EXTENSION SHEET

DNA Sequencing and Precision Medicine

Name: _____ Date: _____

ALS Abstract

ALS GENES

Exome sequencing in amyotrophic lateral sclerosis identifies risk genes and pathways

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Amyotrophic lateral sclerosis (ALS) is a devastating neurological disease with no effective treatment. We report the results of a moderate-scale sequencing study aimed at increasing the number of genes known to contribute to predisposition for ALS. We performed whole-exome sequencing of 2869 ALS patients and 6405 controls. Several known ALS genes were found to be associated, and *TBK1* (the gene encoding TANK-binding kinase 1) was identified as an ALS gene. TBK1 is known to bind to and phosphorylate a number of proteins involved in innate immunity and autophagy, including optineurin (OPTN) and p62 (SQSTM1/sequestosome), both of which have also been implicated in ALS. These observations reveal a key role of the autophagic pathway in ALS and suggest specific targets for therapeutic intervention.

Highlight the following:

Yellow - Background

Pink - Methods

Blue - Results

Orange - Conclusion

Do your best to write the 4 parts of the abstract in simpler terms. Write 1-2 sentences for each part"

Background

Methods

Results

Conclusion

Difficult words	Meaning

How has DNA Sequencing contributed to the understanding and treatment of ALS?

Epilepsy Abstract

Ultra-rare genetic variation in common epilepsies: a case-control sequencing study

Epi4K consortium†, Epilepsy Phenome/Genome Project†

Summary

Background Despite progress in understanding the genetics of rare epilepsies, the more common epilepsies have proven less amenable to traditional gene-discovery analyses. We aimed to assess the contribution of ultra-rare genetic variation to common epilepsies.

Methods We did a case-control sequencing study with exome sequence data from unrelated individuals clinically evaluated for one of the two most common epilepsy syndromes: familial genetic generalised epilepsy, or familial or sporadic non-acquired focal epilepsy. Individuals of any age were recruited between Nov 26, 2007, and Aug 2, 2013, through the multicentre Epilepsy Phenome/Genome Project and Epi4K collaborations, and samples were sequenced at the Institute for Genomic Medicine (New York, USA) between Feb 6, 2013, and Aug 18, 2015. To identify epilepsy risk signals, we tested all protein-coding genes for an excess of ultra-rare genetic variation among the cases, compared with control samples with no known epilepsy or epilepsy comorbidity sequenced through unrelated studies.

Findings We separately compared the sequence data from 640 individuals with familial genetic generalised epilepsy and 525 individuals with familial non-acquired focal epilepsy to the same group of 3877 controls, and found significantly higher rates of ultra-rare deleterious variation in genes established as causative for dominant epilepsy disorders (familial genetic generalised epilepsy: odd ratio [OR] 2·3, 95% CI 1·7–3·2, $p=9·1\times10^{-8}$; familial non-acquired focal epilepsy 3·6, 2·7–4·9, $p=1·1\times10^{-17}$). Comparison of an additional cohort of 662 individuals with sporadic non-acquired focal epilepsy to controls did not identify study-wide significant signals. For the individuals with familial non-acquired focal epilepsy, we found that five known epilepsy genes ranked as the top five genes enriched for ultra-rare deleterious variation. After accounting for the control carrier rate, we estimate that these five genes contribute to the risk of epilepsy in approximately 8% of individuals with familial non-acquired focal epilepsy. Our analyses showed that no individual gene was significantly associated with familial genetic generalised epilepsy; however, known epilepsy genes had lower p values relative to the rest of the protein-coding genes ($p=5·8\times10^{-8}$) that were lower than expected from a random sampling of genes.

Interpretation We identified excess ultra-rare variation in known epilepsy genes, which establishes a clear connection between the genetics of common and rare, severe epilepsies, and shows that the variants responsible for epilepsy risk are exceptionally rare in the general population. Our results suggest that the emerging paradigm of targeting of treatments to the genetic cause in rare devastating epilepsies might also extend to a proportion of common epilepsies. These findings might allow clinicians to broadly explain the cause of these syndromes to patients, and lay the foundation for possible precision treatments in the future.

Funding National Institute of Neurological Disorders and Stroke (NINDS), and Epilepsy Research UK.

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How has DNA Sequencing contributed to the understanding and treatment of epilepsy?