PgmNr 2547: Full genome analysis for identification of single nucleotide and structural variants in genes that cause developmental delay.

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Developmental delay caused by gene mutations are hard to identify due to phenotypic and genetic heterogeneity. While whole exome sequencing (WES) has been used to identify causal mutations, the majority of cases remain unsolved. In this study, we test the hypothesis that full genome analysis (phased whole genome sequencing with assembly based on linked-read sequencing and mapping technologies) of trios provides the best chance of identifying gene mutations, and especially structural variations, that cause developmental delay.
Eight trios with negative finding by WES were subjected to (1) whole genome sequenced (WGS) to 60X coverage on the 10x Genomics linked-read platform, and (2) mapped to 90X coverage on the Bionano Genomics optical mapping platform. The de novo, phased genome assemblies of the patient and his/her two biological parents were compared and the single nucleotide variants (SNVs) and structural variants (SVs), including de novo variants, were identified. After filtering out synonymous SNVs, and common SNVs/SVs against public databases, the remaining variants were further evaluated according to the three possible genetic models: autosomal recessive, autosomal dominant and X-linked recessive. In the autosomal dominant and X-linked recessive models, de novo variants were selected for careful analysis. In each instance, we examined genes affected by SNVs, SVs, or a combination of SNVs and SVs.
Candidate variants (both SNVs and SVs), predicted as deleterious by multiple tools in the web-based wANNOVAR suite, were selected for genotype-phenotype correlation in consultation with the clinicians and a literature search of the candidate genes were performed. Three WES-negative cases that were successfully diagnosed by this full genome analysis approach will be presented.