Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous disorder that affects approximately 1/6,000 individuals. Clinical manifestations of TSC are variable, with the potential for hamartoma involvement in nearly every organ system. Hamartoma development in the brain may lead to seizures and mental retardation. Two causative genes have been identified: TSC1 (located on chromosome 9q34), and TSC2 (located on 16p13). Previous studies have investigated disease differences based on gene involved, but no clear conclusions have been obtained. No studies on TSC have focused exclusively on familial TSC, and information on this population is limited.

Study objectives were 1) to gather phenotypic information on several aspects of familial TSC, including physical, neurological, and behavioral data, and 2) to analyze involvement with respect to gene and type of mutation (missense or protein truncating) present. One hundred seven familial cases of TSC with known mutations were utilized.

Our findings demonstrated a significant difference in the phenotype of TSC based on mutation and mutation type. Specifically, differences in mental retardation, seizures, behavioral manifestations, dermatological, and renal involvement were observed. In addition to the presence or absence of symptoms, severity comparisons were also performed. Differences in the severity of mental retardation, behavioral manifestations, and certain dermatological findings were also observed between gene and mutation type.
Descriptive intrafamilial analyses demonstrated a more consistent phenotype in some families, and a more variable one in others. These findings indicate that mutation and genetic background may influence TSC phenotypic stability with a family.

Our findings provide further evidence to support the hypothesis that there is a difference in overall TSC severity depending on the gene and mutation type involved. Further large-scale studies, especially those focusing on familial TSC, are needed to determine whether family history of TSC and mutation type can be used to predict phenotypic disease severity.