# Acquired Uniparental Disomy in Myeloproliferative Neoplasms

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**KEYWORDS**

• Myeloproliferative neoplasm • Uniparental disomy • SNP array • TET2 • CBL • EZH2 • JAK2

**KEY POINTS**

- Uniparental disomy is where both copies of a chromosome pair or parts of chromosomes have originated from one parent.
- Acquired uniparental disomy in cancer is a mechanism by which adventitious mutations are amplified leading to a growth advantage of these cells.
- Acquired uniparental disomy is now understood to be common in leukemia and renders a malignant or premalignant cell homozygous for a pre-existing mutation.
- Myeloproliferative neoplasms are clonal hematopoietic stem cell disorders characterized by overproliferation of one or more myeloid cell lineages in the bone marrow and increased numbers of mature and immature myeloid cells in the peripheral blood.
- Single nucleotide polymorphism arrays use the most frequent type of variation in the human genome and have enabled the rapid identification of uniparental disomy.
- Identification of tracts of recurrent acquired uniparental disomy, especially in hematologic malignancies, has led to identification of novel driver genes and therefore highlighted new pathways for targeted therapy.

## INTRODUCTION

Cancer genomes are characterized by instability and a progressive accumulation of genetic aberrations. Loss of heterozygosity (LOH) is one such aberration and is widely recognized as a hallmark of cancer genomes.[1–8] LOH is most commonly caused by whole and partial chromosomal loss as a consequence of aneuploidy or somatically acquired deletions but in recent years it has become apparent that LOH may also be caused by uniparental disomy (UPD).

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UPD refers to the situation in which both copies of a chromosome pair or parts of chromosomes have originated from one parent. When it occurs, UPD is often constitutional and arises from errors at meiosis I or meiosis II, the latter giving rise to isodisomy whereby the affected region is genetically identical. Constitutional isodisomy is frequently associated with developmental disorders caused by the abnormal expression of imprinted genes in the affected regions.[9] In cancer, UPD is acquired somatically and was first associated with the development of retinoblastoma.[10] It is now known that acquired UPD (aUPD; also known as acquired isodisomy or copy number neutral LOH) in cancer is a mechanism by which adventitious mutations are amplified, leading to a growth advantage of these cells.[11–13] Acquired UPD is common in solid cancers[14–20] and leukemia[6,12,21–24] and identification of tracts of recurrent aUPD, especially in hematologic malignancies, has led to identification of novel driver genes.[13,21,25–31]

This article describes how single nucleotide polymorphism (SNP) array technology has greatly facilitated the identification of regions of aUPD and led to the identification of novel mutations in myeloproliferative neoplasms (MPNs) and related disorders.

## UPD AND THE IMPORTANCE OF SNP ARRAY TECHNOLOGY

Determining whether or not UPD is present is not possible using conventional cytogenetics, fluorescent *in situ* hybridization, or comparative genomic hybridization because there is no change in copy number and these techniques are usually unable to distinguish between maternal and paternal chromosomes. Before the completion of the Human Genome project and the wealth of SNP data that derived from it,[32] the identification of UPD was cumbersome, involving restriction fragment length polymorphism analysis where only small regions of the genome could be interrogated[10] or microsatellite analysis, which laboriously provided low resolution over the genome.[21] The advent of SNP array technology meant that genetic variation over the entire genome could be identified rapidly at much higher resolution than was previously possible.[33,34]

SNP arrays work by hybridizing the fragmented and fluorescently labeled sample DNA to immobilized oligonucleotide probes on glass plates or in solution. The probes are regularly spaced over the entire genome and used to identify the genotypes at specific polymorphic loci. Laser capture then identifies the ratios of fluorescent sample annealed to the probes.[35]

The first SNP array experiments looking at cancer genomes had only 600 to 1000 probes, and involved polymerase chain reactions of each SNP locus.[15,16] Now preparation of the sample can be done in one tube[35] with the number of probes exceeding 1 million. This has allowed for even higher throughput and resolution of the whole genome. SNP array technology can be used routinely to screen many patients for recurrent regions of aUPD and this information can be used in two ways: to examine if these regions are associated with prognosis,[36] and to determine the minimal affected regions (MARs) of aUPD and thereby target genes that might be mutated.[12]

## ADVANTAGES AND DISADVANTAGES OF aUPD ANALYSIS BY SNP ARRAY TECHNOLOGY

For any given technique there are advantages and disadvantages, and aUPD analysis in leukemia with SNP arrays is no exception. SNP arrays, unlike metaphase cytogenetics, are not reliant on cell growth to yield detailed data on karyotype and although its throughput, resolution, and detailed mapping are vastly superior to microsatellite analysis and metaphase cytogenetics, SNP arrays cannot distinguish between one