PCDHGC4

This gene is a member of the protocadherin gamma gene cluster, one of three related clusters tandemly linked on chromosome five. These gene clusters have an immunoglobulin-like organization, suggesting that a novel mechanism may be involved in their regulation and expression. The gamma gene cluster includes 22 genes divided into 3 subfamilies. Subfamily A contains 12 genes, subfamily B contains 7 genes and 2 pseudogenes, and the more distantly related subfamily C contains 3 genes. The tandem array of 22 large, variable region exons are followed by a constant region, containing 3 exons shared by all genes in the cluster. Each variable region exon encodes the extracellular region, which includes 6 cadherin ectodomains and a transmembrane region. The constant region exons encode the common cytoplasmic region. These neural cadherin-like cell adhesion proteins most likely play a critical role in the establishment and function of specific cell-cell connections in the brain. Alternative splicing has been described for the gamma cluster genes. [provided by RefSeq, Jul 2008].

In all affected individuals who presented with a neurodevelopmental syndrome with progressive microcephaly, seizures, and intellectual disability we identified biallelic disease-causing variants in Protocadherin-gamma-C4 (PCDHGC4). Five variants were predicted to induce premature protein truncation leading to a loss of PCDHGC4 function. The three detected missense variants were located in extracellular cadherin (EC) domains EC5 and EC6 of PCDHGC4, and in silico analysis of the affected residues showed that two of these substitutions were predicted to influence the Ca2+-binding affinity, which is essential for multimerization of the protein, whereas the third missense variant directly influenced the cis-dimerization interface of PCDHGC4.

Iqbal et al. showed that biallelic variants in PCDHGC4 are causing a novel autosomal recessive neurodevelopmental disorder and link PCDHGC4 as a member of the clustered PCDH family to a Mendelian disorder in humans [1)]

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Iqbal M, Maroofian R, Çavdarlı B, Riccardi F, Field M, Banka S, Bubshait DK, Li Y, Hertecant J, Baig SM, Dyment D, Efthymiou S, Abdullah U, Makhdoom EUH, Ali Z, Scherf de Almeida T, Molinari F, Mignon-Ravix C, Chabrol B, Antony J, Ades L, Pagnamenta AT, Jackson A, Douzgou S; Genomics England Research Consortium, Beetz C, Karageorgou V, Vona B, Rad A, Baig JM, Sultan T, Alvi JR, Maqbool S, Rahman F, Toosi MB, Ashrafzadeh F, Imannezhad S, Karimiani EG, Sarwar Y, Khan S, Jameel M, Noegel AA, Budde B, Altmüller J, Motameny S, Höhne W, Houlden H, Nürnberg P, Wollnik B, Villard L, Alkuraya FS, Osmond M, Hussain MS, Yigit G. Biallelic variants in PCDHGC4 cause a novel neurodevelopmental syndrome with progressive microcephaly, seizures, and joint anomalies. Genet Med. 2021 Jul 9. doi: 10.1038/s41436-021-01260-4. Epub ahead of print. PMID: 34244665.