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Familial Exome Sequencing to Decipher the Complex Genetic Basis of Holoprosencephaly

Authors : Artem Kim, Clara Savary, Christele Dubourg, Wilfrid Carre, Houda Hamdi-Roze, Valerie Dupé, Sylvie Odent, Marie De Tayrac, Veronique David

Abstract : Holoprosencephaly (HPE) is a rare congenital brain malformation resulting from the incomplete separation of the two cerebral hemispheres. It is characterized by a wide phenotypic spectrum and a high degree of locus heterogeneity. Genetic defects in 16 genes have already been implicated in HPE, but account for only 30% of cases, suggesting that a large part of genetic factors remains to be discovered. HPE has been recently redefined as a complex multigenic disorder, requiring the joint effect of multiple mutational events in genes belonging to one or several developmental pathways. The onset of HPE may result from accumulation of the effects of multiple rare variants in functionally-related genes, each conferring a moderate increase in the risk of HPE onset. In order to decipher the genetic basis of HPE, unconventional patterns of inheritance involving multiple genetic factors need to be considered. The primary objective of this study was to uncover possible disease causing combinations of multiple rare variants underlying HPE by performing trio-based Whole Exome Sequencing (WES) of familial cases where no molecular diagnosis could be established. 39 families were selected with no fully-penetrant causal mutation in known HPE gene, no chromosomic aberrations/copy number variants and without any implication of environmental factors. As the main challenge was to identify disease-related variants among a large number of nonpathogenic polymorphisms detected by WES classical scheme, a novel variant prioritization approach was established. It combined WES filtering with complementary gene-level approaches: transcriptome-driven (RNA-Seq data) and clinically-driven (public clinical data) strategies. Briefly, a filtering approach was performed to select variants compatible with disease segregation, population frequency and pathogenicity prediction to identify an exhaustive list of rare deleterious variants. The exome search space was then reduced by restricting the analysis to candidate genes identified by either transcriptome-driven strategy (genes sharing highly similar expression patterns with known HPE genes during cerebral development) or clinically-driven strategy (genes associated to phenotypes of interest overlapping with HPE). Deeper analyses of candidate variants were then performed on a family-by-family basis. These included the exploration of clinical information, expression studies, variant characteristics, recurrence of mutated genes and available biological knowledge. A novel bioinformatics pipeline was designed. Applied to the 39 families, this final integrated workflow identified an average of 11 candidate variants per family. Most of candidate variants were inherited from asymptomatic parents suggesting a multigenic inheritance pattern requiring the association of multiple mutational events. The manual analysis highlighted 5 new strong HPE candidate genes showing recurrences in distinct families. Functional validations of these genes are foreseen.

Keywords : complex genetic disorder, holoprosencephaly, multiple rare variants, whole exome sequencing
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