WHAT'S HAPPENING IN Neurology® Genetics

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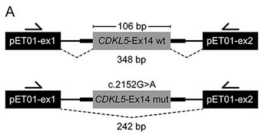
Abstracts

Articles appearing in the December 2017 issue

CDKL5 variants: Improving our understanding of a rare neurologic disorder



Objective To provide new insights into the interpretation of genetic variants in a rare neurologic disorder, CDKL5 deficiency, in the context of population sequencing data and an updated characterization of the *CDKL5* gene.

Methods We analyzed all known potentially pathogenic *CDKL5* variants by combining data from large-scale population sequencing studies with *CDKL5* variants from new and all available clinical cohorts and combined this with computational methods to predict pathogenicity.

Results The study identified several variants that can be reclassified as benign or likely benign. With the addition of novel *CDKL5* variants, we confirm that pathogenic missense variants cluster in the catalytic domain of CDKL5 and reclassify a purported missense variant as having a splicing consequence. We provide further evidence that missense variants in the final 3 exons are likely to be benign and not important to disease pathology. We also describe benign splicing and nonsense variants within these exons, suggesting that isoform hCDKL5_5 is likely to have little or no neurologic significance. We also use the available data to make a preliminary estimate of minimum incidence of CDKL5 deficiency.

Conclusions These findings have implications for genetic diagnosis, providing evidence for the reclassification of specific variants previously thought to result in CDKL5 deficiency. Together, these analyses support the view that the predominant brain isoform in humans (hCDKL5_1) is crucial for normal neurodevelopment and that the catalytic domain is the primary functional domain.

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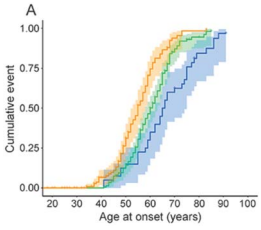
Factors influencing the age at onset in familial frontotemporal lobar dementia: Important weight of genetics



Objective To quantify the effect of genetic factors and generations influencing the age at onset (AAO) in families with frontotemporal lobar dementia (FTD) due to *C9ORF72* hexanucleotide repeat expansions and *GRN* mutations.

Methods We studied 504 affected individuals from 133 families with *C9ORF72* repeat expansions and 90 FTD families with mutations in *GRN*, 2 major genes responsible for FTD or amyotrophic lateral sclerosis. Intrafamilial correlations of AAO were analyzed, and variance component methods were used for heritability estimates. Generational effects on hazard rates for AAO were assessed using mixed-effects Cox proportional hazard models.

Results A generational effect influencing AAO was detected in both *C9ORF72* and *GRN* families. Nevertheless, the estimated proportion of AAO variance explained by genetic factors was high in FTD caused by *C9ORF72* repeat expansions (44%; $p = 1.10^{e-4}$), 62% when the AAO of dementia was specifically taken into account ($p = 8.10^{e-5}$), and to a lesser degree in *GRN* families (26%; $p = 0.17$). Intrafamilial correlation analyses revealed a significant level of correlations in *C9ORF72* families according to the degree of kinship. A pattern of intrafamilial correlations also suggested potential X-linked modifiers acting on AAO. Nonsignificant correlation values were observed in *GRN* families.

Conclusions Our results provide original evidence that genetic modifiers strongly influence the AAO in *C9ORF72* carriers, while their effects seem to be weaker in *GRN* families. This constitutes a rationale to search for genetic biomarkers, which could help to improve genetic counseling, patient care, and monitoring of therapeutic trials.

NPub.org/NG/9012b

Most-Cited Articles

As of January 18, 2018

CHCHD10 variant p.(Gly66Val) causes axonal Charcot-Marie-Tooth disease

M. Auranen, E. Ylikallio, M. Shcherbii, et al. 2015;1:e1.

Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk

B. Rhead, M. Bäärnhielm, M. Gianfrancesco, et al. 2016; 2:e97.

A novel *DYNC1H1* mutation causing spinal muscular atrophy with lower extremity predominance

Q. Niu, X. Wang, M. Shi, and Q. Jin. 2015;1:e20.

Complete callosal agenesis, pontocerebellar hypoplasia, and axonal neuropathy due to AMPD2 loss

A.P.L. Marsh, V. Lukic, K. Pope, et al. 2015;1:e16.

Expanding genotype/phenotype of neuromuscular diseases by comprehensive target capture/NGS

X. Tian, W.C. Liang, Y. Feng, et al. 2015;1:e14.