Genetic landscape of opsoclonus myoclonus ataxia syndrome in children

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Background

- Only 3% of pediatric patients with neuroblastoma develop OMAS
- Two studies have also demonstrated that a higher percentage of parents of children with OMAS have an autoimmune disease compared to controls
- These findings suggest that other factors, which may include genetic background, contribute to the development of OMAS
- Rare monogenic neurological disorders involving immunological (*TREX1*, *RNASEH2B*) or non-immunological (*KCTD7*, *SLC2A1*, *SGCE*) mechanisms have also been reported to mimic OMAS

Krasenbrink I, et al; Santoro JD, et al; Alburaiky S, et al; Blumkin L, et al; Appavu B, et al; Drivenes B, et al

Background

- Prior genetic studies in OMAS have been limited
- In one study, low resolution human leukocyte antigen (HLA) typing by PCR for loci A, B and DRB1 in 43 children with OMAS (21 with neuroblastoma) and 100 healthy controls showed a higher percentage of patients with *HLA-DRB1*01* compared to controls
- Another study which inferred HLA types from tumor derived transcriptome data showed a higher frequency of *HLA-DRB1*01* and *HLA-DOB*01:01* in OMAS with NB compared to NB without OMAS, but did not include patients with OMAS without NB

Hero B, et al; Rosenberg MI, et al

Human leukocyte antigen

- Main genetic risk factor for autoimmune disorders
- Most dense and diverse region of the human genome
- Divided into 3 regions: classes I-III
  - Class I: A, B and C
  - Class II: DP, DQ, DR (and also DO)
- Class II genes encode for the α or β chains of the class II HLA molecule and contain peptide-binding groove

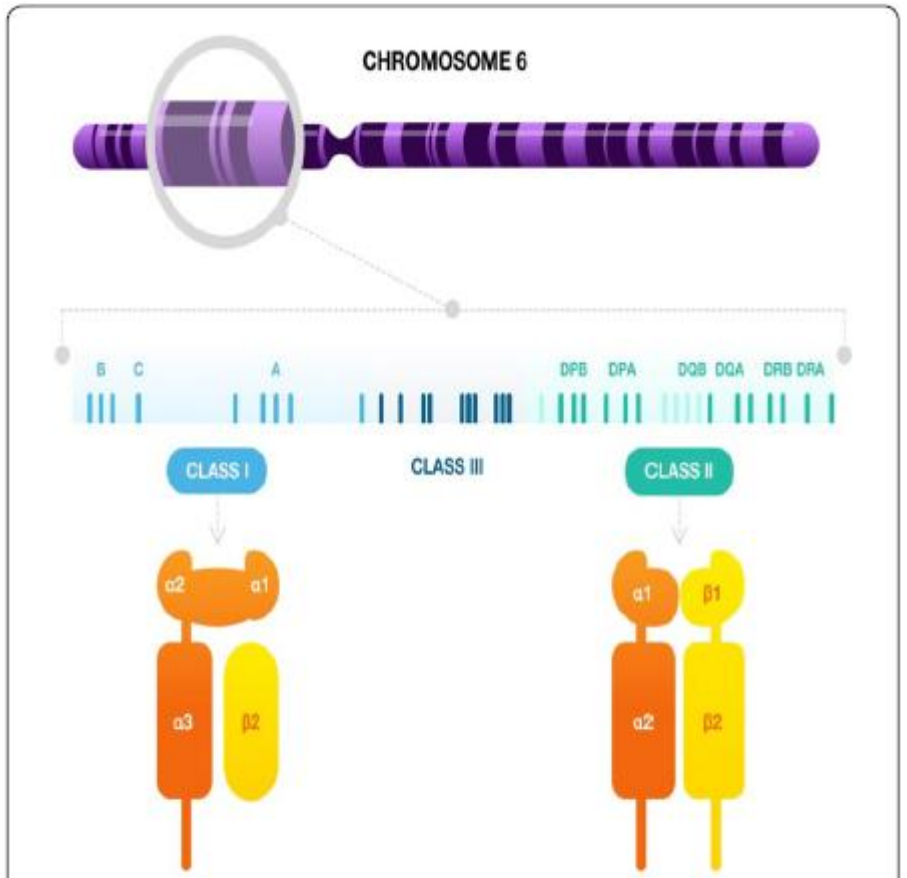

Fig. 1 HLA-complex on chromosome 6, showing the main class I and II HLA genes (top). Structure of class I (bottom left) and class II (bottom right) HLA molecules. The alpha chain of class I molecule has three domains (α1–3) and includes the peptide-binding groove. The β2-microglobulin (β2) is not encoded by HLA genes. The class II molecules are made up of one alpha and one beta chain that each contains two domains (α1, α2, β1, β2); both form the peptide-binding groove

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Class II HLA molecules

- Only present in antigen presenting cells (dendritic cells, macrophages and B cells)
- Present peptides from extracellular proteins to CD4+ T-cells
- Also plays a role in elimination of autoreactive T cells in the thymus
- Association with numerous autoimmune disorders including type I diabetes, multiple sclerosis, rheumatoid arthritis and others
- Recently described associations with multiple different antibody mediated autoimmune neurological disorders

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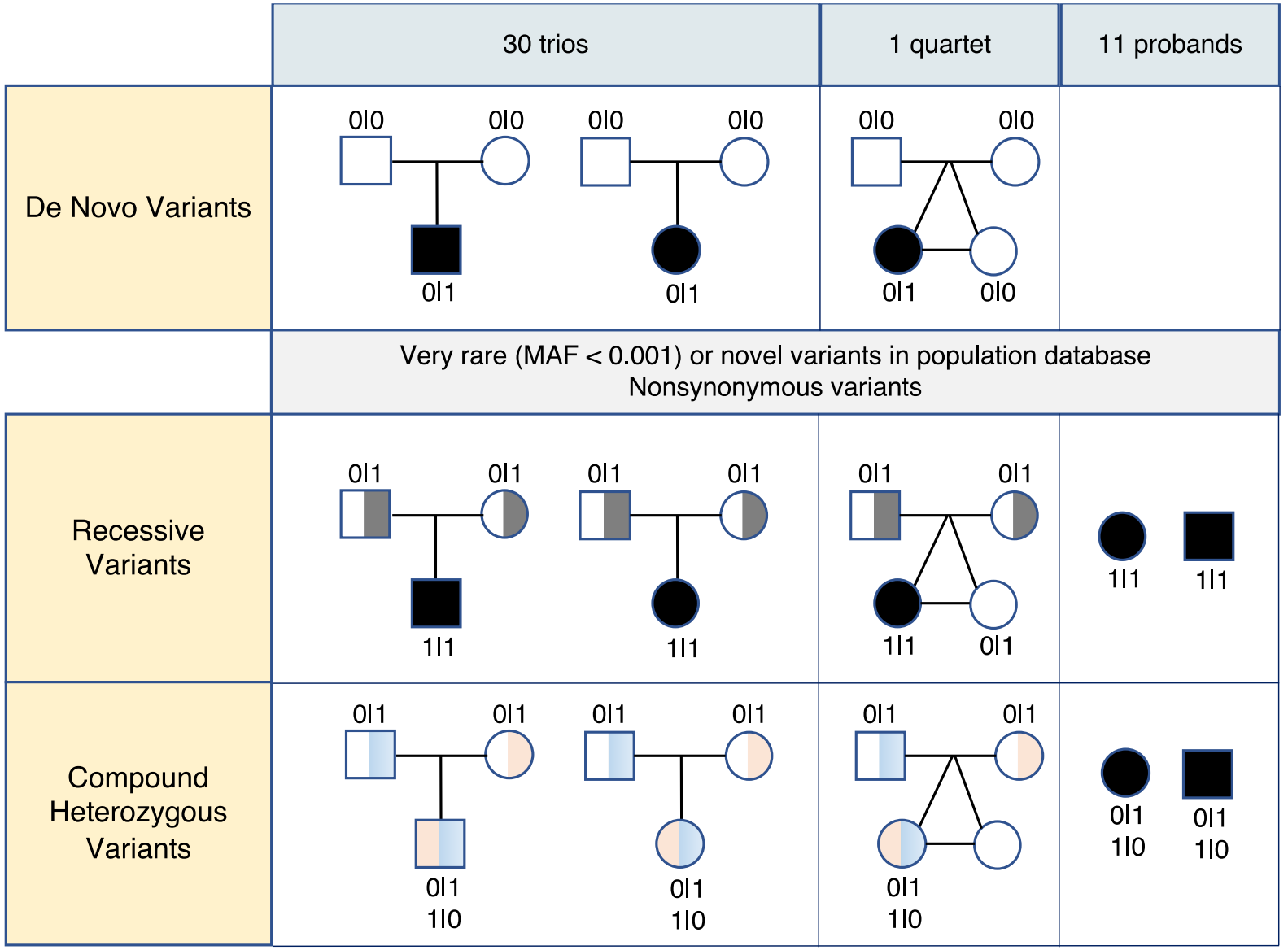
Methods

- Patients with OMAS (defined by Genoa criteria) with age of onset ≤ 18 years (1992-2017) and their biological parents (when available) were identified prospectively and/or through medical records text search at Boston Children's Hospital and enrolled between April 2018 and October 2019
- Final cohort included 30 complete trios, 1 quartet (including an unaffected twin sibling), and 11 independent probands (total 105)
- Genomic DNA was extracted from blood or saliva, sequenced using a third generation linked-read protocol and analyzed using the 10x Genomics Long Ranger analysis pipeline (v2.2.2)


30 trios
1 quartet
11 probands
De Novo Variants
0|0
0|1
Very rare (MAF < 0.001) or novel variants in population database
Nonsynonymous variants
Recessive Variants
1|1
Compound Heterozygous Variants
1|0

Methods

- De novo variant candidates were confirmed with Sanger sequencing
- High-resolution haplotyping of class I and II HLA regions was conducted using HLA-HD (version 1.3.0)

	Entire Cohort (n = 42)
Age of onset (months)	28.4 ± 22.7
Age at diagnosis (months)	35.7 ± 29.9
Sex (n female, % female)	23 (54.8%)
Race/Ethnicity	
Caucasian	28 (66.7%)
African American	1 (2.4%)
Asian	2 (4.8%)
Hispanic (Caucasian)	3 (7.1%)
Native Hawaiian/Islander	1 (2.4%)
Not Recorded	7 (16.6%)
Tumor Identified	23 (54.8%)
Clinical Course	
Monophasic	10 (23.8%)
Multiphasic (relapsing)	32 (76.8%)
Brain MRI available	39 (92.8%)
Atrophy present	5 (12.8%)
Family History of Autoimmunity	16 (38.1%)

Results

- In nine patients out of 31 families (29.0%), a total of 12 DNVs were confirmed via Sanger sequencing, and three patients had two DNVs
- However, no gene with recurrent DNVs across probands was found
- Several DNVs were found in genes highly expressed in the brain, but the clinical phenotypes linked to mutations in these genes are either undocumented or associated with autosomal recessive inheritance
- Of these, a protein-truncating DNV in the *CACNA2D2* gene (p.Gly950AlafsTer66) was the most notable due to its high expression level in the cerebellum and the reported association of ataxia with recessive mutations in this gene

Results

- No definitive disease-causing recessive or compound heterozygote mutations were identified

Results

- *HLA-DRB1*01* haplotype was found in 27 of 84 (32.1%) alleles in probands
  - Similar to the previously reported rate in patients with OMAS (30/86, 35%; Chi square p=0.69) and higher than the rate in controls in the prior publication (21/200, 10.5%; Chi-square test, p <0.0001)
  - No significant difference between those with and without NB in our cohort
- *HLA-DOB*01:01* haplotype was found in 72 of 84 (85.7%) alleles in probands
  - Higher than the previously reported rate in patients with OMAS (63%) and NB without OMAS (36%)
  - No significant difference between those with and without NB in our cohort

	BCH			Rosenberg et al		Hero			
		NB+	NB-	NB+	NB+ OMAS-		NB+	NB-	Controls
N	42	23	19	38	26	43	21	22	100
DRB1*01:01	0.32			0.2	0.09	0.35			0.21
		0.30	0.34				0.29	0.41	
DOB*01:01	0.86			0.63	0.36		-	-	-
		0.83	0.89						

Monogenic mimic

- During the study period, a 3-year-old patient previously diagnosed with OMAS at an outside institution was evaluated for a second opinion
- Given the early onset of abnormal eye movements at 2 months and subsequent development of epilepsy, a monogenic mimic of OMAS was suspected
- This was clinically confirmed as glucose transporter deficiency, attributed to a mutation in the *SLC2A1* gene

Conclusions

- We did not identify any recurrent DNVs in the same gene, suggesting that there is not a monogenic cause for OMAS
- During the study period, we clinically identified one patient with glucose transporter deficiency (*SLC2A1* gene) but did not identify any unsuspected monogenic mimics
- Therefore, we recommend clinical application of WES or WGS only in patients with atypical features of OMAS including
  - Age of onset less than 6 months old
  - Epilepsy
  - Pre-existing developmental delay

Conclusions

- We confirm two prior studies suggesting that the allele frequency of *HLA-DRB1*01* may be higher in OMAS than the general population
  - *HLA-DRB1*01* has been implicated in other autoimmune disorders including rheumatoid arthritis, juvenile idiopathic arthritis, and Henoch-Schönlein purpura
- We also confirm a high allele frequency of *HLA-DOB*01:01* in OMAS and extend this finding to include those without NB
  - HLA associations in other paraneoplastic neurological disorders such as anti-LGI1 encephalitis

Karami J, et al; De Silvestri A, et al; Gonzalez-Gay MA, et al

Limitations and strengths

- Limitations
  - Relatively small sample size
  - Did not include patients for whom OMAS was on the differential diagnosis but not confirmed as final clinical diagnosis
  - Lack of in-study control group for *HLA* analyses
- Strengths
  - First WGS of OMAS
  - Carefully diagnosed cohort
  - Utilization of third-generation linked-reads sequencing technique which enabled precise high-resolution HLA typing

OMAS disease framework

- Pathogenesis of OMAS likely involves polygenic predisposition, including *HLA-DRB1*01* and *HLA-DOB*01:01*, combined with as yet unidentified additional genetic and environmental risk factors

Future directions

- Assess the allele frequency of *HLA-DRB1*01* and *HLA-DOB*01:01* in patients with OMAS both with and without NB compared to healthy and disease (NB without OMAS) controls to determine if they are genetic risk factors for OMAS
  - Are there existing available cohorts of patients with NB without OMAS who have undergone genetic testing to allow for HLA comparisons?
- Genome wide association studies (GWAS) to identify other genetic risk factors may be challenging given the typically small relative risk contributions of genes identified in GWAS, the large samples sizes required, and the rarity of OMAS