Revealing molecular mechanism of disease

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Abstracts:

J Alzheimers Dis. 2013 Oct 10. [Epub ahead of print]

A Novel p.Leu(381)Phe Mutation in Presenilin 1 is Associated with Very Early Onset and Unusually Fast Progressing Dementia as well as Lysosomal Inclusions Typically Seen in Kufs Disease.

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Abstract

Whole exome sequencing in a family with suspected dominant Kufs disease identified a novel Presenilin 1 mutation p.Leu(381)Phe in three brothers who, along with their father, developed progressive dementia and motor deficits in their early 30 s. All affected relatives had unusually rapid disease progression (on average 3.6 years from disease onset to death). In silico analysis of mutation p.Leu(381)Phe predicted more detrimental effects when compared to the common Presenilin 1 mutation p.Glu(280)Ala. Electron microscopy study of peripheral fibroblast cells of the proband showed lysosomal inclusions typical for Kufs disease. However, brain autopsy demonstrated typical changes of Alzheimer's disease.

KEYWORDS:

Alzheimer's disease, fast progressing dementia, kufs disease, lysosomal inclusions, presenilin 1 mutation

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A mutation in a ganglioside biosynthetic enzyme, ST3GAL5, results in salt & pepper syndrome, a neurocutaneous disorder with altered glycolipid and glycoprotein glycosylation.

Boccuto L, Aoki K, Flanagan-Steet H, Chen CF, Fan X, Bartel F, Petukh M, Pittman A, Saul R, Chaubey A, Alexov E, Tiemeyer M, Steet R, Schwartz CE.

Abstract

'Salt & Pepper' syndrome is an autosomal recessive condition characterized by severe intellectual disability, epilepsy, scoliosis, choreoathetosis, dysmorphic facial features and altered dermal pigmentation. High-density SNP array analysis performed on siblings first described with this syndrome detected four shared regions of loss of heterozygosity (LOH). Whole-exome sequencing narrowed the candidate region to chromosome 2p11.2. Sanger sequencing confirmed a homozygous c.994G>A

transition (p.E332K) in the ST3GAL5 gene, which encodes for a sialyltransferase also known as GM3 synthase. A different homozygous mutation of this gene has been previously associated with infantile-onset epilepsy syndromes in two other cohorts. The ST3GAL5 enzyme synthesizes ganglioside GM3, a glycosophingolipid enriched in neural tissue, by adding sialic acid to lactosylceramide. Unlike disorders of glycosphingolipid (GSL) degradation, very little is known regarding the molecular and pathophysiologic consequences of altered GSL biosynthesis. Glycolipid analysis confirmed a complete lack of GM3 ganglioside in patient fibroblasts, while microarray analysis of glycosyltransferase mRNAs detected modestly increased expression of ST3GAL5 and greater changes in transcripts encoding enzymes that lie downstream of ST3GAL5 and in other GSL biosynthetic pathways. Comprehensive glycomic analysis of N-linked, O-linked and GSL glycans revealed collateral alterations in response to loss of complex gangliosides in patient fibroblasts and in zebrafish embryos injected with antisense morpholinos that targeted zebrafish st3gal5 expression. Morphant zebrafish embryos also exhibited increased apoptotic cell death in multiple brain regions, emphasizing the importance of GSL expression in normal neural development and function.

PLoS One. 2013 Jun 14;8(6):e66273. doi: 10.1371/journal.pone.0066273. Print 2013.

Cancer missense mutations alter binding properties of proteins and their interaction networks.
Nishi H, Tyagi M, Teng S, Shoemaker BA, Hashimoto K, Alexov E, Wuchty S, Panchenko AR.

Abstract

Many studies have shown that missense mutations might play an important role in carcinogenesis. However, the extent to which cancer mutations might affect biomolecular interactions remains unclear. Here, we map glioblastoma missense mutations on the human protein interactome, model the structures of affected protein complexes and decipher the effect of mutations on protein-protein, protein-nucleic acid and protein-ion binding interfaces. Although some missense mutations over-stabilize protein complexes, we found that the overall effect of mutations is destabilizing, mostly affecting the electrostatic component of binding energy. We also showed that mutations on interfaces resulted in more drastic changes of amino acid physico-chemical properties than mutations occurring outside the interfaces. Analysis of glioblastoma mutations on interfaces allowed us to stratify cancer-related interactions, identify potential driver genes, and propose two dozen additional cancer biomarkers, including those specific to functions of the nervous system. Such an analysis also offered insight into the molecular mechanism of the phenotypic outcomes of mutations, including effects on complex stability, activity, binding and turnover rate. As a result of mutated protein and gene network analysis, we observed that interactions of proteins with mutations mapped on interfaces had higher bottleneck properties compared to interactions with mutations elsewhere on the protein or unaffected interactions. Such observations suggest that genes with mutations directly affecting protein binding properties are preferably located in central network positions and may influence critical nodes and edges in signal transduction networks.

Hum Mol Genet. 2013 Sep 15;22(18):3789-97. doi: 10.1093/hmg/ddt229. Epub 2013 May 21.

A Y328C missense mutation in spermine synthase causes a mild form of Snyder-Robinson syndrome.
Zhang Z, Norris J, Kalscheuer V, Wood T, Wang L, Schwartz C, Alexov E, Van Esch H.

Abstract

Snyder-Robinson syndrome (SRS, OMIM: 309583) is an X-linked intellectual disability (XLID) syndrome, characterized by a collection of clinical features including facial asymmetry, marfanoid habitus, hypertonia, osteoporosis and unsteady gait. It is caused by a significant decrease or loss of spermine synthase (SMS) activity. Here, we report a new missense mutation, p.Y328C (c.1084A>G), in SMS in a family with XLID. The affected males available for evaluation had mild ID, speech and global delay, an asthenic build, short stature with long fingers and mild kyphosis. The spermine/spermidine ratio in lymphoblasts was 0.53, significantly reduced compared with normal (1.87 average). Activity analysis of SMS in the index patient failed to detect any activity above background. In silico modeling demonstrated that the Y328C mutation has a significant effect on SMS stability, resulting in decreased folding free energy and larger structural fluctuations compared with those of wild-type SMS. The loss of activity was attributed to the increase in conformational dynamics in the mutant which affects the active site geometry, rather than preventing dimer formation. Taken together, the biochemical and in silico studies confirm the p.Y328C mutation in SMS is responsible for the patients having a mild form of SRS and reveal yet another molecular mechanism resulting in a non-functional SMS causing SRS.