Detection of clonal blood cells with specific chromosomal abnormalities in the general population

Jan Cools[1,2]

[1]*Center for the Biology of Disease, VIB, Leuven;* [2]*Center for Human Genetics, KU Leuven, Leuven, Belgium*

doi:10.3324/haematol.2012.072298

The hematopoietic system is a highly active tissue that produces millions of genetically identical blood cells every day throughout the life of an individual. This process of blood formation can go wrong in many ways, for example, by inherited genetic defects in individuals with Fanconi's anemia or Diamond-Blackfan anemia,[1-3] or by acquired mutations that cause leukemia. Two new studies published in the June issue of Nature Genetics[4-5] now demonstrate that in a significant subset of healthy individuals, clonal expansions of blood cells with chromosomal abnormalities can be detected. These anomalies (also referred to as chromosomal mosaicism) are observed in about 1% of individuals and are possibly associated with an increased risk of leukemia development.

In their studies, Jacobs *et al.*[4] and Laurie *et al.*[5] use data derived from single nucleotide polymorphism (SNP) arrays that were previously collected on thousands of individuals in the course of various genome-wide association studies (GWAS). For these studies, blood cells were used as the source to obtain 'germline' DNA from these individuals. SNP array data are powerful tools to study millions of SNPs in the genome and to perform association studies. In addition, SNP array data can also be used to detect the presence of chromosomal copy number variations and copy-neutral loss of heterozygosity (LOH), even in a subset of the cells, based on the deviation of SNP allele frequency from what is expected for a homogeneous group of cells (Figure 1). In this way, chromosomal abnormalities can be detected and it can be estimated in what percentage of cells these chromosomal abnormalities are present.

Using this technology, Jacobs and colleagues detect clonal populations of cells with chromosomal abnormalities in almost 1% of healthy individuals. About half of the detected abnormalities were copy-neutral LOH, 15% were chromosomal gains and 35% were chromosomal losses. Laurie *et al.* confirm these findings in a separate study in which a clear correlation between age and the presence of chromosomal mosaicism is observed. In that study, the frequency of individuals with detectable abnormal cells was found to increase significantly over the age of 50 years to up to 3%. These data may be indicative of a decline in genomic maintenance mechanisms in older individuals, but may also reflect the effect of positive selection of specific clones. This may indeed be the case, as it is clear from these studies that the chromosomal abnormalities were not random. Trisomy of chromosome 8, 12 and 15 were recurrently found, as well as LOH of chromosome 9p (where the gene *CDKN2A* (*p16*) is located), and losses of parts of chromosomes 13q or 20q. The study by Laurie *et al.* reported similar observations, including recurrent 13q deletions (overlapping with the *RB1* gene or miRNAs MIR15A and MIR16-1), 4q deletions (214 kb deletion containing only the *TET2* gene), 2p deletions (*DNMT3A* gene), 22q deletions (several genes, including *PRAME*), and several other gains and losses.

These data correlate with the chromosomal regions and with the list of tumor suppressor genes that are known to be implicated in the development of leukemia. Loss of the cell cycle regulator *CDKN2A* is found in many leukemias, including acute lymphoblastic leukemia, *TET2* and *DNMT3A* are often deleted or mutated in myeloid leukemias,[6] and gain of chromosome 12 or deletion of *PRAME* is frequently detected in chronic lymphocytic leukemia.[7] Furthermore, in both studies, there is a clear link between the presence of mosaicism and the risk of leukemia development.

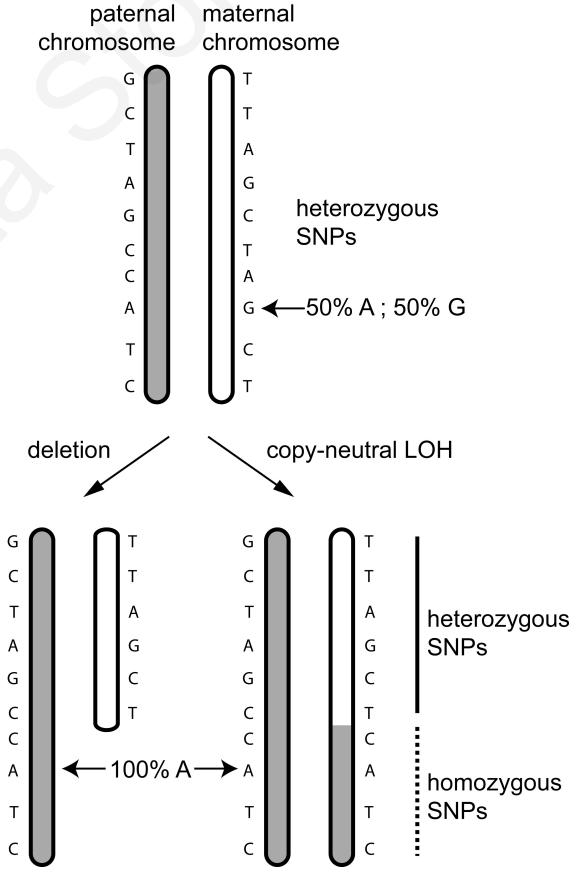

Figure 1. Schematic overview of how the study of single nucleotide variants (SNPs) can be used to detect chromosomal anomalies. Human cells contain 22 chromosome pairs plus XX or XY chromosomes. Here, one pair of chromosomes is schematically represented (paternal chromosome in gray, maternal chromosome in white), and variations in the DNA sequence on both chromosomes are indicated (heterozygous SNPs). In normal cells this will be detected by SNP arrays as 50% of the DNA of these normal cells with have the A sequence and 50% will have the G sequence. In cells with a deletion of part of that chromosome, part of the SNPs will now be detected as homozygous (only A sequence detected). Copy-neutral loss of heterozygosity (LOH) occurs when one chromosome (here the maternal chromosome) has exchanged DNA with the other chromosome (the paternal), so that for a specific part of the chromosome pairs the sequence is now identical (derived from the paternal chromosome). This phenomenon is known as uniparental disomy (UPD). SNP arrays can identify these defects, even if these chromosomal rearrangements are only present in a subset of the cells.

Individuals with a detected clonal population of blood cells with a chromosomal anomaly had a 10-fold higher risk of developing leukemia than individuals without mosaicism.[4-5]

These data make it tempting to speculate that these observations are likely to be related to early events of clonal selection as they are taking place during leukemia development. These two studies show that in about 1% of individuals (and even up to 3% in individuals above 70 years), clonal expansion of white blood cells can be detected that have genetic anomalies, including losses of entire chromosomes, copy-neutral LOH of parts of chromosomes and interstitial deletions/duplications.[4-5] Such chromosomal anomalies could lead to clonal expansion, given the fact that these can inactivate classical tumor suppressor genes, such as *CDKN2A* and *RB1*, or affect epigenetic regulators such as *TET2* or *DNMT3A*, genes that are all linked with leukemia development and clonal expansion of hematopoietic cells.[8-9] Further studies will be required to confirm whether the abnormal clones described in these studies are indeed the cells that contribute to the development of the leukemia. Furthermore, additional studies with serial sampling before and after leukemia development will be required to investigate the predictive nature of detectable clonal mosaicism.

These studies could open up new ways for early detection of leukemia development. The SNP array technology is now well advanced and could be used in a diagnostic setting to identify such early steps of leukemia development. Individuals in whom mosaicism is detected in the blood may then be followed more frequently by blood counts and further genetic testing. Eventually, if there is strong evidence that critical genes are affected that are known to drive leukemia development, early treatment could be considered with the aim of removing these clones before the cells become fully malignant and refractory to therapy. There is still a long way to go. These studies demonstrate the power of SNP arrays for the detection of abnormal clones in the blood of healthy individuals and show that early detection of leukemia clones with chromosomal abnormalities could be possible.

References

1. Ceccaldi R, Parmar K, Mouly E, Delord M, Kim JM, Regairaz M, et al. Bone Marrow Failure in Fanconi Anemia Is Triggered by an Exacerbated p53/p21 DNA Damage Response that Impairs Hematopoietic Stem and Progenitor Cells. Cell Stem Cell. 2012 Jun 7. [Epub ahead of print]
2. Quarello P, Garelli E, Carando A, Brusco A, Calabrese R, Dufour C, et al. Diamond-Blackfan anemia: genotype-phenotype correlations in Italian patients with RPL5 and RPL11 mutations. Haematologica. 2010;95 (2):206-13.
3. Dokal I, Vulliamy T. Inherited bone marrow failure syndromes. Haematologica. 2010;95 (8):1236-40.
4. Jacobs KB, Yeager M, Zhou W, Wacholder S, Wang Z, Rodriguez-Santiago B, et al. Detectable clonal mosaicism and its relationship to aging and cancer. Nat Genet. 2012;44(6):651-8.
5. Laurie CC, Laurie CA, Rice K, Doheny KF, Zelnick LR, McHugh CP, et al. Detectable clonal mosaicism from birth to old age and its relationship to cancer. Nat Genet. 2012;44(6):642-50.
6. Patel JP, Gönen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366(12):1079-89.
7. Del Giudice I, Rossi D, Chiaretti S, Marinelli M, Tavolaro S, Gabrielli S, et al. NOTCH1 mutations in +12 chronic lymphocytic leukemia (CLL) confer an unfavorable prognosis, induce a distinctive transcriptional profiling and refine the intermediate prognosis of +12 CLL. Haematologica. 2012;97(3):437-41.
8. Moran-Crusio K, Reavie L, Shih A, Abdel-Wahab O, Ndiaye-Lobry D, Lobry C, et al. Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation. Cancer Cell. 2011;20(1):11-24.
9. Challen GA, Sun D, Jeong M, Luo M, Jelinek J, Berg JS, et al. Dnmt3a is essential for hematopoietic stem cell differentiation. Nat Genet. 2011;44(1):23-31.