PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING

HEREDITARY SENSORY NEUROPATHY, TYPE IE VIA THE *DNMT1* GENE-SEQUENTIAL TEST

CLINICAL FEATURES AND GENETICS

Clinical Features

Hereditary sensory neuropathy type IE (HSN1E, OMIM 614116) was first described in a multi-generation American family with adult-onset distal sensory impairment and subsequent progressive memory and sensorineural hearing loss. Onset of dementia occurred between the second and fourth decades of life and death occurred in the fifth and sixth decades of life (Wright and Dyck, *Neurology* 45:560-562, 1995). A sibship of affected individuals from Japan has also been reported with early adulthood-onset peripheral sensory neuropathy, followed by hearing loss and progressive dementia (Hojo et al. *Europ J Neurol* 6:357-361, 1999). Neuropathology studies showed almost complete loss of myelinated nerve fibers and moderate loss of unmyelinated fibers and brain imaging revealed frontal atrophy. In affected individuals from both published families no autonomic or motor symptoms were present. Two other HSN1E families were reported with development of sensorineural deafness and sensory neuropathy between 20 and 35 years of age (Klein et al. *Nat Genet* 43:595-600, 2011). Brain imaging showed cerebral atrophy and other studies were consistent with a length-dependent progressive sensory axonal loss. Sensory loss often leads to painless trauma and ulcerations of the extremities and subsequent amputations of distal extremities in approximately half of patients (Klein. *GeneReviews* 2012).

Citations

Hojo et al. Europ J Neurol 6:357-361, 1999 PubMed ID: 10210919

Klein et al. Nat Genet 43:595-600, 2011 PubMed ID: 21532572

Wright and Dyck, Neurology 45:560-562, 1995 PubMed ID: 7898717

Genetics

Hereditary sensory neuropathy type IE is inherited as an autosomal dominant disorder. To date only two mutations of the *DNMT1* gene (OMIM 126375) have been reported in four unrelated families (Klein et al. *Nat Genet* 42:595- 600, 2011). Three American families and one Japanese family here found to have a c.1532A>G (p.Tyr511Cys) mutation and two European families were found to have a c.1518_1520delTCCinsATA (p.Asp506_Pro507delinsGluTyr) mutation. Both mutations are located within the targeting-sequence domain of *DNMT1* (amino acids p.Pro306_Ile620, exons 12-22).

Citations

Klein et al. Nat Genet 43:595-600, 2011 PubMed ID: 21532572

Testing Strategy

The DNA methyltransferase-1 protein is coded by exons 1-41 of the *DNMT1* gene on chromosome

19p13.2. Testing is accomplished by amplifying coding exons and ~20 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. Exons 12-22 of the *DNMT1* gene, which correspond to the targeting-sequence domain, are tested first. The remaining exons of the *DNMT1* gene will be secondarily tested if requested. We will also sequence any single exon (Test #100) in family members of patients with a known mutation or to confirm research results.

Indications for Test

Patients with adult onset peripheral sensory loss, progressive hearing loss, and early-onset dementia.

GENE(S)

Offical Gene Symbol	OMIM Id
DNMT1	126375

Gene References

Genomic	mRNA	Protein	CCDS
NC_000019.9	NM_001130823.1	NP_001124295.1	CCDS45958.1

DISEASE(S)

Name	OMIM Id
Neuropathy, Hereditary Sensory, Type Ie	614116

RELATED TESTS

Hereditary Sensory Neuropathy, Type IE via the *DNMT1* Gene- Tier 1

Hereditary Sensory Neuropathy, Type IE via the *DNMT1* Gene- Tier 2

CONTACTS

Genetic Counselor

Christina Zaleski, MS, CGC - clinicaldnatesting@preventiongenetics.com

Gina Robinson-Haase, MS - clinicaldnatesting@preventiongenetics.com

Geneticist

Thomas L. Winder, PhD, FACMG - tom.winder@preventiongenetics.com

METHODS AND PRICING

TEST METHODS

BI-DIRECTIONAL SANGER SEQUENCING

**DNMT1* Tier 1= Test #908

DNMT1 Tier 2= Test #909

Test Number	Test	Price	CPT Code
	DNMT1 Sanger Sequencing (Tier 1)	$720	81479
915	DNMT1 Sanger Sequencing (Tier 2)	$1,450	81479
	Full Gene	$1,890	81479

Test	CPT

Number	Test	Price	Code
100	DNMT1 Targeted Familial Mutations - Single Exon Sequencing	$240	81479
200	DNMT1 Targeted Familial Mutations - Double Exon Sequencing	$360	81479
300	DNMT1 Targeted Familial Mutations - Triple Exon Sequencing	$430	81479

Test Procedure

As required, DNA is extracted from the patient specimen using a 5 Prime ArchivePure DNA Blood Kit. PCR is used to amplify the indicated exons plus additional flanking intronic or other non-coding sequence. After cleaning of the PCR products, cycle sequencing is carried out using the ABI Big Dye Terminator v.3.0 kit. Products are resolved by electrophoresis on an ABI 3730xl capillary sequencer. Sequencing is performed separately in both the forward and reverse directions.

Clinical Sensitivity

Too few cases of HSN1E have been reported to estimate clinical and analytical sensitivity.

Analytical Validity

As of July 2013, we compared 7.3 megabases of Sanger DNA sequence generated at PreventionGenetics to NextGen sequence generated in other labs. We detected only 4 errors in our Sanger sequences, and these were all due to allele dropout during PCR. For Proficiency Testing, both external and internal, in the 9.5 years of our lab operation we have Sanger sequenced roughly 2,000 PCR amplicons (~ 1 megabase). No errors have been identified.

Our Sanger sequencing is capable of detecting virtually all nucleotide substitutions within the PCR amplicons. Similarly, we detect essentially all heterozygous or homozygous deletions within the amplicons. Homozygous deletions which overlap one or more PCR primer annealing sites are detectable as PCR failure. Heterozygous deletions which overlap one or more PCR primer annealing sites are usually not detected (see Analytical Limitations). All heterozygous insertions within the amplicons up to about 100 nucleotides in length appear to be detectable. Larger heterozygous insertions may not be detected. All homozygous insertions within the amplicons up to about 300 nucleotides in length appear to be detectable. Larger homozygous insertions may masquerade as homozygous deletions (PCR failure).

Analytical Limitations

In exons where our sequencing did not reveal any variation between the two alleles, we cannot be certain that we were able to PCR amplify both of the patient's alleles. Occasionally, a patient may carry an allele which does not amplify, due for example to a deletion or a large insertion. In these cases, the report contains no information about the second allele.

Similarly, our sequencing tests have almost no power to detect duplications, triplications, etc. of the gene sequences.

In most cases, only the indicated exons and roughly 20 bp of flanking non-coding sequence on each side are analyzed. Test reports contain little or no information about other portions of the gene, including many regulatory regions.

In nearly all cases, we are unable to determine the phase of sequence variants. In particular, when we find two likely causative mutations for recessive disorders, we cannot be certain that the mutations are on

different alleles.

Our ability to detect minor sequence variants, due for example to somatic mosaicism is limited. Sequence variants that are present in less than 50% of the patient's nucleated cells may not be detected.

Runs of mononucleotide repeats (eg (A)n or (T)n) with n >8 in the reference sequence are generally not analyzed because of strand slippage during PCR and cycle sequencing.

Unless otherwise indicated, the sequence data that we report are based on DNA isolated from a specific tissue (usually leukocytes). Test reports contain no information about gene sequences in other tissues.

Turnaround Time

Maximum of 40 days, although many tests are completed in 2-3 weeks.

Version: 1.4

Last Updated 11/06/2012