GENETIC TESTING RESULTS
FirstStep^{Dx} PLUS Chromosomal Microarray

bionano laboratories

Patient Name: SAMPLE	**Provider Name:** SAMPLE	**Sample Type:** Buccal
Patient Date of Birth: SAMPLE	**Provider Phone:** SAMPLE	**Sample Collected:** 08/31/2022
Patient Sex: Male	**Provider Fax:** SAMPLE	**Sample Received:** 09/02/2022
Patient ICD-10 code(s): F84.0, R62.5	**Provider Institution:** SAMPLE	**Order Date:** 08/31/2022
Accession Number: SAMPLE		**Report Date:** 09/26/2022

Test Result Summary: Pathogenic

Chromosomal Microarray Analysis (CMA) identified one pathogenic copy number variant. The 17q12 deletion is clinically significant and is consistent with 17q12 deletion syndrome.

Sex chromosomes by CMA: XY

ISCN: arr[GRCh37] 17q12(34815551_36245768)x1

Chromosomal Microarray Results

Copy Number Change	Chromosome Region	Base Pair Coordinates (GRCH37)	Approximate Size (bp)	Classification	Syndrome Name
Loss	17q12	34815551_36245768	1430217	Pathogenic	17q12 deletion syndrome

Clinical Interpretation and Discussion

17q12, Loss, Pathogenic

This finding is clinically significant and is consistent with 17q12 deletion syndrome. As there is an increased risk of symptoms due to this finding, additional evaluations may be recommended.

17q12 deletion syndrome is characterized by a triad of clinical features including kidney abnormalities, maturity onset diabetes of the young type 5 (MODY5), and neurodevelopmental and/or psychiatric conditions (PMID: 27929632). Kidney and urinary tract abnormalities occur in 85-90% of individuals and may be structural (cysts, dysplasia, hydronephrosis) and/or functional (tubulointerstitial disease, hypomagnesemia). MODY5 is present in about 40% of individuals and is typically diagnosed in early adulthood (range 10-50 years). Neurodevelopmental and/or psychiatric conditions are present in about 50% of individuals and may include developmental delay, intellectual disability (mild-severe), autism spectrum disorder, schizophrenia, and bipolar disorder.

Other symptoms reported in individuals with 17q12 deletion syndrome may include hyperparathyroidism, genital, liver, eye, pancreas, cardiac, or brain anomalies, premature birth, short stature, joint hypermobility, seizures, and mild dysmorphic facial features (PMIDs: 27929632, 27409573, 21055719, 26429400, 20587423, 22511894, 24991439, 24487052). Rarely, additional symptoms such as hypomagnesemia with vascular calcifications, sensorineural hearing loss, or other congenital anomalies such as duodenal atresia and diaphragmatic hernia have been reported (PMIDs: 31500578, 32028929, 27929632).

Approximately 73% of 17q12 deletions are *de novo* (not inherited), while 27% have been inherited from a parent. Penetrance is estimated to be high, and it is likely that a parent who carries the deletion would have some clinical features (PMIDs: 27929632, 21055719, 26429400). Parental testing may be considered and would assist in genetic counseling for recurrence risk. A medical geneticist or genetic counselor can help determine a testing strategy for this family.

Genes Included in 17q12 Loss: *ZNHIT3, MYO19, PIGW, GGNBP2, DHRS11, MRM1, LHX1-DT, LHX1, AATF, MIR2909, ACACA, SNORA90, C17orf78, TADA2A, DUSP14, SYNRG, DDX52, MIR378J, HNF1B, YWHAEP7*

References

The references in this report can be found by searching the PubMed IDs (PMID) from the PubMed home page: http://www.ncbi.nlm.nih.gov/pubmed/

For more information on how to use PubMed, see the following tutorial: http://www.nlm.nih.gov/bsd/disted/pubmedtutorial/cover.html

PubMed IDs referenced in this report:

Mitchel MW, et al. 2020. PMID: 27929632

Rasmussen M, et al. 2016. PMID: 27409573

Moreno-De-Luca D, et al. 2010. PMID: 21055719

Jones GE, et al. 2015. PMID: 26429400

Loirat C, et al. 2010. PMID: 20587423

George AM, et al. 2012. PMID: 22511894

Roberts JL, et al. 2014. PMID: 24991439

Palumbo P, et al. 2014. PMID: 24487052

Li H, et al. 2019. PMID: 31500578

Du T, et al. 2020. PMID: 32028929

Genetic Counseling and Family Resources

A genetic test called chromosomal microarray analysis (CMA) was completed. CMA primarily looks for missing (deletion) or extra (duplication) genetic material.

Bionano Laboratories genetic counselors are available by phone to speak with providers or the family about this test result. You can schedule a time to speak with a Bionano Laboratories genetic counselor by calling 801-931-6191.

A genetic counselor can help review what these results mean for an individual and family members, background on genetics, and discuss additional resources or next steps that may be helpful. Additionally, the genetic counselor may review medical,

developmental, and family history of the person tested. This will help the genetic counselor better answer questions about how a specific result may impact the family. To best prepare for a genetic counseling session, it may be helpful for a family to create a list of questions. Additionally, it may help to review some information on basic genetic concepts such as what are genes and chromosomes. The following resource(s) may be helpful for families to review:

MedlinePlus: This website can be used to find information about genetic topics, genes, specific genetic conditions, and broad topics like autism spectrum disorder. It also provides links to other websites for more in-depth information about genetic conditions, patient support and advocacy resources, and relevant clinical trials. https://medlineplus.gov/genetics

MyGene2: This is a resource for connecting families with rare conditions to other families, clinicians, and researchers. http://mygene2.org/MyGene2/

17q12 Foundation: This is a non-profit organization that represents individuals and families with 17q12 deletions and duplications. http://www.chromo17q12.org

Unique- The Rare Chromosome Disorder Support Group: This group has a brochure written by professionals and parents about 17q12 microdeletions and a Facebook support group.
http://www.rarechromo.org and http://www.facebook.com/groups/896016120494473/

Bionano Laboratories' Comprehensive Interpretation Process

Copy number variations (CNVs) identified by FirstStep[Dx] PLUS chromosomal microarray are analyzed with a comprehensive interpretation process. Guidelines from the American College of Medical Genetics and Genomics (ACMG) and Clinical Genome Resource (ClinGen) are applied to variants reported (PMID: 31690835). The interpretation process involves collaboration between experts including laboratory directors, variant analysts, and certified genetic counselors. This team completes an up-to-date review of the medical literature, patient databases (PMIDs: 19344873, 26582918), a proprietary gene database (NeuroSCORE; PMID: 35361823), and control datasets (PMIDs: 24174537, 32461652). This process provides comprehensive information about the current evidence for CNVs and the role of the genes involved. Results are correlated with an individual's reported symptoms from available medical records. The relevant evidence from this interpretation process is summarized in each report.

Methodology and Limitations

Methodology: DNA was prepared according to Illumina specifications for the Global Screening Array v2 (GSA) custom chip. It includes approximately 700,000 genome-wide markers with an average spacing of 4 kilobases (kb) and targets a minor allele frequency of 5% as reported in the HapMap data. The Illumina chip was scanned on Illumina's iScan Platform, and data was processed using Genome Studio v2.0. Single nucleotide polymorphic (SNP) probes on the chromosomal microarray (CMA) are used for the detection of genomic deletions and duplications, known as copy number variations (CNVs), and absence of heterozygosity (AOH) that may suggest uniparental disomy (UPD) or regions of the genome identical by descent. The NxClinical software manufactured by Biodiscovery, Inc is utilized to analyze and interpret the CMA data. Detected CNVs are reported when found to have clear or suspected clinical relevance; CNVs devoid of relevant gene content or reported as common findings in the general population may not be reported. Due to probe placement on the CMA, the smallest size CNV that is detectable is variable by region. Certain small deletions or duplications may not be detectable by CMA technology. For example, the DupE5-E9 recurrent duplication associated with Cystinuria type A may not be detectable on this array. Deletions smaller than 100 kb and duplications smaller than 400 kb may not be reviewed. When applicable, Lineagen may complete confirmatory testing of a CNV prior to reporting. When restricted to a single chromosome, AOH is reported when greater than 8-15 megabases (Mb; dependent upon chromosomal location and likelihood of imprinting disorder). AOH is also reported when the total proportion across all autosomes is greater than 3% (only autosomal AOH greater than 3 Mb are considered for this estimate). In some cases, with lab director discretion based on the specific regions in question, AOH less than 3% or single chromosome regions below 8 Mb may be reported. Genomic linear positions are

given relative to NCBI build 37 (hg19). Illumina, Inc. has manufactured this CMA. Gene by Gene, Ltd. has performed the technological work for the purpose of identifying DNA CNVs associated with large chromosomal imbalances and AOH that may be disease-causing. A certified laboratory director has interpreted this data.

Limitations: Gene by Gene and Bionano Laboratories has validated this assay per standard guidelines; however, it is not feasible to validate every potential genomic imbalance in the human genome. CMA only identifies the regions of imbalance; it does not provide information regarding the structure or mechanisms responsible. For example, CMA does not detect whether an aberration is present as an unbalanced translocation, supernumerary marker chromosome, tandem duplication, etc. This technology will not allow for detection of all forms of polyploidy or balanced rearrangements such as inversions and balanced chromosomal translocations. CMA cannot detect deletions and duplications with limited probe coverage, point mutations, gene expansions, variants within the mitochondrial DNA, and low-level mosaic conditions. For mosaic conditions, CMA cannot differentiate between specific number of copies present (ex: trisomy of a whole chromosome arm vs. tetrasomy in 50% of cells tested). CMA cannot determine whether a copy number variant is *de novo* or inherited. Due to these limitations, we may recommend that some CMA results have additional follow up studies. Examples include but are not limited to fluorescence *in situ* hybridization (FISH), standard chromosome analysis, or testing additional tissue types. Note that additional testing could be complicated by factors such as tissue specific mosaicism. It is also important to note that additional literature may become available that changes the current understanding about the clinical significance of this result.

References: South S et al. Genet Med. 2013; Nov;15(11):901-9 (PMID: 24071793) and Shao L et al. Genet Med. 2021; Oct;23(10):1818-1829 (PMID: 34131312).

Disclaimer: This test and its performance characteristics were determined by Gene by Gene, a CAP accredited (CAP Number 7212851) and CLIA certified Clinical Laboratory located at 1445 North Loop West, Suite 820 Houston, TX 77008. The U.S. Food and Drug Administration (FDA) has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

Gene by Gene, Ltd. is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing (CLIA# 45D1102202). Gene by Gene CLIA Laboratory Director: Rachel L. Beddard M.D.

Lineagen, Inc.'s (DBA Bionano Laboratories) CMA interpretation and reporting service is certified under CLIA (CLIA#46 D2042721).
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Report Electronically Signed By: SAMPLE