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Painful or Painless Diabetic Neuropathy? The ion channel gene variants make the difference

Aim: Numerous factors make it difficult to understand whether painless diabetic neuropathy (DN) and painful DN represent different diseases or are different manifestations of the same disease: the limited number of studies, the different methods of defining DN, and the multiple risk factors. Pathogenic ion channel gene (ICG) variants may contribute to the development of neuropathic pain in diabetic peripheral neuropathy.
Methods: Using single molecule molecular inversion probes-next generation sequencing (smMIPs-NGS), the Authors analyzed the following ion channel variants in 222 painful- and 304 painless-DN patients: 5 transient receptor potential (TRP) cation channels, 7 voltage-gated potassium (Kv) channels, 2 hyperpolarization-activated and cyclic nucleotide-gated channels (HCN), and 2 anoctamins Ca2+-activated Cl- channel (ANO), all involved in pain modulation and processing and/or painful neuropathies.
Results: MIP-NGS data analysis of patients with painful-DN identified 13 potentially pathogenic variants in 6 ICG genes (ANO3, HCN1, KCNK18, TRPA1, TRPM8, TRPV4). All 13 variants were classified as variants of uncertain clinical significance (VUS). Twelve painful-DN (5.4%) patients showed potentially pathogenic variants (5 nonsense/frameshift, 7 missense, 1 out-of-frame deletion) in ANO3 (n=3), HCN1 (n=1), KCNK18 (n=2), TRPA1 (n=3), TRPM8 (n=3) and TRPV4 (n=1). Nine painful-DN patients with ICG variants reported higher 24h maximal pain intensity scores (NRS 7.2 +/−2.4), compared to patients with painful-DN without an ICG variant (PI-NRS 6.0 +/−3.0, n=150). Interestingly, a patient with painful-DN and a potentially causative variant in the TRP gene had severe or very severe pain during the night (NRS 8.5 +/−1.29) and day (NRS 8.0 +/−0.82) and impaired thermal sensation. Fourteen painless-DN patients had a potentially pathogenic variant in one of 13 ICG, but none had more than one ICG variant (4.6%:3 nonsense/frameshift, 9 missense, 1 out-of-frame deletion). Patients with painless-DN with an ICG VUS variant reported fewer autonomic complaints, especially diarrhea, dry mouth, orthostatic dizziness, sheet intolerance, and restless leg.
Conclusions: This study identified potentially pathogenic variants in 5.4% of the patients with painful-DN and 4.6% of the those with painless-DN, although they were predominantly VUS.

Comments. This study, part of PROPANE study, identified new ion channel variants, including TRPs, which can be genetic contributors to neuropathic pain. TRPV1, TRPM8, and TRPA1 are thermal and chemical detectors that activate sensory neurons to produce pain, while TRPV4 mediates nociceptive behaviors by hyper- and hypotonic stimuli. Although limited in number, painful-DN patients with ICG variants reported specific pain presentation characteristics (higher maximal pain intensity) or abnormal thermal thresholds. These results show that ion channels play a specific role in the presence and in the characteristics of neuropathic pain, making them attractive candidates for further investigation and potential targets for therapy of neuropathic pain. An effective and resolving treatment remains a difficult challenge to achieve in painful diabetic peripheral neuropathy, and these data add a step towards achieving this goal.

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Reference. Ślęczkowska M, Almomani R, Marchi M, de Greef BTA, Sopacua M, Hoeijmakers JGJ, Lindsey P, Salvi E, Bönhof GJ, Ziegler D, Malik RA, Waxman SG, Lauria G, Faber CG, Smeets HJM, Gerrits MM. Peripheral Ion Channel Gene Screening in Painful- and Painless-Diabetic Neuropathy. Int J Mol Sci. 2022 Jun 28;23(13):7190. doi: 10.3390/ijms23137190.
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