Determining the clinical epidemiology, genetic architecture, and sex-differences in psychogenic nonepileptic seizures

S. Goleva[1,2,3], C. Leu[4], Y.-C. Feng[5], S. Venkatesh[6,7], G. Voloudakis[6,7], A. D. Borglum[8,9,10], P. Roussos[6,7], J. W. Smoller[5], D. Lal[4], L. K. Davis[2,3,1]

[1]Vanderbilt University, [2]Vanderbilt University Medical Center, [3]Vanderbilt Genetics Institute, [4]Lerner Research Institute Cleveland Clinic, [5]Massachusetts Gen Hosp, [6]James J. Peters VA Medical Center, [7]Icahn School of Medicine at Mount Sinai, [8]iPSYCH, [9]Aarhus University

Abstract

Background: Psychogenic nonepileptic seizures (PNES) are paroxysmal episodes clinically similar to epileptic seizures with no aberrant brain signaling.

Methods: We have conducted a multi-site PNES GWAS meta-analysis, which is also the first PNES GWAS reported to date.

Results: PNES has a heritability of 7.2% and 6 SNPs exceeded genome-wide significance, including the neuronal gene SYN3.

Conclusions: We determined the narrow sense heritability of PNES and identified variants and genes associated with PNES.

Introduction

Psychogenic nonepileptic seizures (PNES) are paroxysmal episodes clinically similar to epileptic seizures with no aberrant brain signaling. PNES is related to psychiatric distress and around 75% are female.

We recently developed an algorithm (Figure 1) to characterize the clinical epidemiology of a PNES patient population observed at Vanderbilt University Medical Center (VUMC; 0.14% prevalence).[1] We corroborated previously reported and identified novel associations, including post-traumatic stress disorder, sexual assault trauma, and cerebrovascular disease.

Methods

We have conducted a multi-site PNES GWAS meta-analysis, which is also the first PNES GWAS reported to date. Results in-hand include cases and controls identified from our BioVU samples, the Cleveland Clinic, the Million Veterans Program, Massachusetts General BioBank (MGBB), and Mt. Sinai, resulting in n=1,482 cases and 437,800 controls. The sites used SAIGE, Bolt-LMM, Plink, Saige, and Saige, respectively to perform the analyses. Then, all five summary statistics were meta-analyzed using Metal. We used LDSC to calculate the heritability of PNES.

Results

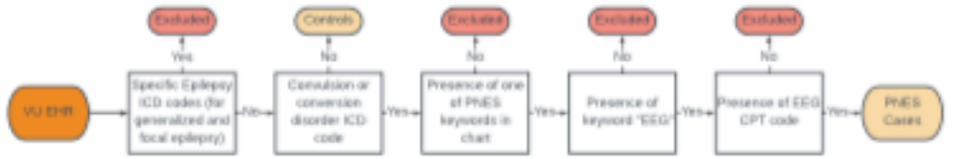

Fig 1. Automated phenotyping algorithm used to identify PNES patients in the BioVU biobank

Using LDSC, we calculated the heritability of PNES to be 0.072 (SE = 0.0008). 6 SNPs exceeded genome-wide significance threshold - rs35250557 (associated gene SYN3), rs187064156 , rs74182007 (associated gene LINC01730), rs3121800, rs73005268, and rs78997133. SYN3 encodes neuronal phosphoproteins and has previously been associated with several neuropsychiatric diseases, including visual epilepsy and schizophrenia.

Figure 1: Manhattan plot of PNES meta-analysis p-values

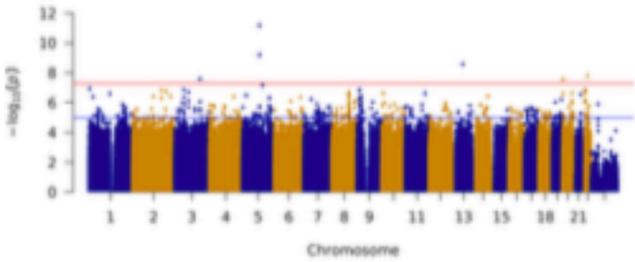

Fig 2. Manhattan plot of meta-analysis results. Blue horizontal line is suggested significance level, while the red line is the genome wide significance level (p<5e-08).

Figure 2: QQ plot of PNES meta-analysis p-values

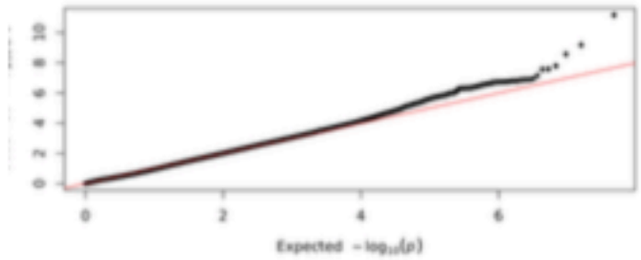

Fig 3. A QQ-plot of the association of SNPs with psychogenic nonepileptic seizure patients that were meta-analyzed.

Marker Name	A1	A2	Freq1	Beta	SE	P value	Direction	Het I2	Het P-val	Gene
rs187064156	t	g	0.02	0.04	0.006	6.59E-12	??-?+	24.3	0.25	
rs78997133	a	c	0.02	0.04	0.006	6.36E-10	??-+	68.0	0.04	
rs3121800	t	c	0.08	0.02	0.003	2.66E-09	????+	0.0	1	
rs35250557	t	c	0.98	-0.01	0.003	1.57E-08	+-+-+	61.2	0.04	SYN3
rs73005268	t	c	0.002	1.34	0.24	2.57E-08	??+-?	70.4	0.07	
rs74182007	a	t	0.98	-0.04	0.007	2.71E-08	???-	0.0	0.97	LINC01730

Table 1. Genome wide significant SNPs. Included is each SNP's frequency, effect size, standard error, meta analysis p value, site-specific direction of effect, heterogeneity I^2 value, and heterogeneity p value.

Conclusions

- PNES is heritable and larger sample sizes are needed to robustly identify associated variants.

References: 1) Goleva SB et al, 2020 (under review).