Trabalhos Científicos

Título: Trio-Based Whole Exome Sequencing In Patients With Ectopic Posterior Pituitary

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Resumo: Ectopic posterior pituitary (EPP) is a rare congenital abnormality, sometimes associated with other midline defects, such as pituitary stalk interruption syndrome (PSIS), in which thin or absent pituitary stalk and anterior pituitary hypoplasia are combined to EPP. Most cases are sporadic, with few reports of familial cases, and many congenital hypopituitarism (CH) cases remain unsolved. To search for candidate genes associated with this condition, we performed trio-based whole-exome sequencing (WES) on patients with EPP, including two familial cases.This study included subjects diagnosed with EPP and PSIS by a simplified MRI protocol (FAST1.2). We performed two distinct analyses in the trio-based WES. We looked for previously described candidate gene variants associated with the pituitary. Next, we investigated the whole exome for variants inherited in a pattern consistent with a monogenic etiology. Trios´ analysis allowed the elimination of single-nucleotide variation (SNV) in genes associated with hypopituitarism and variants of uncertain significance (VUS) present in parents.Ten families with EPP were evaluated, eight were composed of a child with EPP and healthy parents, one has two affected siblings, and one family has a son and mother with EPP. When analyzing the previously described candidate variants associated with pituitary development, we found two variants (GLI2 and FGFR1) in three families. We also found six other variants of interest in four patients in the investigation of the whole exome: MAP1A, GALR3, RTN4R, SEMA3A, NIPBL, and DSCAML1. The analysis allowed us to find three GLI2 variants previously reported in patients with EPP plus one variant with no prior description. We also found a variant in FGFR1, not previously reported, whose mutations are related to CH. Furthermore, trios´ analysis allowed us to find six other variants of interest in four patients, all associated with neuronal development. Functional analysis remains fundamental to confirm the pathogenicity of new variants found. Future investigations may clarify the roles of these variants in the etiology of EPP and PSIS.