CNGnome™ Report

CLIENT	SPECIMEN	PATIENT
Client Name:	Specimen Type:	Patient Name:
Hospital/Institution:	Collection Date:	Date of Birth:
Mailing Address:	Receive Date:	Gender:
Phone Number:	Report Date:	Patient's PKI ID:
		Accession ID:
		Cross Reference:

Test Performed: **CNGnome™**
Reason for Testing: Microcephaly, Dysmorphism, Developmental delay, Squint, Hypospadiasis, Caudal regression, Bulbous tip of nose, Prominent little finger pads, High arched palate

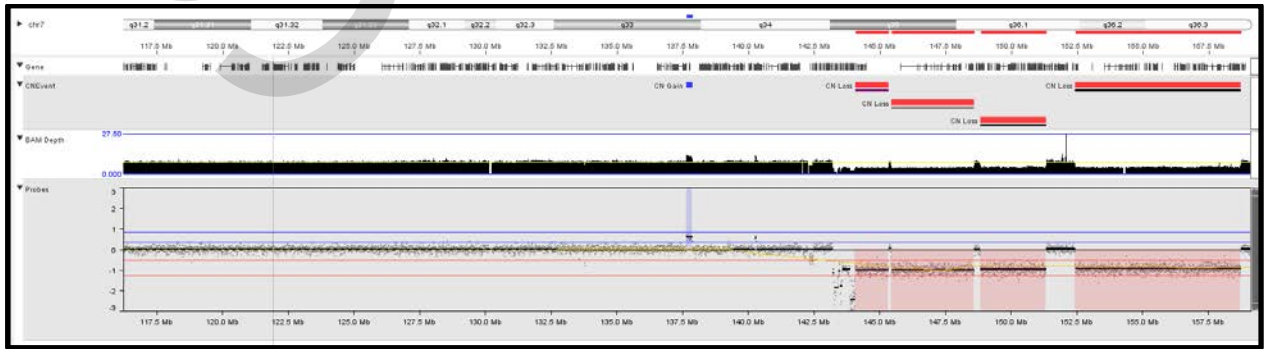
TEST RESULT SUMMARY

Pathogenic 7q deletion: Multiple Copy Number Losses of Chr 7q35q36.3

ISCN Nomenclature: seq [hg19] 7q35q36.1(145448731_148600230)x1, 7q35q36.1(145448731_148600230)x1, 7q36.1(148843231_151338630)x1, 7q36.1q36.3(152440831_158744830)x1

CNGnome testing was performed to identify copy number variations (CNV) in the clinical specimen from this individual. The whole genome was interrogated for copy number changes (gains/losses) and absence of heterozygosity (AOH).

Event	Chromosome Region	Cytoband	Length (bp)	OMIM Genes Count	OMIM Morbid Map	Classification
CN Loss	chr7:144,080,031-145,348,130	7q35	1268100	2	*NOBOX, TPK1*	Pathogenic
CN Loss	chr7:145,448,731-148,600,230	7q35q36.1	3151500	3	*CNTNAP2, EZH2*	Pathogenic
CN Loss	chr7:148,843,231-151,338,630	7q36.1	2495400	38	*KCNH2, NOS3, CDK5, ASB10, PRKAG2*	Pathogenic
CN Loss	chr7:152,440,831-158,744,830	7q36.1q36.3	6304000	19	*DPP6, SHH, LMBR1, MNX1, DNAJB6, WDR60*	Pathogenic



INTERPRETATION

A ~13.2 Mb copy loss region of chr 7q35q36.3 was identified in this assay. It is important to note that within this large region, 4 smaller deletions interspersed by normal genomic dosage were identified. This region contains a total of 61 OMIM genes of which the following have OMIM Morbid entries: *NOBOX, TPK1, CNTNAP2, EZH2, KCNH2, NOS3, CDK5, ASB10, PRKAG2, DPP6, SHH, LMBR1, MNX1, DNAJB6, WDR60.* This is a rare contiguous gene deletion syndrome known as "7q DELETION SYNDROME". Partial monosomy of chromosome 7q has been characterized by wide phenotypic manifestations, but holoprosencephaly (HPE) and sacral agenesis have been reported with this deletion. Other clinical features of this syndrome include facial dysmorphism, intellectual disability, developmental delay and congenital anomalies[1]. Multiple studies have reported the pathogenicity associated with the size of this CNV, hence these copy losses are being classified as **pathogenic** changes.

Multiple deletions with 6 or more breaks in the genome/chromosome qualify as the "chromothripsis" phenomenon. This phenomenon has been reported in literature as a mechanism for the origin of complex *de novo* germline structural variations[3]. Chromothripsis phenomenon involves the "shattering" of chromosomes and then rearrangements by non-homologous repair mechanisms[4] and could lead to multiple gains and losses occurring across the chromosome/genome thereby causing genetic disorders.

1. Clin Genet. 1977 Oct;12(4):233-8.
2. Am J Med Genet A. 2016 Apr;170A(4):896-907.
3. Hum Mol Genet. 2011 May 15;20(10):1916-24.
4. Cell Rep. 2012 Jun 28;1(6):648-55.

RECOMMENDATIONs

These results must be interpreted in the context of this individual's personal and family history.

1. **Parental testing by CNGnome test is recommended to determine whether these CNV's are inherited or *de novo*.**

2. **Parental karyotyping studies are also recommended to determine if this rearrangements result from a balanced/complex structural variation event.** Genetic counseling is recommended for best patient care.

Targeted testing for the pathogenic variant identified in this individual is available for affected and at risk family members. For more information, please contact the laboratory at 1-866-354-2910

METHODS AND LIMITATIONS

Direct sequencing of genomic DNA was performed using 2X150bp reads on Illumina next generation sequencing (NGS) systems at a mean coverage of 5X in the target region. Alignment to the human reference genome (hg19) was performed and copy number variant (CNV) calls made using the NxClinical software v5.0 (BioDiscovery, Inc., El Segundo, CA). CNVs meeting internal quality assessment guidelines are confirmed by real time quantitative PCR (qPCR) for records after results are reported. Some CNVs are confirmed by qPCR before reporting at a director's discretion.

This assay cannot detect CNVs in regions of the genome that are not amenable to NGS and does not interrogate CNVs in mitochondrial DNA. This assay will not detect tandem repeats, balanced alterations (reciprocal translocations, Robertsonian translocations, inversions, and balanced insertions), point mutations, methylation abnormalities, genomic imbalances in segmentally duplicated regions and mosaicism; possible cases of mosaicism may be investigated at the discretion of the laboratory director. Small pathogenic CNVs within the exon, some small intragenic deletions or duplications, as well as complex rearrangements may not be detected. This assay has been validated to detect copy number variants >25 Kb and also has the ability to detect copy number changes such as homozygous deletions. This assay may not be able to discern between CNVs that are high copy number gains such as, duplication >=4X. CNVs involving genes with pseudogenes and pseudoexons may not be reliable detected or reported. Due to high similarity of certain regions on chromosome X and chromosome Y, CNVs in the following regions may not be detected for male patients (chrX: 60000-2699520; chrX:154930289-155260560; chrY:10000-2649520; chrY:59033286-59363566).

Patient Name: Accession Number: Cross Reference Number:

NOTE: The interpretation of CNV changes is based on our current understanding of the genome. These interpretations may change over time as more information about this gene becomes available. Possible diagnostic errors include CNV call errors, sample misidentification, and other sources. Genomic coordinate numbering is based on GRCh37/hg19.

Possible sources of testing error include rare genetic variants that interfere with analysis, sample misidentification, and other sources. Pursuant to the requirements of CLIA '88, this technical component and the professional component was performed by PerkinElmer Genomics. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

Electronic Signature – Clinical Laboratory Director, PerkinElmer Genomics Laboratory