. Of note, the heterozygous mutation p.Gly573Ser was noted in four individuals; one of their other cases also had a different mutation in the same amino acid, p.Gly573Cys, and the other subject was heterozygous for p.Trp692Gly. The TRPV3 protein contains six transmembrane domains (S1–S6) with a pore region between S5 and S6. The mutation, p.Gly573Ser, alters a conserved intracellular linker region located between S4 and S5. Interestingly, the same mutation can develop spontaneously in the mutant DS-Nh mice. These mice exhibit hairlessness and dermatitis and were previously considered to be an animal model of atopy. In addition, Trpv3 knockout mice present with abnormal hair morphology and skin barrier dysfunction. Although the TRPV3 channel is a thermosensitive cation channel which is activated at 33°C, patients with OS do not report abnormal heat sensation. The striking cutaneous phenotype seen in patients with OS suggests that TRPV3 has a major role to play in skin physiology. This is further evidenced by the discovery that TRPV3 is involved in calcium entry associated with the transforming growth factor-α/epidermal growth factor receptor signalling complex that orchestrates keratinocyte terminal differentiation. Functional studies of the human mutations have shown that these are gain-of-function mutations that promote calcium influx and apoptosis, thereby providing a link between TRPV3 and the clinical...
features of abnormal keratinization that are present in patients with OS.

The advent of exome sequencing has dramatically revolutionized and speeded up research in gene discovery. For sporadic cases of rare autosomal dominant disorders, screening of case–parents trios by exome sequencing represents an optimal approach compared with analysis of affected individuals alone. Moreover, exome sequencing represents a cost-effective and productive strategy in identifying causative genes in hitherto uncharacterized genetic diseases. In summary, we have elucidated the molecular basis of OS in an Indian subject using comparative exome sequencing and Sanger sequencing data. Our findings support the recent finding of TRPV3 as the gene implicated in OS and suggest that the mutation p.Gly573Ser may be a recurrent abnormality in this genodermatosis.

What's already known about the topic?

- Olmsted syndrome is a rare disorder of keratinization.
- The genetic basis of Olmsted syndrome has recently been elucidated with the discovery of pathogenic mutations in the TRPV3 gene.

What does this study add?

- We have clarified the molecular basis of the first Indian case of Olmsted syndrome and identified a recurrent pathogenic mutation, p.Gly573Ser, in the TRPV3 gene.

References


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