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Exome Sequencing Uncovers Molecular Determinants of Trigeminal Neuralgia

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Introduction

Trigeminal neuralgia (TN) is a complex neuropathic pain condition[1-3]. Neurosurgical dogma has stressed the role of vascular compression of the trigeminal ganglion or nerve root in the pathogenesis of TN, reinforcing the use of invasive microvascular decompression (MVD) for treatment. However, the symptoms of many patients with TN are recalcitrant to MVD, and other TN patients are disturbingly found to have no vascular compression at the time of surgery, suggesting other factors. It has long been long recognized that familial forms of TN exist, but to date no gene associated with TN has been definitely identified.

Methods

Exome capture was performed on genomic DNA samples isolated from 131 unrelated trigeminal neuralgia (TN) probands, including case-parent trios (total n=215). Sequencing reads were aligned to the human reference genome and further processed for variant calling. Variants were annotated with ANNOVAR[4]. MetaSVM was used to predict the deleteriousness of missense mutations. Enrichment detection for rare damaging mutations was performed using binomial analysis.

Results

Gene burden analysis[5] revealed genome-wide significant enrichment of rare damaging mutations in one member of the calcium voltage-gated channel proteins (n=6; 4.5%; p-value = 9.21x10-7) among patients with MVD-resistant TN. Additionally, a considerably significant rare damaging mutation burden was found in a gene belonging to the basic helix-loop-helix (bHLH) family of transcription factors highly expressed in trigeminal pain pathways (n=3, p-value = 1.72x10-5). A novel, damaging de novo mutation was also identified in a GABA receptor subunit in an MVD-resistant patient.

Conclusions

This work represents the first exome-sequenced TN cohort in the world, and uncovers genetic determinants and molecular mechanisms underlying TN pathogenesis. These findings suggest: 1) microvascular compression is an incomplete explanation for TN pathogenesis; 2) some patients with gene mutations may not benefit from MVD; and 3) specific ion transport molecules may be potential pharmacotherapeutic targets.

Learning Objectives

By the conclusion of this session, participants should be able to 1) Recognize that microvascular compression may only partially describe the TN pathogenesis, 2) Describe mutations in ion channels that may be potential pharmacotherapeutic targets, 3) Discuss the possibility TN patients with genetic mutations may not benefit from MVD

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