Creatine Deficiency Syndromes Panel

PANEL GENE LIST
SLC6A8, GAMT, GATM

CLINICAL FEATURES
Creatine deficiency syndromes are a clinically and genetically heterogeneous group of disorders caused by defects in the transport (*SLC6A8*) and biosynthesis (*GAMT, GATM*) of creatine.[1-4] Clinical findings in affected individuals may include intellectual disability, developmental delay, hypotonia, myopathy, autism spectrum disorder, behavioral disorders, seizures, and movement disorder.[1-4] Females with creatine transporter deficiency due to heterozygous pathogenic *SLC6A8* variants exhibit a phenotypic spectrum ranging from asymptomatic to a severe phenotype similar to that of males.[4] Creatine deficiency syndromes are characterized by cerebral creatine deficiency on brain MR spectroscopy.[4] Biochemical analysis of guanindinoacetate, creatine, and creatinine in both urine and plasma may help distinguish between creatine deficiency syndromes.[4] The age-of-onset of clinical symptoms depends on the specific diagnosis, and can range from the neonatal period to adulthood.[4] The confirmation of a clinical diagnosis with molecular testing can help direct treatment and medical management.

INHERITANCE PATTERN
Variants in *SLC6A8* are inherited in an X-linked recessive manner. Variants in *GAMT* and *GATM* are inherited in an autosomal recessive manner.[4]

GENETICS
In individuals affected with a creatine deficiency syndrome, ~56% are found to harbor a variant in *SLC6A8*, ~39% are found to harbor biallelic variants in *GAMT*, and ~5% are found to harbor biallelic variants in GATM.[4]

Many types of variants have been reported in *SLC6A8* and *GAMT*, ranging from missense and splice-site, to gross deletions. The few variants that have been reported in *GATM* include various types of point mutations.[5]

TEST METHODS
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data. Concurrent exon-level deletion/duplication analysis, including most of the SLC6A8 exons, is performed by multiplex ligation-dependent probe amplification (MLPA). Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. For the *GAMT* gene, deletion/duplication analysis may only detect large (multi-exon) events.

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Exon-level deletion/duplication testing via MLPA can also be ordered separately for the *SLC6A8* gene.

CLINICAL SENSITIVITY

In 101 males from 85 families affected with X-linked creatine transporter deficiency, all were found to harbor a *SLC6A8* variant. Approximately 95% of variants were identified via sequencing and approximately 5% of variants were identified via deletion/duplication analysis.[6] In 33 individuals with either undetectable GAMT activity in cultured fibroblasts/lymphoblasts and/or biochemical features of guanidinoacetate methyltransferase (GAMT) deficiency, all had biallelic variants in the *GAMT* gene.[2,7] In a retrospective study of arginine:glycine amidinotransferase (GAMT/AGAT) deficiency, 16 affected individuals from 8 families all had biallelic variants in the *GATM* gene. [8]

REFERENCES:

1. Mencarelli et al. (2011) American Journal Of Medical Genetics. Part A 155A (10):2446-52 (PMID: 21910234)
2. Mercimek-Mahmutoglu et al. (2006) Neurology 67 (3):480-4 (PMID: 16855203)
3. Longo et al. (2011) American Journal Of Medical Genetics. Part C, Seminars In Medical Genetics 157C (1):72-8 (PMID: 21308988)
4. Mercimek-Mahmutoglu S, Salomons GS. Creatine Deficiency Syndromes. 2009 Jan 15 [Updated 2015 Dec 10]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK3794/
5. Stenson et al. (2014) Human Genetics 133 (1):1-9 (PMID: 24077912)
6. van de Kamp et al. (2013) J. Med. Genet. 50 (7):463-72 (PMID: 23644449)
7. Mercimek-Mahmutoglu et al. (2014) Human Mutation 35 (4):462-9 (PMID: 24415674)
8. Stockler-Ipsiroglu et al. (2015) Mol. Genet. Metab. 116 (4):252-9 (PMID: 26490222)