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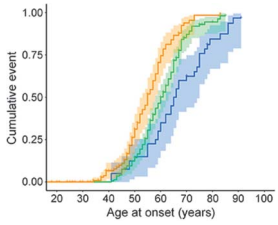
Abstracts

Articles appearing in the December 2017 issue

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.

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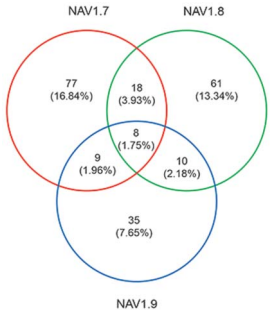
Na_V channel variants in patients with painful and nonpainful peripheral neuropathy



Objective To examine the incidence of nonsynonymous missense variants in *SCN9A* ($Na_V1.7$), *SCN10A* ($Na_V1.8$), and *SCN11A* ($Na_V1.9$) in patients with painful and nonpainful peripheral neuropathy.

Methods Next-generation sequencing was performed on 457 patient DNA samples provided by the Peripheral Neuropathy Research Registry (PNRR). The patient diagnosis was as follows: 278 idiopathic peripheral neuropathy (67% painful and 33% nonpainful) and 179 diabetic distal polyneuropathy (77% painful and 23% nonpainful).

Results We identified 36 (*SCN9A*), 31 (*SCN10A*), and 15 (*SCN11A*) nonsynonymous missense variants, with 47.7% of patients carrying a low-frequency (minor allele frequency <5%) missense variant in at least 1 gene. The incidence of previously reported gain-of-function missense variants was low (≤3%), and these were detected in patients with and without pain. There were no significant differences in missense variant allele frequencies of any gene, or *SCN9A* haplotype frequencies, between PNRR patients with painful or nonpainful peripheral neuropathy. PNRR patient *SCN9A* and *SCN11A* missense variant allele frequencies were not significantly different from the Exome Variant Server, European American (EVS-EA) reference population. For *SCN10A*, there was a significant increase in the alternate allele frequency of the common variant p.V1073A and low-frequency variant pS509P in PNRR patients compared with EVS-EA and the 1000 Genomes European reference populations.

Conclusions These results suggest that identification of a genetically defined subpopulation for testing of $Na_V1.7$ inhibitors in patients with peripheral neuropathy is unlikely and that additional factors, beyond expression of previously reported disease "mutations," are more important for the development of painful neuropathy than previously discussed.

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

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

19th Workshop of the International Stroke Genetics Consortium, April 28–29, 2016, Boston, MA

2017;3:S2-S11.

What's happening in *Neurology*® *Genetics*

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