THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Sequencing for Temple-Baraitser syndrome

Clinical Features:

Temple-Baraitser syndrome [OMIM# 611816] is a rare neurodevelopmental disorder resulting in severe intellectual disability, abnormalities of thumb and big toe (hallux), and seizures in most cases [1]. Aplasia or hypoplasia of toe nails and the presence of a proximally implanted and distally broadened thumb and hallux are common features as well as characteristic radiographic findings of the fingers and toes [1, 3, 5]. Affected individuals may have mild dysmorphic facial features including a pseudo-myopathic facies, and demonstrate poor visual contact and autistic-like behaviors. Most individuals are delayed in their early milestones and seizures usually present in childhood or later [1, 3-5]. Some affected individuals have been reported with heart defects and gastrointestinal issues [4, 5]

Molecular Genetics:

Pathogenic variants in *KCNH1* gene have been implicated as a causative etiology in Temple-Baraitser syndrome. *KCNH1* codes for a voltage-gated potassium channel protein that is suggested to play a role in the regulation of cell proliferation and is likely fundamental to developmental processes. It is proposed that pathogenic variants in this gene disrupt cell proliferation and migration along with neuronal development. All reported pathogenic variants to date are missense variants, resulting in a gain of function of *KCNH1*, with a decreased activation threshold and delayed deactivation period [2]. Gain of function mutations in *KCNH1* can also cause Zimmermann-Laband syndrome [OMIM# 135500] [6], which is characterized by gingival hyperplasia, dysplastic or absent nails, hypoplasia of distal phalanges, scoliosis, hepatosplenomegaly, hirsutism, and cartilaginous abnormalities of the nose and/or ears [7].

Inheritance:

KCNH1-associated disorders are autosomal dominant and the majority of pathogenic variants described to date have been *de novo*. Mosaic pathogenic *KCNH1* variants have been identified in a subset of parents of children with Temple-Baraitser syndrome. These carriers of mosaic *KCNH1* pathogenic variants typically have isolated seizures with no additional features of Temple-Baraitser syndrome [2]. Recurrence risk for parents of an affected child may depend on their carrier status.

Test Methods:

We offer full gene sequencing of all coding exons and intron/exon boundaries of *KCNH1* by direct sequencing of amplification products in both the forward and reverse directions.

KCNH1 sequencing

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$900
CPT codes:	81406
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.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Temple, I.K. and M. Baraitser, *Severe mental retardation and absent nails of hallux and pollex.* Am J Med Genet, 1991. **41**(2): p. 173-5.
2. Simons, C., et al., *Mutations in the voltage-gated potassium channel gene KCNH1 cause Temple-Baraitser syndrome and epilepsy.* Nat Genet, 2015. **47**(1): p. 73-7.
3. Gabbett, M.T., R.C. Clark, and J.M. McGaughran, *A second case of severe mental retardation and absent nails of hallux and pollex (Temple-Baraitser syndrome).* Am J Med Genet A, 2008. **146A**(4): p. 450-2.
4. Yesil, G., et al., *Report of a patient with Temple-Baraitser syndrome.* Am J Med Genet A, 2014. **164A**(3): p. 848-51.
5. Jacquinet, A., et al., *Temple-Baraitser syndrome: a rare and possibly unrecognized condition.* Am J Med Genet A, 2010. **152A**(9): p. 2322-6.
6. Kortüm, F., et al., *Mutations in KCNH1 and ATP6V1B2 cause Zimmermann-Laband syndrome.* Nat Genet, 2015. **47**(6): p. 661-7.
7. Balasubramanian, M. and M.J. Parker, *Zimmermann-Laband syndrome in a child previously described with brachydactyly, extrahepatic biliary atresia, patent ductus arteriosus and seizures.* Clin Dysmorphol, 2010. **19**(1): p. 48-50.

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