Molecular Genetic Testing: Diagnostic Studies

Mills et al [2006], Plecko et al [2007], and Scharer et al [2010] studied 39 families with "classic neonatal pyridoxine-dependent epilepsy," all of whom were determined to be homozygous or compound heterozygous for pathogenic variants in $ALDH7A$. These include a variety of missense mutations, nonsense mutations, single base deletions, and splice site mutations. One of the mutated alleles was a deletion of exon 7 [Plecko et al 2007]. No individuals with atypical presentation were included in the three studies.

Kanno et al [2007] reported five individuals with neonatal-onset pyridoxine-dependent epilepsy that was clinically proven by pyridoxine withdrawal. Four were compound heterozygotes for mutations in $ALDH7A1$; one of these mutated alleles was a deletion of exon 17. In one individual, pathogenic variants were not detected. This individual had normal plasma levels of pipecolic acid, and therefore it is unlikely that pathogenic variants in $ALDH7A1$ are responsible for the seizures that are clinically pyridoxine dependent.

Bennett et al [2009] studied 18 kindreds with pyridoxine dependency. Of 12 with classic neonatal-onset seizures, 11 were either homozygous or compound heterozygous for pathogenic variants in $ALDH7A1$; one had one mutated allele along with a significant elevation in plasma pipecolic acid concentration. Six of the kindreds had late-onset seizures, and three were either homozygous or compound heterozygous for pathogenic variants in $ALDH7A1$ while the other three had no detectable $ALDH7A1$ pathogenic variants.

Mills et al [2010] studied an additional 30 families with pyridoxine-dependent epilepsy. Twenty-seven of the families were either homozygous or compound heterozygous for pathogenic variants in $ALDH7A1$. Only one mutated allele was detected in the remaining three families.

Bok et al [2012] studied 11 Dutch families with neonatal-onset pyridoxine-dependent epilepsy, eight of whom had homozygous mutations in $ALDH7A1$ while the other three had compound heterozygous mutations.

Tlili et al [2013] studied seven consanguineous Tunisian families and documented homozygous mutations in $ALDH7A1$ in all seven.

Perez et al [2013] studied 11 patients from Spain and one from India. Nine of these patients had either homozygous or compound heterozygous mutations in $ALDH7A1$, while one patient was heterozygous for a 23-kb deletion encompassing exons 12-18. The final patient had only one mutated $ALDH7A1$ allele identified.
References


