PrgmNr 3545 - Developmental genomics of congenital limb malformations: further evidence for gene dosage effects


Disclosure Block: R. Duan: None.

Congenital limb malformations represent a broad spectrum of intrauterine developmental perturbations involving the upper and/or lower extremities, which can occur as a deformation, disruption, or an isolated developmental event (i.e., malformation) or be a manifestation of a partial trait, i.e., endophenotype, of a Mendelian condition. Phenotypic manifestations of extremity anomalies can involve anterior-posterior (AP), dorsal-ventral (DV), or proximal-distal (PD) planes of the body axes of development and can be associated with complex genetic etiologies. Genetic heterogeneity, reduced penetrance and variable expressivity have all been described in families. Using family-based genomics and rare variant analyses, we applied exome sequencing (ES) combined with whole-genome array-based comparative genomic hybridization (aCGH) to investigate 14 families with limb defects. Studies in 8 out of 14 families revealed likely pathogenic single nucleotide variants (SNVs) or copy number variants (CNVs) at previously reported disease associated loci: BHLHA9, HOXD13, GLI3, WNT10B and NPR2. Multi-locus pathogenic variation (MPV) was observed in one family seemingly driven by the absence of heterozygosity (AOH) resulting from identity-by-descent (IBD); total AOH = 89.1Mb in a child of parents from the same small village, but with no known consanguinity. Notably, breakpoint junction analyses for 2 novel pathogenic duplication CNVs of BHLHA9 were demonstrated to be generated by Alu/Alu-mediated rearrangement (AAMR). Interestingly, homozygosity for BHLHA9 duplication CNV was observed in association with a more severe limb malformation, the Gollop-Wolfgang Complex. We propose a gene dosage model at this locus potentially underlies both the reduced penetrance and the more severe phenotype observed with homozygous duplication. Further studies will explore whether genes acting in the Apical Ectodermal Ridge (AER) may be particularly vulnerable to stochastic fluctuations in expression during development in the distal proximal plane and whether such a gene dosage expression model significantly contributes to limb anomalies.