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Tracy I. George, MD, Chief Medical Officer

Patient Report

Patient Age/Sex: Male

Specimen Collected: 20-Dec-21 09:56

X-Cytogenomic SNP Microarray - Oncology | **Received: 21-Dec-21 10:50** | **Report/Verified: 21-Dec-21 10:52**

Procedure	Result	Units	Reference Interval
Cytogenomic Microarray SNP -Oncology	**Abnormal** * f1 i1		Normal

Result Footnote

f1: Cytogenomic Microarray SNP - Oncology
Test Performed: Cytogenomic SNP Microarray - Oncology (CMA ONC)
Specimen Type: Bone marrow
Indication for Testing: AML

RESULT SUMMARY
Mixed Male/Female Genomes (sex-mismatched donor cells) Detected with Abnormal Microarray Result

Clinically Significant CNVs and/or ROH (Tier 1 and Tier 2 Variants):
- Gain of 1q
- Copy-Neutral Loss of Heterozygosity (CN-LOH) 6p

RESULT DESCRIPTION
The above abnormalities were observed at 10-20 percent in the sample, consistent with a somatic (acquired) origin. The SNP pattern is also consistent with mixed male and female genomes (chimerism) at every locus.

Based on the SNP patterns and Clinical history, the most likely cause of this finding is a sex-mismatched donor. The female DNA component was estimated at 80-90 percent.

NOTE: Chimerism at this level can limit the detection of alterations below approximately 10-20 Mb in size. Therefore, this analysis could only rule out autosomal aneuploidy and other large genomic alterations.

INTERPRETATION
This result is consistent with a sex-mismatched donor genotype with presence of 1q gain and CN-LOH of 6p.

Acquired gains involving 1q have been reported in both lymphoid and myeloid diseases and are often associated with unbalanced translocations. However, gains of 1q associated with dicentric and isodicentric chromosomes are also frequent findings in AML and MDS following treatment with alkylating agents.

Acquired CN-LOH 6p is a recurrent finding in cytogenetically normal AML patients and is associated with elevated bone marrow blasts. The proposed mechanisms for CN-LOH in carcinogenesis include unmasking mutations of tumor suppressor genes, as well as providing selective advantage to cells harboring gain-of-function mutations in some proto-oncogenes.

Please correlate this result with clinical and other laboratory findings.

NOTE: A concurrent chromosome analysis reported under ARUP accession XX-XXX-XXXXXX showed 46,XY,psu dic(1;1)(q42;p13),del(11)(p11.2),add(11)(q25), add(16)(p13),t(16;21)(p11.2;q22)[10]//46,XX[10], consistent with this finding. A concurrent FISH analysis reported under ARUP accession XX-XXX-XXXXXX showed a gain present within 1q25.2 (ABL2), consistent with this finding.

Recommendation:
If monitoring CN-LOH 6p is clinically indicated, please follow-up with a SNP-based microarray analysis, as this is a copy neutral finding and cannot be detected by chromosome analysis or FISH.

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*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

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References:
1) Beach et al. Duplication of chromosome 1 [dup(1)(q21q32)] as the sole cytogenetic abnormality in a patient previously treated for AML. Cancer Genet. 2012 Dec;205(12):665-8. PMID: 23168243.
2) Andersen et al. Increased frequency of dicentric chromosomes in therapy-related MDS and AML compared to de novo disease is significantly related to previous treatment with alkylating agents and suggests a specific susceptibility to chromosome breakage at the centromere. Leukemia. 2000 Jan;14(1):105-11. PMID: 10637484.
3) Bullinger et al. Identification of acquired copy number alterations and uniparental disomies in cytogenetically normal acute myeloid leukemia using high-resolution single-nucleotide polymorphism analysis. Leukemia. 2010 Feb;24(2):438-49. PMID: 20016533.
4) Walker et al. Genetic Characterization and Prognostic Relevance of Acquired Uniparental Disomies in Cytogenetically Normal Acute Myeloid Leukemia. Clin Cancer Res. 2019 Nov 1;25(21):6524-31. PMID: 31375516.
5) Makishima et al. Pathogenesis and consequences of uniparental disomy in cancer. Clin Cancer Res. 2011 Jun 15;17(12):3913-23. PMID: 21518781.
6) O'Keefe et al. Copy neutral loss of heterozygosity: a novel chromosomal lesion in myeloid malignancies. Blood. 2010 Apr 8;115(14):2731-9. PMID: 20107230.

Cytogenomic Nomenclature (ISCN):
arr[GRCh37] 1q21.1q44(143932350_249224684)x2-3
arr[GRCh37] 6p25.3p11.1(184719_58741497)x2 mos hmz

Technical Information
- This assay was performed using the CytoScan(TM) HD Suite (Thermo Fisher Scientific) according to validated protocols within the Genomic Microarray Laboratory at ARUP Laboratories
- This assay is designed to detect alterations to DNA copy number state (gains and losses) as well as copy-neutral alterations (regions of homozygosity; ROH) that indicate a loss- or absence-of-heterozygosity (LOH or AOH)
- Copy-neutral LOH (CN-LOH) may be present due to acquired UPD (segmental or whole chromosome)
- AOH may be present due to parental relatedness (consanguinity) or uniparental disomy (UPD)
- The detection sensitivity (resolution) for any particular genomic region may vary dependent upon tumor burden, the number of probes (markers), probe spacing, and thresholds for copy number and ROH determination
- The CytoScan HD array contains 2.67 million markers across the genome with average probe spacing of 1.15 kb, including 750,000 SNP probes and 1.9 million non-polymorphic probes
- Genome-wide resolution varies from approximately 25-50 kb for copy number changes and approximately 3 Mb for ROH for samples with high tumor content (generally greater than 70 percent), to several Mb for samples with lower tumor content (20-30 percent)
- The limit of detection for clonality (mosaicism) varies dependent upon the size and type of genomic imbalance. In general, genotype mixture due to mosaicism (distinct cell lines from the same individual) or chimerism (cell lines from different individuals) will be detected when present at greater than 20-30 percent in the sample
- Genomic coordinates correspond to the Genome Reference Consortium human genome build 37/human genome issue 19 (GRCh37/hg19)

Variant Classification and Reporting Criteria
- Variant analysis is performed in accordance with recommendations by the American College of Medical Genetics and Genomics (ACMG), using tiered classification terminology
- Acquired/somatic or constitutional/germline cancer-associated copy number variants (CNVs) and ROH are classified and reported using the following clinical significance categories: Clinically Significant CNVs and/or ROH (Tier 1 and Tier 2 Variants) and Other Clonal Variants (Tier 3)
- Constitutional/germline CNVs not associated with cancer are classified according to the ACMG recommended 5-tier classification system: pathogenic, likely pathogenic, variant of uncertain

Result Footnote

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significance (VUS), likely benign, and benign
-In general, only constitutional CNVs classified as pathogenic or likely pathogenic will be reported using the following clinical significance category: Other Variants (Likely Constitutional)
- Constitutional CNVs conferring non-cancer recessive disease risk will generally not be reported
- CNVs classified as Tier 4, likely benign or benign that are devoid of relevant gene content or reported as common findings in the general population, are generally not reported
- ROH are generally reported when known or suspected to be mosaic and representative of CN-LOH
- Total autosomal homozygosity (only autosomal ROH greater than 3 Mb are considered for this estimate) consistent with AOH at a level of greater than 10 percent will generally be reported; AOH less than 10 percent may be reported, dependent upon on the concern for masked CN-LOH and/or a recessive disorder

Limitations
This analysis cannot provide structural (positional) information associated with genomic imbalance. Therefore, additional cytogenetic testing by chromosome analysis or fluorescence in situ hybridization (FISH) may be recommended.

Certain genomic alterations may not or cannot be detected by this technology. These alterations may include, but are not limited to:
- CNVs below the limit of resolution of this platform
- Sequence-level variants (mutations) including point mutations and indels
- Low-level mosaicism (generally, less than 20-30 percent)
- Balanced chromosomal rearrangements (translocations, inversions and insertions)
- Genomic imbalance in repetitive DNA regions (centromeres, telomeres, segmental duplications, and acrocentric chromosome short arms)

This result has been reviewed and approved by Cinthya J. Zepeda Mendoza, PhD

Test Information

i1: Cytogenomic Microarray SNP - Oncology
INTERPRETIVE INFORMATION: Cytogenomic Microarray SNP - Oncology

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

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