Title: Tuberous Sclerosis Complex – Somatic Mosaicism
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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 exon/whole-gene deletions or duplications and the difficulty in detecting mosaicism for single nucleotide variants (SNVs) and small intra-exon 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-based sequencing processes. (2) It has been estimated that levels of mosaicism greater than 20% in lymphocyte DNA can be detected with confidence by Sanger 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. Although detection of somatic mosaicism between 1% and 9.5% has been reported [Tyburczy et al 2015], confirmation for the presence of the pathogenic variants from multiple tissue organs is absolutely necessary before variant information can be utilized as future diagnostic tool for the affected family.

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.

References

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