PNPLA6 mutations cause Boucher-Neuhauser and Gordon Holmes syndromes as part of a broad neurodegenerative spectrum.

Boucher-Neuhauser and Gordon Holmes syndromes are clinical syndromes defined by early-onset ataxia and hypogonadism plus chorioretinal dystrophy (Boucher-Neuhauser syndrome) or brisk reflexes (Gordon Holmes syndrome). Here we uncover the genetic basis of these two syndromes, demonstrating that both clinically distinct entities are allelic for recessive mutations in the gene PNPLA6. In five of seven Boucher-Neuhauser syndrome/Gordon Holmes syndrome families, we identified nine rare conserved and damaging mutations by applying whole exome sequencing. Further, by dissecting the complex clinical presentation of Boucher-Neuhauser syndrome and Gordon Holmes syndrome into its neurological system components, we set out to analyse an additional 538 exomes from families with ataxia (with and without hypogonadism), pure and complex hereditary spastic paraplegia, and Charcot-Marie-Tooth disease type 2. We identified four additional PNPLA6 mutations in spastic ataxia and hereditary spastic paraplegia families, revealing that Boucher-Neuhauser and Gordon Holmes syndromes are allelic for recessive mutations in the gene PNPLA6.
Holmes syndromes in fact represent phenotypic clusters on a spectrum of neurodegenerative diseases caused by mutations in PNPLA6. Structural analysis indicates that the majority of mutations falls in the C-terminal phospholipid esterase domain and likely inhibits the catalytic activity of PNPLA6, which provides the precursor for biosynthesis of the neurotransmitter acetylcholine. Our findings show that PNPLA6 influences a manifold of neuronal systems, from the retina to the cerebellum, upper and lower motor neurons and the neuroendocrine system, with damage of this protein causing an extraordinarily broad continuous spectrum of associated neurodegenerative disease.

Zeitschriftentitel / Abkürzung:
Brain

Jahr:
2014

Band:
137

Heft / Issue:
Pt 1

Seiten:
69-77

Sprache:
eng

Pubmed:

Print-ISSN:
0006-8950

TUM Einrichtung:
Institut für Humangenetik

Occurences:
Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Institut für Humangenetik > 2014