

Abstract 71

TWO-PERCENT OF PATIENTS SUSPECTED OF HAVING ANGELMAN SYNDROME HAVE *TCF4* MUTATIONS

Kyoko Takano, Md PhD, Chris Moyes, MD, Michael Lyons, MD, Julie Jones, PhD,
Charles E. Schwartz, PhD
Greenwood Genetic Center, Greenwood, SC

Haploinsufficiency as well as various mutations in the *TCF4* gene have been found to be associated with the Pitt-Hopkins syndrome (PTHS). PTHS (OMIM 610954) is characterized by severe mental retardation, a wide mouth plus other distinctive facial features (fleshy lips, beaked nose, broad nasal bridge) and breathing difficulties. Because of some phenotypical overlap with Angelman syndrome, some have suggested that PTHS be considered in its differential diagnosis. To explore this possibility, we screened 86 patients who were suspected of having Angelman syndrome. All the patients were negative for UBE3A testing and 53 were negative for methylation analysis. We identified 2 *TCF4* mutations in this cohort: one frame shift mutation, c.1151delG (p.S384Tfsx7) and a missense mutation, c.1746G>C (p.R582P). The p.R582P mutation lies within the critical bHLH (basic helix-loop-helix) domain of *TCF4* in which six other missense mutations have been reported. The patient with the c.1151deG mutation is a 7 year old male with global developmental delay, microcephaly, a broad nasal bridge, an open and wide mouth and a large lower lip. The patient with the p.R582P mutation is a 16 year old male with severe mental retardation, cyanotic episodes, mild hyperventilation, blond hair, bright red lips and an abnormal gait. In summary we found 2 *TCF4* mutations in 86 patients (2%) suspected to have Angelman syndrome. Therefore, mutations in this gene should be considered in patients who are thought to have Angelman syndrome. *TCF4* should certainly be screened in any such patients who have been negative for methylation and UBE3A testing.