HELPFUL RESOURCES FOR SNP MICROARRAY INTERPRETATION (BOTH CONSTITUTIONAL AND ONCOLOGY)

Chromosomal microarray serves as a potent tool in identifying genomic aberrations in oncology cases, such as submicroscopic deletions/duplications, loss of heterozygosity, chromothripsis, and amplifications. Oncology specimens often exhibit intricate genomic profiles, containing numerous abnormalities across various levels, thereby posing a challenge during analysis.

Together with copy number probe data, the allele tracks produced by SNP probes, such as allele difference and B-allele frequency (BAF), assist in interpreting genomic aberrations. For instance, BAF is valuable for estimating the proportion of cells containing an aberration. Evaluating the percentage of abnormal cells can offer insights into tumor burden, tumor heterogeneity, subclonal events, and clonal evolution in oncology cases.

In the constitutional setting, BAF patterns are helpful in evaluation of mosaicism/chimerism as well as maternal cell contamination (MCC) in prenatal testing.

Of note, region of homozygosity (ROH) or area of homozygosity (AOH) are terms used most often in the constitutional setting. The homozygous SNPs of an ROH are expected to originate from a shared ancestral haplotype in both parents, or biallelic inheritance from one parent, and therefore represent a germline event. On the other hand, loss of heterozygosity (LOH) is a term used in the oncology setting. The homozygous SNPs of an LOH are expected to originate through somatic events, for example through the loss of one allele, and gain of the other allele in a somatic mutation and/or repair process

IMPORTANT RESOURCES USED BY EXPERTS IN THIS AREA

Resource 1

Rowsey et al. Whole-Genome Single Nucleotide Polymorphism Microarray for Copy Number and Loss of Heterozygosity Analysis in Tumors. Methods Mol Biol 2019:1908:89-111. PMID: 30649723

- This book chapter offers a comprehensive overview of the SNP chromosomal microarray technique and its application in analyzing data from oncology specimens.

- It presents examples of aberrations observed in oncology cases such as small deletions of tumor suppressor genes, focal amplifications of oncogenes, tetraploidization, chromothripsis, pseudohyperdiploid, and chimerism.
- It discusses the difficulties in determining ploidy states in oncology samples, where ploidy changes are common, and explains how analyzing allele tracks can help determine ploidy status. Figure 8 demonstrates the differences in BAF between hyperdiploid and pseudohyperdiploid (doubled haploid genome), while the copy number data exhibit a similar pattern for both cases. Figure 9 illustrates how known common genomic profiles are integrated into the assessment of array data to determine ploidy status.

Resource 2

Conlin LK et al. Mechanisms of mosaicism, chimerism and uniparental disomy identified by single nucleotide polymorphism array analysis. Hum Mol Genet 2010 Apr 1;19(7):1263-75 PMID: 20053666

Laura Conlin “Genome-Wide Mosaicism, Chimerism, and Contamination: Recognizing and Interpreting Genotyping Pattern” 2018 CGC Annual Meeting https://www.youtube.com/watch?v=G2Spdq1xm9Y

- This paper and the talk describe the BAF patterns across different mosaic levels for deletion, duplication, trisomy, uniparental disomy (UPD) and chimerism, and the mechanism of aberrations implicated by the BAF pattern.
- Table S1 displays the expected BAF at various percentage of mosaic levels. This is useful when estimating mosaic levels of aberrations in analyzing cases.

Resource 3

SNP interpretation guide (Greenwood Genetic Center; scroll down to “Laboratory Resources”)

- This guide was produced by Timothy Fee, PhD as a resource for laboratory geneticists involved in SNP array analysis.

- It provides simulated SNP array data, comprising copy number plots and B-allele frequency (BAF), illustrating different aberrations at various mosaic levels. This

encompasses SNP array data showcasing various combinations of aberrations, such as single copy loss with loss of heterozygosity (LOH), LOH with two-copy gain, as well as simple aberrations such as single copy loss or LOH. This resource is especially beneficial for analyzing intricate array data in oncology microarray analysis, where simultaneous occurrences of multiple aberrations or the presence of multiple clones at varying levels are common.

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