Title: Tuberous Sclerosis Complex – Somatic Mosaicism

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Note: The following information is provided by the authors listed above and has not been reviewed by *GeneReviews* staff.

Somatic mosaicism has been described in many individuals with TSC and parents of children with TSC. However, an estimate of the frequency of somatic mosaicism is complicated by:

- The sensitivity of the pathogenic variant screening methods and the difficulty of detecting low-level mosaicism;
- The relative ease of detecting mosaicism for exonic / whole-gene deletions or duplications and the difficulty in detecting mosaicism for single nucleotide variants (SNVs) and small intra-exonic deletions or duplications;
- The likely overestimate of the percent of mosaicism in some studies because only affected persons who did not have a pathogenic variant identified by other molecular genetic test methods (sequencing and/or gene-targeted deletion/duplication analysis) were evaluated for mosaicism; and
- The fact that the phenotypes caused by mutation of *TSC1* and *TSC2* cannot be differentiated clinically; therefore, the proportion of individuals with each phenotype is unknown at the outset of studies screening for somatic mosaicism.

Note: (1) It is difficult to identify with confidence low-level mosaicism for pathogenic missense and other variants involving a few nucleotides because these sequence variants may be artifacts possibly introduced by the PCR processes. (2) It was estimated that levels of mosaicism greater than 20% in lymphocyte DNA can be detected with current exon sequencing and next-generation sequencing methods [Qin et al 2010, Authors, personal observation]. Using targeted deep next-generation sequencing of *TSC1* and *TSC2,* somatic mosaic pathogenic variants at 9.5% in an affected individual who did not have a pathogenic variant identified by exon sequence analysis or gene-targeted deletion/duplication analysis was reported [Nellist et al 2015]. However, it has not yet been determined whether levels of somatic mosaicism below 9.5% can be detected by deep next-generation sequencing.

The frequency of somatic mosaicism for large deletions and duplications of *TSC1* and *TSC2* in affected individuals (who did not have a pathogenic variant identified by sequence analysis or other similar methods) has been reported as about 5% (N=165) [Kozlowski et al 2007; Author, personal observation]. Seven of the eight individuals with mosaic pathogenic variants had deletions in *TSC2*; one had a duplication in *TSC2* [Kozlowski et al 2007].

Because somatic mosaicism for a pathogenic variant in *TSC2* has been reported in seven of 26 families with a combined TSC/PKD (autosomal dominant polycystic kidney disease) phenotype and six of 62 probands in another series, DNA testing of other

tissues (e.g., tumors, saliva, skin, and/or hair follicles) is warranted when somatic mosaicism is suspected and routine molecular genetic testing has not revealed a pathogenic variant.

No assay kit or service laboratory for testing somatic mosaicism exists at this time. Somatic mosaicism testing is currently only available from research groups on research basis.

References

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