4-2024

The analysis of NOTCH3 Gene Variants in CADASIL

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ABSTRACT

Autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a vascular disease. Patients diagnosed with CADASIL have experienced migraines with an aura. Auras are the causes of sensory disturbances in the body. Sensitivity to light, and temporary to full loss of vision are some of the many symptoms. The extreme migraine pain usually comes after an aura has occurred. Patients with CADASIL also have an increased risk of an ischemic stroke with lacunar syndrome. The purpose of this study is to identify gene variants associated with CADASIL. Simple ClinVar analysis was used to identify genes associated with this disease phenotype. NOTCH3 was identified to be associated with CADASIL. NOTCH3 is a single-pass transmembrane receptor, that has a crucial role in proper vascular smooth muscle cell development and maintenance. Computational analysis tools, such as SIFT and PolyPhen2, were used to help identify gene variants. Missense mutation analysis by SIFT and PolyPhen2 shows that Arg169Cys is predicted to be pathogenic and damaging to protein structure. Expression analysis shows that NOTCH3 is mostly expressed in the arteries. CADASIL is one of the most common causes of inherited strokes and migraines with aura in adults. The goal of this study is to provide research to the medical community and potentially treat and prevent this condition.

INTRODUCTION

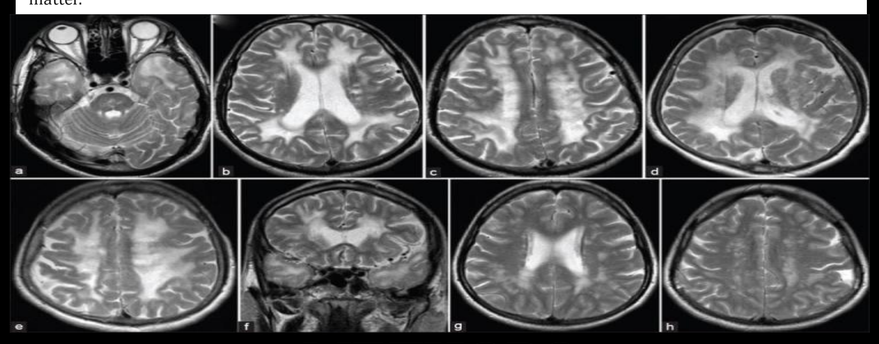
Autosomal dominant cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a vascular disease that is identified by many things. The main two diseases are recurring strokes along with strong migraines. About 40% of patients diagnosed with CADASIL have experienced migraines with an aura. Migraines with aura(MA), and Migraines without an aura(MO) are the two distinct types of migraines. These auras come before the migraine itself and causes sensory disturbances. Studies have showed an increase in white matter hyperintensities on brain MRI along with inherited strokes. There are four Notch receptors that mammals have (Notch1, Notch2, Notch3, Notch4). These pathways have an important role in the expression of its target genes through activation by its ligands, translocation, and post-translational modifications. NOTCH3 protein is very important to the survival and activity of the vascular smooth muscles. It controls the volume of the blood vessels along with the local blood pressure. The mutation of the NOTCH3 gene causes the CADASIL disease.

When small perforating cerebral arteries are most effected with a collection of granular and osmophili substances that are contained in vascular smooth muscle cell membranes (VSMC). The expansion of the extracellular matrix is not expressed to the regular tension within the arteries. VSMC slowly begin to degenerate with mural fibrosis. Stenosis begins in the distal segment of the medullary arteries causing the cerebral vessels begin to lose autoregulation. This process results in small infarcts within the white and deep grey matter along with the pons. White Matter Hyperintensities is the first imaging signs of CADASIL, and are usually found in the periventricular regions.

T2-Weighted Images

1. (b,d,g) Figures show axial T2-weighted images show periventricular hyperintensities.

2. (c,e,h) Figures show axial T2-weighted images show hyperintensities in the deep white matter.

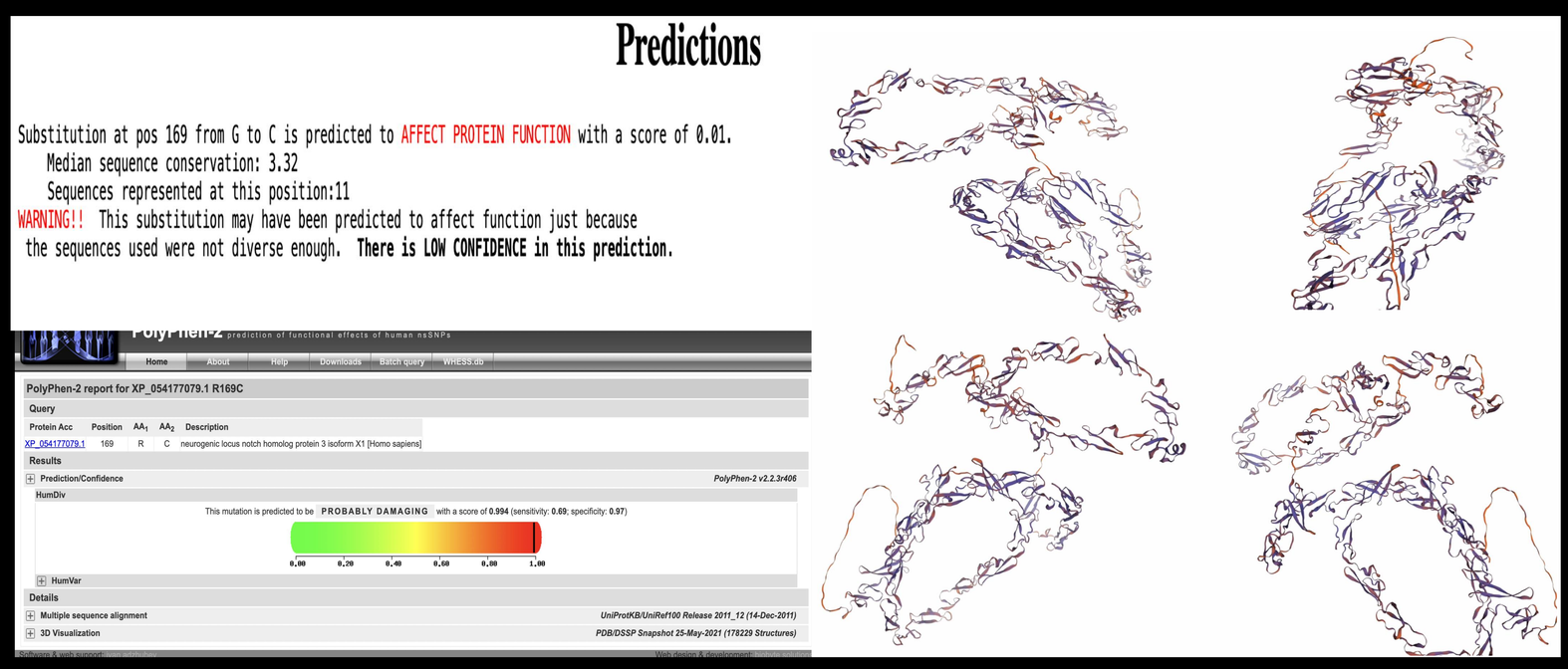


METHODS

Methods that were used to preform this study include Simple-ClinVar, SIFT, PolyPhen2, SWISS Modeling, and a literature search. These tools and methods were used to determine the function, the pathogenicity, structure and the role of causing disease.

- Simple-Clin Var was used to explore genes that are associated with CADASIL and then used to explore mutations that contribute the rise of CADASIL.
- ☐Clin Var was used to examine the conserved domains of the proteins.
- ☐SIFT and PolyPhen2 were used to analyze and test the pathogenicity of the gene mutations.
- ☐SWISS Modeling was utilized to explore the structure of the proteins the NOTCH3 genes code for.
- A literature search was performed to learn more about cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and the roles of the NOTCH3 gene

RESULTS



Conserved Domains of NOTCH3

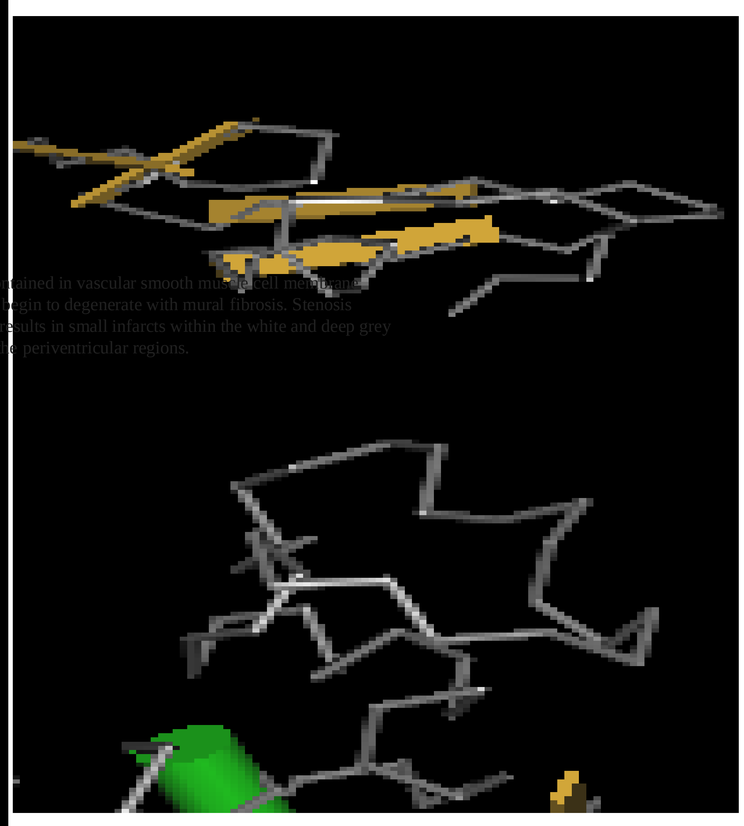


Figure 1.The LNR (Lin-12/Notch repeat) domain is found in three tandem copies in Notch related proteins. The structure of the domain has been determined by NMR and was shown to contain three disulfide bonds and coordinate a calcium ion. Three repeats are also found in the PAPP-A peptidase.

Figure 2. Calcium-binding EGF-like domain, present in a large number of membrane-bound and extracellular (mostly animal) proteins. Many of these proteins require calcium for their biological function and calcium-binding sites have been found to be located at the N-terminus of particular EGF-like domains; calcium-binding may be crucial for numerous protein-protein interactions. Six conserved core cysteines form three disulfide bridges as in non calcium-binding EGF domains, whose structures are very similar. EGF_CA can be found in tandem repeat arrangements.

DISCUSSION AND CONCLUSION

In conclusion, results showed that the NOTH3 gene has a primary play in the development of CADASIL. The results from the Computational analysis data, Arg169Cys mutation is predicted to be pathogenic and damaging to protein structure. This specific mutation functional disruption the protein and caused it to malfunction. Arg169Cys mutation in NOTCH3 protein caused problems within the vascular smooth muscles which led to CADASIL disease.

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ACKNOWLEDGEMENTS

This research was supported by the Oakwood University Biology Department, the HudsonAlpha, and MSEIP-iSTEM.

HudsonAlpha Institute for Biotechnology
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