The first human acute myeloid leukemia genome ever fully sequenced

Brunangelo Falini
Institute of Hematology and CREO, University of Perugia, Perugia, Italy.
E-mail: brunangelo.falini@unipg.it

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TITLE	DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome.
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In 2008 a paper appeared in *Nature* that was to change the way we approach the study of the cancer genome. Ley *et al.*[1] succeeded in sequencing the whole genome of a cytogenetically normal acute myeloid leukemia (AML-M1) from a woman in her mid-50s who presented with a high peripheral white blood cell count (105x10^9/L, 85% myeloblasts), asthenia and bleeding. The patient achieved a complete remission but relapsed 11 months later acquiring a new clonal cytogenetic abnormality, t(10;12) (p12; p13). Whole DNA sequencing was performed on bone marrow cells at diagnosis and relapse, using the patient's normal skin cells as a control to exclude germline mutations. Using several filtering tools and sequencing to a depth of >30-fold coverage, the authors finally ended up with the discovery of somatic mutations affecting ten genes. Recurrent mutations of *NPM1* and *FLT3* had been previously described,[2] whereas the other mutations were new and involved members of the protocadherin/cadherin family (*CDH24* and *PCLKC*), G-protein-coupled receptors (*GPR123* and *EBI2*), a protein phosphatase (*PTPRT*), a potential guanine nucleotide exchange factor (*KNDC1*), a peptide/drug transporter (*SLC15A1*) and a glutamate receptor (*GRINL1B*). With the exception of *FLT3*, the mutations were detectable in virtually all leukemic cells both at diagnosis and relapse, suggesting that "*the patient had a single dominant clone containing all of the mutations*".

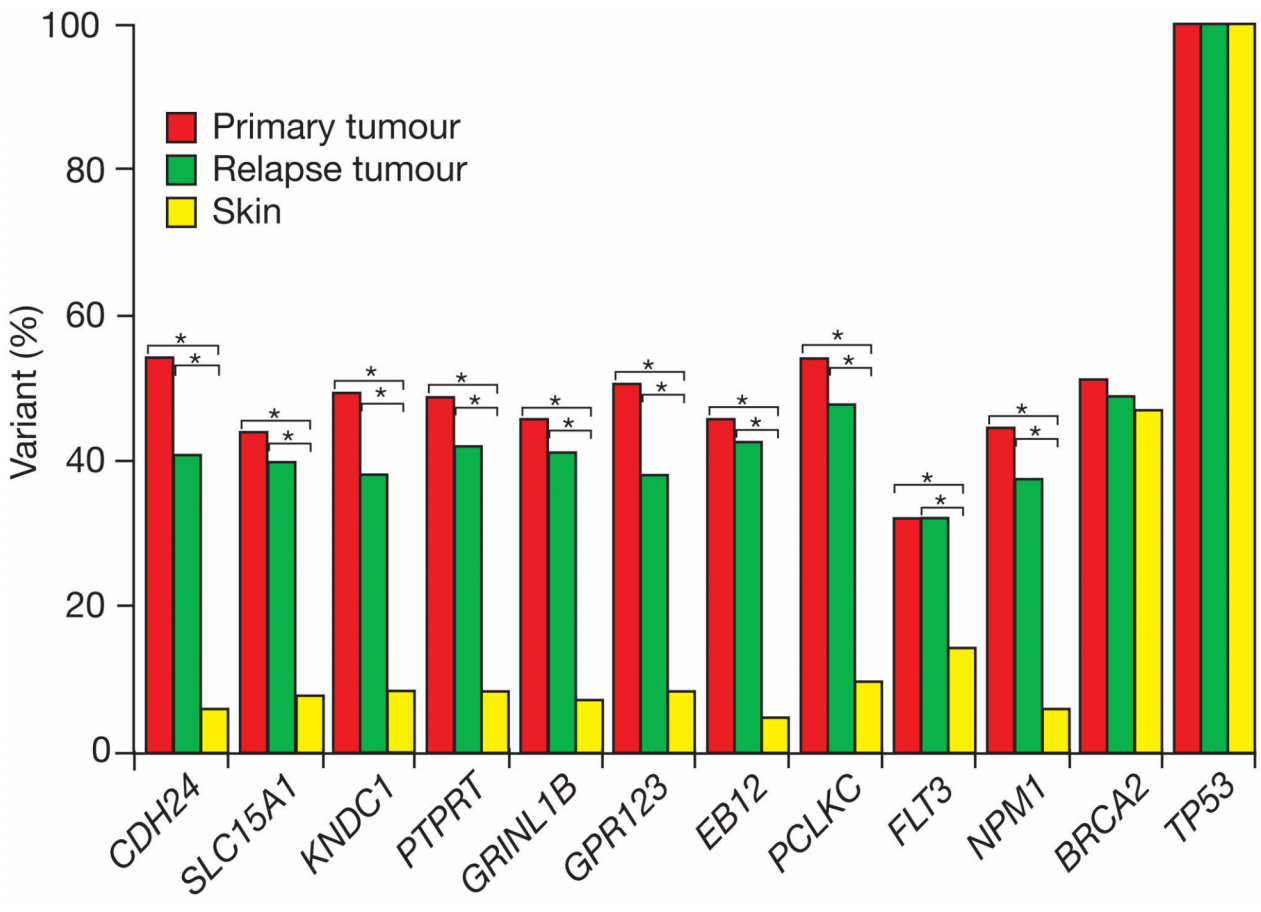

Figure 1. Summmary of Roche/454 FLX readcount data obtained for ten somatic mutations and two validated single nucleotide polymorphisms in the primary tumor, relapse tumor and skin specimens. The readcount data for the variant alleles in the primary tumor sample and relapse tumor sample are statistically different from those of the skin samples for all mutations (P<0.000001 for all mutations, Fisher exact test, denoted by an asterisk in all cases). Note that the skin sample was contaminated by leukemic cells containing the somatic mutations. The patient's white blood cell count was 105x10^9/L (85% blasts) when the skin punch biopsy was obtained. (*Figure 3 from Ley TJ et al. Nature. 2008;456(7218):66-72.*

When the genome from the same patient was re-sequenced with a greater coverage depth (a technique not available in 2007-2008) an inactivating *DNMT3A* L723fs mutation causing haploinsufficiency was discovered.[3] In retrospect, the eight non-synonymous mutations (other than *NPM1* and *FLT3*), none of which was recurrent, most likely represented "pre-existing" pathogenically irrelevant mutations of the hematopoietic stem cell that were "captured" by the *DNMT3A*-mediated clonal expansion leading, in cooperation with *NPM1* and *FLT3* mutations, to the development of AML.

This landmark study describing the first human AML (and in general the first human cancer) genome ever fully sequenced clearly demonstrated the value of whole-genome sequencing as an unbiased method for unraveling cancer-initiating mutations in previously unidentified genes. Moreover, it highlighted the limits of hypothesis-driven (for example, candidate gene-based) investigation of tumor genomes by polymerase chain reaction-directed or capture-based methods that can miss key mutations.

The impact of the study by Ley *et al.*[1] in accelerating the analysis of the genomes of many hematologic and solid malignancies has been dramatic. Thousands of AML genomes have now been fully sequenced, enabling the identification of the mutational landscape of AML, which consists of more than 20 recurrent mutations,[4] including *NPM1*, *FLT3*, *DNMT3A*, *IDH1* and *IDH2*. This led to elucidation of the role of *DNMT3A* mutations (discovered by whole-genome sequencing) in sustaining clonal hematopoiesis and promoting the development of AML in cooperation with other mutations, e.g. *NPM1*. Moreover, several targeted therapies were developed against *IDH1* and *IDH2* mutants (also discovered by whole-genome sequencing) in AML. Finally, clinical trials of AML patients stratified according to mutational profiles allowed groups with different prognoses to be defined. Currently, next-generation sequencing of a selected panel of key genes (carrying AML driver mutations) is being increasingly used to define the genomic profile of each AML patient before treatment and also to assess the molecular response to therapy. Whole-genome sequencing can be applied in cases in which cytogenetic analysis is unsuccessful since, in addition to mutations, it can detect copy number alterations and chromosomal rearrangements.

Disclosures

No conflicts of interest to disclose.

References

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