Abstract: P362

Title: OPTICAL GENOME MAPPING (OGM) AS A NEW GENETIC DIAGNOSTIC TOOL FOR T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (T-ALL)

Abstract Type: Poster Presentation

Topic: Acute lymphoblastic leukemia - Biology & translational research

Background:

Current genetic tests for T-cell acute lymphoblastic leukemia (T-ALL) diagnosis require a combination of karyotype, FISH and/or arrays or multiple ligation-dependent probe amplification. Optical genome mapping (OGM) can detect genome-wide numerical and structural aberrations, including deletions, duplications and balanced/unbalanced genomic rearrangements in a single test.

Aims:

To evaluate whether OGM can replace all, or part of, the current diagnostic methods to facilitate the identification of new genetic lesions that might contribute to an improvement of the current T-ALL classification.

Methods:

Cryopreserved cells from 92 T-ALL patients enrolled in different PETHEMA (Programa Español de Tratamientos en Hematología) trials were used to extract high-molecular weight DNA. Raw data obtained from Saphyr™ (Bionano Genomics) were analyzed with the Access software 1.7.2 (Bionano Genomics) with standard and personalized filters (≥6 Kb for structural variants [SV] and ≥500 Kb for copy number variants [CNV]). Data from karyotype (n=92) and CNV (n=84) obtained by SNP-a (CytoScanTM HD, ThermoFisher) were used to validate OGM results.

Results:

A total of 2,421 alterations were obtained by OGM, 75% of which were selected for the descriptive analysis. Of these, 41% were non-coding, and the remaining 59% were coding alterations. Focusing on coding alterations, 45% were categorized as of unknown significance, 38% pathogenic and 17% probably pathogenic. By type of alteration, 59% were deletions (del); 16% inter-chromosomal translocations; 13% duplications (dup); 7% insertions, 4% intra-chromosomal translocations and 1% inversions, with a non-homogeneous distribution among patients (Figure 1). We compared OGM results, with those from SNP-a in a subset of 50 T-ALL cases. A high level of reproducibility (94% of concordance) was observed for detection of gains and losses. Regarding karyotype, we observed that, in all the cases analyzed, OGM detected more alteration than conventional cytogenetics.

Next, we analyzed recurrent alterations found by OGM in ≥4 patients, and confirmed del(9)(p21.3) affecting the *CDKN2A/B* genes (41.3%) as the most frequent structural alteration found in T-ALL. Other frequent CNVs observed included: del(1)(p36.31) affecting the *RPL22* gene (14.1%) which was the smallest del (21,36 Kb) identified in our cohort. Of note, due to the high sensitivity and resolution of OGM, we were able to detect more patients with del(6)(p21.33) affecting the *LTA* and *TNF* genes (5.4%), compared to SNP-a data. Regarding rearrangements, the most frequent inter-chromosomal translocations identified by OGM were: t(10;14)(q24.31;q11.2) that generates the *TLX1NB::TCRA* fusion gene, 9.8%, and t(10;11)(p12.31;q14.2) with the *MLLT10::PICALM* fusion gene, 6.5%.

One of the interesting applications of OGM relied on the re-definition of genetic complexity and the identification of the chromoanagenesis phenomena. We identified two cases of chromoplexy: t(7;10;14)(q34;q24.31;q11.2) with a *TLX1NB::TCRA* and *TCRB::TLX1NB* gene fusions and t(4;9;22) (q35.1;q34.12; q11.23) with the *ABL1::BCR* gene fusion.

Summary/Conclusion:

OGM allows simultaneous analysis of CNV and SV in the same sample with a high reproducibility between CNV data found with OGM and SNP-a. OGM can detect novel structural alterations with potential impact on T-ALL leukemogenesis (i.e., inversions) and complex rearrangements that define new complex genotypes with potential prognostic implications.

Acknowledgements

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Figure 1. Distribution of number of alterations per patient.

Keywords: Diagnosis, Adult, T cell acute lymphoblastic leukemia, Molecular cytogenetics