

Clinical Genomics Laboratory
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Laboratory Phone: 402.280.3963
Website: <http://www.cml.md/genomics/>
 Patient: XXXXXXXXXXXXXXXX

Patient Name: XXXXXXXXXXXXXXXX
 DOB: XX/XX/XXXX
 Gender: X
 Specimen Type: peripheral blood
 Submitters Name: Dr. XXXXXXXX
 Submitters Institution: XXXXXXXX

CML Accession Number: CML09_GDXXXXX
 Date specimen obtained: XX/XX/XXXX
 Date specimen received: XX/XX/XXXX
 Report date: XX/XX/XXXX
 Test Indication: CLL

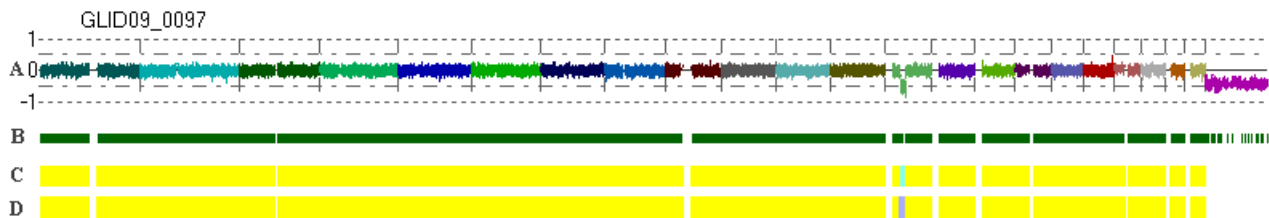
Result:

Peripheral blood, SNP oligonucleotide microarray karyotype:

13q14 deletion

arr snp 13q13.3-q14.3(37675701-52582043)x1

Interpretation: The virtual karyotype of this sample shows an isolated 13q14 deletion, which confers a favorable prognosis.



Copy Number		Color Code
Deletions	Normal/diploid	Gains
Dark blue = 0	Yellow = 2	Pink = 3
Light blue = 1		Pink-Red = 4
		Red = amplified

Whole genome view SNP array karyogram for this sample. Chromosomes are plotted in numeric order from left (chromosome 1) to right (X chromosome). A) Log2ratio, zero = copy number of 2. B) Green = heterozygous call in tumor. C) The copy number Hidden Markov Model (HMM) is color-coded as indicated to the left. D) LOH likelihood HMM (yellow = low, blue = high).

The following is a summary of clinically relevant genetic lesions in chronic lymphocytic leukemia: Trisomy 12 is a common clonal abnormality in B cell CLL occurring in 16% of cases, and it is associated with an intermediate prognosis.(1) Loss of the ATM tumor suppressor gene on the long arm of chromosome 11 has been reported in 18% of cases with B cell CLL and is associated with an adverse prognosis.(2) Loss of ATM is usually associated with extensive adenopathy and advanced disease(2). The 13q14 deletion represents the most frequent chromosomal rearrangement in B cell CLL (55%), and when it is the sole abnormality it confers a more favorable prognosis(2). Typically, it occurs in patients with highly stable and indolent disease often requiring no treatment(3). Homozygous loss of 13q14.3 (D13S319) may be associated with a more aggressive disease(4). Loss of the TP53 at 17p occurs in about 7% of CLL cases and it is the strongest predictor of poor survival(5) and is associated with failure to respond to either alkylating agents(6) or fludarabine(7) . Deletions at 6q occur in 6% of patients.(2) These patients tend to have higher white blood cell counts and more extensive lymphadenopathy at presentation(8), but the prognostic significance of the 6q lesion itself is unclear(1).

Copy number polymorphisms, if present, are not reported here, but are archived in the CML Clinical Genomics Laboratory.

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Methods: DNA was extracted from EDTA anti-coagulated peripheral blood sample following a density-based enrichment for B lymphocytes. Whole genome comparative genomic hybridization was done using Affymetrix 250K Nsp SNP array which can detect uniparental disomy and copy number changes as small as 500kb. The assay was performed according to the manufacturer's protocol. All controls performed as expected. Analysis was performed using Affymetrix GTYPE 2.1 and CNAGv3.0(9) software programs. The normal reference DNA used for analysis was chosen by the CNAG software from a library of data files obtained from normal specimens.

References:

1. Cotter FE, Auer RL. Genetic alteration associated with chronic lymphocytic leukemia. *Cytogenetic and genome research* 2007;118(2-4):310-9.
2. Dohner H, Stilgenbauer S, Benner A, *et al.* Genomic aberrations and survival in chronic lymphocytic leukemia. *The New England journal of medicine* 2000;343(26):1910-6.
3. Guarini A, Gaidano G, Mauro FR, *et al.* Chronic lymphocytic leukemia patients with highly stable and indolent disease show distinctive phenotypic and genotypic features. *Blood* 2003;102(3):1035-41.
4. Dewald GW, Brockman SR, Paternoster SF, *et al.* Chromosome anomalies detected by interphase fluorescence in situ hybridization: correlation with significant biological features of B-cell chronic lymphocytic leukaemia. *Br J Haematol* 2003;121(2):287-95.
5. Oscier DG, Gardiner AC, Mould SJ, *et al.* Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. *Blood* 2002;100(4):1177-84.
6. el Rouby S, Thomas A, Costin D, *et al.* p53 gene mutation in B-cell chronic lymphocytic leukemia is associated with drug resistance and is independent of MDR1/MDR3 gene expression. *Blood* 1993;82(11):3452-9.
7. Dohner H, Fischer K, Bentz M, *et al.* p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias. *Blood* 1995;85(6):1580-9.
8. Cuneo A, Rigolin GM, Bigoni R, *et al.* Chronic lymphocytic leukemia with 6q- shows distinct hematological features and intermediate prognosis. *Leukemia* 2004;18(3):476-83.
9. Yamamoto G, Nannya Y, Kato M, *et al.* Highly sensitive method for genomewide detection of allelic composition in nonpaired, primary tumor specimens by use of affymetrix single-nucleotide-polymorphism genotyping microarrays. *American journal of human genetics* 2007;81(1):114-26.

This SNP based oligonucleotide microarray was developed by Affymetrix, Inc (Santa Clara, CA, USA) and its performance determined by the Genomics Laboratory of Creighton Medical Laboratories for the sole purpose of identifying the gain or loss of DNA copy numbers and regions of loss of heterozygosity. This microarray will not detect balanced chromosomal aberrations, such as Robertsonian translocation, reciprocal translocations, inversion or balanced insertions, nor imbalances in regions that are not represented on the microarray, nor low-level mosaicism or tumor burden. This method cannot detect epigenetic events, such as aberrant methylation, or point mutations. The method is based on relative copy number estimates; therefore polyploidy cannot be reliably detected without a cell-based assay. Clinical implications of chromosomal aberrations may be unknown at the time of analysis. This test is used for clinical purposes. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Pursuant to the requirement of CLIA'88, this laboratory has established and verified the test's accuracy and precision.