Regions of Homozygosity: Finding the Needle in the Haystack Efficiently & Effectively

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Background & Objectives: In addition to identifying copy number variants, single nucleotide polymorphism chromosomal microarray technology allows for the identification of regions of homozygosity (ROH) in individuals. Analysis of ROH can be particularly helpful in developing a differential diagnosis when an autosomal recessive condition is suspected. Presented below are two illustrative cases.

Method (s) and Results: ROH were analyzed using Franklin (https://franklin.genoox.com) with incorporation of phenotypic features based on clinical evaluation by Medical Genetics.

Case 1: A two-week-old Mexican (Guerrero) boy is evaluated for intrauterine growth retardation, hypotonia, and poor feeding. Postnatal microarray reveals several ROH, including a region of chromosome 6 containing *PEX6*, identified to have the strongest genotype-phenotype relation. Newborn screening on day of life 19 is positive for elevated C26 without an identified variant in *ABCD1*, concerning for Zellweger spectrum disorder (ZSD). Molecular testing reveals a homozygous likely-pathogenic variant in *PEX6* (c.1409G>C, p.G470A), consistent with a diagnosis of ZSD. Biochemical testing further supports the diagnosis and the variant is later reclassified as pathogenic.

Case 2: A five-week-old Guatemalan (Chiquimula) boy with negative prenatal infectious screening and negative postnatal urine cytomegalovirus testing is evaluated for microcephaly, bilateral cataracts and hearing impairment, and neonatal cholestasis. Postnatal microarray reveals a 29.9 Mb interstitial ROH on chromosome 19 containing *ERCC2*, identified to have the strongest genotype-phenotype relation. Molecular testing reveals a homozygous likely-pathogenic variant in *ERCC2* (c.1997G>A, p.R666Q), consistent with a diagnosis of *ERCC2*-related disorder.

Conclusions (Significance and Impact of the Study): Analysis of ROH is a resourceful tool for developing a narrow list of genes for further molecular analysis in individuals suspected to have an autosomal recessive condition, particularly when broad-based genetic testing is inaccessible. Analysis of ROH has the potential to decrease time to diagnosis and lead to the identification and/or reclassification of rare disease-causing variants.

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Keywords: regions of homozygosity (ROH), chromosomal microarray, autosomal recessive, homozygous variant, diagnosis