KIR3DL1*004 is Associated with PANS (Pediatric Acute-Onset Neuropsychiatric Syndrome)

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Introduction

PANS is a relatively-recently described condition in which children exhibit rapid onset of inexplicable OCD-like behaviors, restrictive-dieting, anxiety, depression, memory deficits, and sleep disorders (Figure 1). PANS has been observed primarily in patients who have had a recent, prior infection of the upper respiratory tract, typically streptococcal infection. The diagnosis is made when symptoms are not better explained by known neurological or medical disorders such as Sydnham's Chorea or Autoimmune Encephalitis. The majority of PANS patients have a 1st degree family member with an inflammatory or autoimmune disease and inflammation of the basal ganglia, a major center for cognitive and motor function in the brain, has been observed at disease onset. Due to the evident immunopathology involved in PANS, the elucidation of the role of HLA and KIR could help us better understand the immunological mechanisms of this little-understood disease.

In this study, we analyzed six HLA loci and related KIR loci in a cohort of PANS patients of European ancestry.

Methods

We used custom NGS methods on the Illumina platform including targeted enrichment with hybrid-capture probes to target six HLA loci. We performed allele-level and amino acid level analysis of 172 samples (Figure 2) from PANS patients of European ancestry at 2 field resolution. Amino acid-level analysis of HLA-B indicated a strong signal at position 80-I, implicating the Bw4 epitope. From the initial dataset, we conducted custom NGS of 164 samples (Figure 2) using targeted enrichment with a panel adapted from the Norman lab to target 13 KIR loci with a focus on KIR3DL1 and completed genotyping using PING. We considered the interaction between KIR3DL1 with HLA-Bw4 and Bw4i at the allele level in a logistic regression model in which we included sex as a covariate.

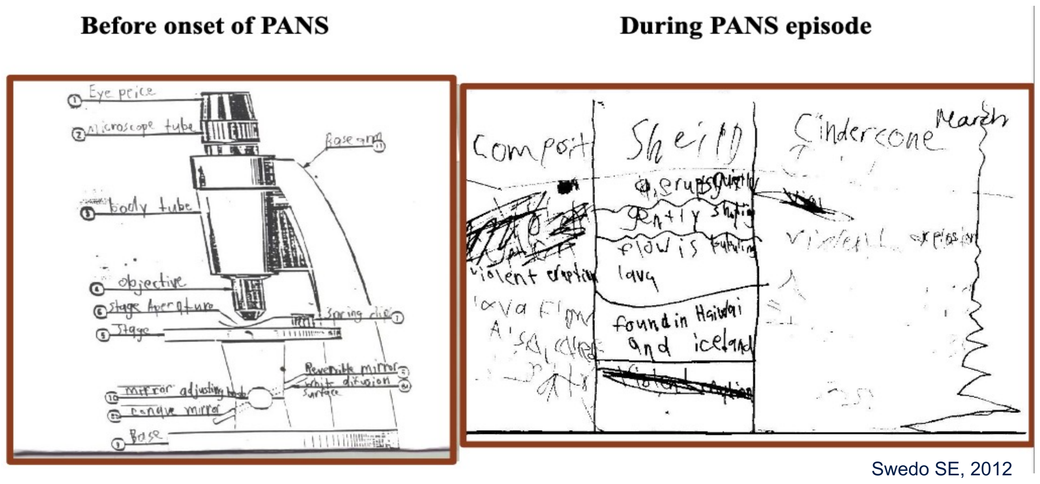

Figure 1. Drawings produced by the same patient before and after onset of a PANS episode

HLA Analysis

	Cases (n=172)	Controls (n=2026)
Male	108 (63%)	883 (43%)
Female	64 (37%)	1143 (57%)

KIR Analysis

	Cases (n=164)	Controls (n=1664)
Male	104 (63%)	563 (42%)
Female	60 (37%)	801 (58%)

Figure 2. Datasets for HLA analysis and subsequent KIR analysis including PANS patients with self-reported European ancestry

Results

The strongest effect was observed at HLA-B position 80-I (Isoleucine) (P = 6.7 x 10-5, OR = 2.00, 95% CI = 0.35, 1.03) along with the remaining positions (81-83) that define the Bw4 epitope (Figure 3). Given its role as ligand, we next sequenced KIR3DL1 at allelic resolution and found a strong risk signal for KIR3DL1*004 in the presence of HLA-Bw4i (P = 5.74 x 10-4, OR = 2.23, 95% CI = 0.34, 1.26) (Figure 4). Of the inhibitory KIR3DL1 receptors, the 004 allotype is unusual as it manifests as a misfolded yet stable protein that is known to bind the HLA-Bw4 epitope with increased affinity, although the precise functional interaction remains unclear.

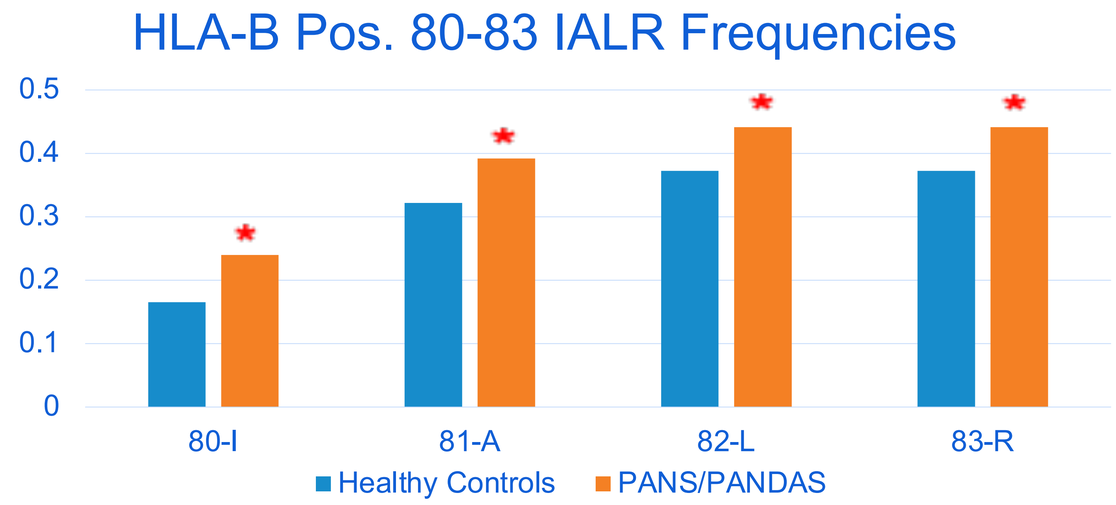

Figure 3. Bw4 epitope amino acid frequencies

Positions 77-83 of HLA-B define the Bw4 epitope which is located on the alpha 1 helix of HLA. The IALR sequence at positions 80-83 is the most common Bw4 amino acid motif. The Bw4 isoform with Isoleucine at position 80 has been shown to increase binding affinity to KIR3DL1.

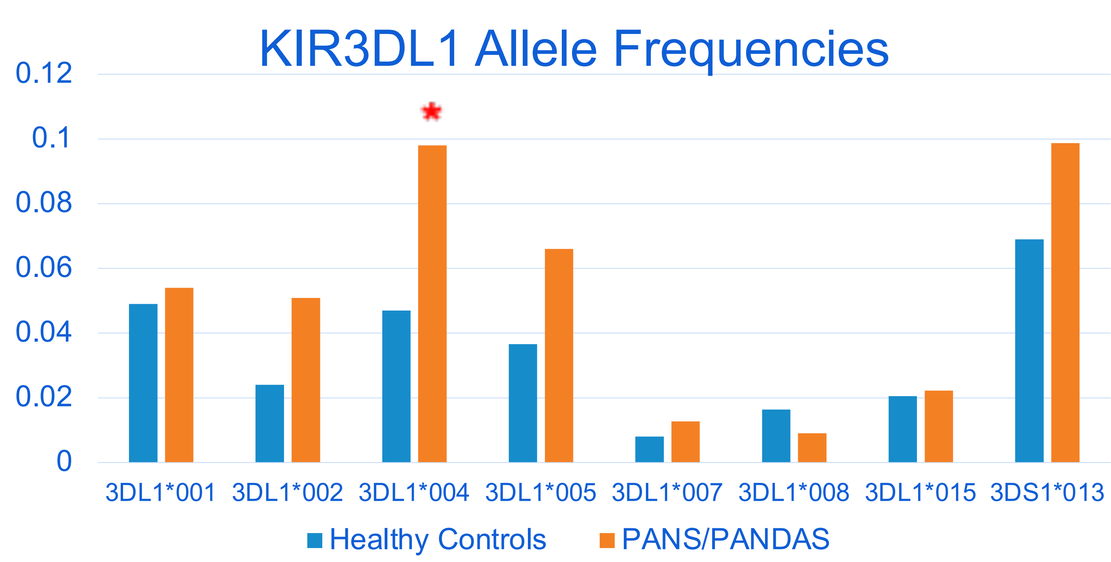

Figure 4. KIR3DL1 allele frequencies in the presence of Bw4i

KIR3DL1*004 is an unusual allele that encodes a misfolded protein and thus is retained in the endoplasmic reticulum of the cell. Very low surface expression of this receptor has been observed.

Conclusion

Our results provide strong evidence for a role of KIR-HLA interaction in PANS, suggesting the involvement of NK-mediated immunopathology in this enigmatic pediatric neurological disease.