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TCF4 Sequencing for Pitt-Hopkins Syndrome

Clinical Features:

Pitt-Hopkins syndrome (PHS) [OMIM #610954] is a severe congenital encephalopathy that occurs in approximately 1 in 40,000 individuals (1). PHS is characterized by severe mental retardation and characteristic facial features, including enopthalmia, large beaked nose, wide mouth, fleshy lips and widely spaced teeth. Facial features tend to coarsen with age. Other commonly observed features include hyperventilation episodes, epilepsy, acquired microcephaly, short stature, strabismus, myopia and brain abnormalities such as hypoplasia of the corpus callosum. Affected patients typically display stereotypic hand movements such as mouthing or flapping, and speech is absent in the vast majority of cases. The majority of patients have infantile hypotonia, which is followed by delayed development of motor skills. Affected patients are described as typically having a happy disposition, however behavioral problems such as anxiety and self-aggression may also be observed (2).

The PHS phenotype overlaps with Angelman, Mowat-Wilson and Rett syndromes. Patients with PHS are typically less ataxic than those with Angelman syndrome. Epilepsy and sleep disturbances have been reported features of PHS, but are more typical of Angelman syndrome. The PHS phenotype does not include cardiac or urogenital anomalies, in contrast to Mowat-Wilson syndrome, where such anomalies are seen in 50% of cases. Rett syndrome and PHS share only a limited number of features, such as epilepsy and mouthing of the hands, however individuals with PHS do not show loss of purposeful hand movements, which is a typical feature of Rett syndrome (2).

Molecular and Biochemical Genetics:

PHS is associated with mutations in the gene *TCF4* [OMIM #602272], located at 18q21.1 (3). *TCF4* consists of 20 exons and encodes at least 2 isoforms of the transcription factor-4 (TCF4) protein. The TCF4 protein belongs to the E-protein family, which is characterized by a basic helix-loop-helix (bHLH) structural motif. *TCF4* is thought to be specifically required for brain development, and has a role in pontine neuron differentiation. The pathology of *TCF4* mutations is thought to be linked to haploinsufficiency of the *TCF4* protein product (4).

The majority of mutations observed are deletions or nonsense mutations, however missense mutations within conserved regions of the bHLH domain have also been reported in patients with PHS (1). Deletions may be associated with limited flexion and absent flexion crease in the thumb, and seizures have been found to be significantly more frequent in individuals with missense mutations (1). De Pontual et al [2009] detected *TCF4* mutations in 13 of 36 patients with severe psychomotor delay and facial features consistent with PHS, some of whom had previously been investigated for Angelman, Mowat-Wilson or Rett syndrome (4). Giurgea et al [2008] detected deletions of the TCF4 gene in 4 of 30 patients initially evaluated for Angelman, Mowat-Wilson, or Rett syndrome whose phenotype overlapped PHS (2).

Inheritance:

Mutations in *TCF4* are inherited in an autosomal dominant pattern. All reported cases are due to *de novo* mutations, with the exception of one case of maternal mosaicism (2).

Test Methods:

The University of Chicago Laboratory offers mutation analysis of all 20 coding exons and intron/exon boundaries of *TCF4* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *TCF4* gene by MLPA or oligonucleotide array-CGH to identify deletions/duplications of one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

TCF4 sequencing analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1500
CPT codes:	81406
Turn-around time:	4 weeks

TCF4 deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81405
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

References:

1. Rosenfeld JA, Leppig K, Ballif BC et al. Genotype-phenotype analysis of TCF4 mutations causing Pitt-Hopkins syndrome shows increased seizure activity with missense mutations. Genet Med 2009: 11: 797-805.
2. Giurgea I, Missirian C, Cacciagli P et al. TCF4 deletions in Pitt-Hopkins Syndrome. Hum Mutat 2008: 29: E242-251.
3. Amiel J, Rio M, de Pontual L et al. Mutations in TCF4, encoding a class I basic helix-loop-helix transcription factor, are responsible for Pitt-Hopkins syndrome, a severe epileptic encephalopathy associated with autonomic dysfunction. Am J Hum Genet 2007: 80: 988-993.
4. de Pontual L, Mathieu Y, Golzio C et al. Mutational, functional, and expression studies of the TCF4 gene in Pitt-Hopkins syndrome. Hum Mutat 2009: 30: 669-676.