Journal of Neurology (2022) 269:6512–6529
https://doi.org/10.1007/s00415-022-11325-2

ORIGINAL COMMUNICATION

Association of rare variants in genes of immune regulation with pediatric autoimmune CNS diseases

Saba Jafarpour[1] · Abhik Banerjee[2] · Natalie K. Boyd[1] · Benjamin N. Vogel[2] · Kelli C. Paulsen[1] · Nusrat Ahsan[1,3] · Wendy G. Mitchell[1,3] · Shafali S. Jeste[1,3] · Jonathan D. Santoro[1,3,4]

Received: 26 June 2022 / Revised: 2 August 2022 / Accepted: 3 August 2022 / Published online: 12 August 2022

Abstract

Background There is a gap in the literature regarding genetic underpinnings of pediatric autoimmune CNS diseases. This study explored rare gene variants implicated in immune dysregulation within these disorders.

Methods This was a single-center observational study of children with inflammatory CNS disorder who had genetic testing through next generation focused exome sequencing targeting 155 genes associated with innate or adaptive immunity. For in silico prediction of functional effects of single-nucleotide variants, Polymorphism Phenotyping v2, and Sorting Intolerant from Tolerant were used, and Combined Annotation Dependent Depletion (CADD) scores were calculated. Identified genes were analyzed using Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

Results Of 54 patients, 42 (77.8%) carried variant(s), among which 12 (22.2%) had 3–8 variants. Eighty-eight unique single-nucleotide variants of 55 genes were identified. The most variants were detected in *UNC13D, LRBA, LYST, NOD2, DOCK8, RNASEH2A, STAT5B, and AIRE*. The majority of variants (62, 70.4%) had CADD > 10. KEGG pathway analysis revealed seven genes associated with primary immunodeficiency (Benjamini $1.40E-06$), six genes with NOD-like receptor signaling (Benjamini $4.10E-04$), five genes with Inflammatory Bowel Disease (Benjamini $9.80E-03$), and five genes with NF-kappa B signaling pathway (Benjamini $1.90E-02$).

Discussion We observed a high rate of identification of rare and low-frequency variants in immune regulatory genes in pediatric neuroinflammatory CNS disorders. We identified 88 unique single-nucleotide variants of 55 genes with pathway analysis revealing an enrichment of NOD2-receptor signaling, consistent with involvement of the pathway within other autoinflammatory conditions and warranting further investigation.

Keywords Autoimmune · Neuroinflammatory · Demyelinating · Genetics · Variants of unknown significance · Next-generation sequencing

Introduction

Autoimmune and neuroinflammatory central nervous system (CNS) disorders are being increasingly recognized in children as a complex group of disorders with a wide range of clinical manifestations [1]. The genetic basis of inflammatory disorders of the CNS remains largely unknown, and among these, multiple sclerosis (MS) has been the most widely investigated. Studies of MS genetic predisposition have historically focused on identifying common variants or single-nucleotide polymorphisms (SNPs) that are associated with increased risk of developing the disease. Genome-wide association studies (GWAS) have uncovered more than 230 such SNPs [2, 3]. Of the hundreds of susceptibility genetic loci implicated in MS, the Major Histocompatibility

✉ Jonathan D. Santoro
santoroj@usc.edu

1 Children's Hospital Los Angeles, Los Angeles, CA, USA

2 Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

3 Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

4 Division of Neurology, Children's Hospital Los Angeles, 4650 Sunset Blvd., MS82, Los Angeles, CA 90027, USA

Complex (MHC) locus constitutes the largest component of genetic risk [4]. Studies have shown that roughly 20% of MS heritability is explained by common variants from GWAS, while 5% are explained by coding, rare variants that are not identified through GWAS. Despite all efforts, 75% of MS is still unexplained, which underscores the remarkable genetic complexity of these conditions [3].

Many genes implicated in autoimmune and inflammatory disorders are pleotropic. Nearly a third of the genetic variants associated with MS also have been reported in other autoimmune diseases, and studies of multiple, different autoimmune diseases has shown that almost two-thirds of loci are shared between these diseases [4–6]. Identification of rare variants associated with different conditions could shed light on pathophysiologic mechanisms underlying these diseases.

Considering the sparsity of literature, especially in pediatric patient populations, the authors sought to explore rare variants of genes implicated in immune dysregulation in pediatric autoimmune and inflammatory CNS disorders.

Methods

Patient population

IRB approval was obtained through Children's Hospital Los Angeles and University of Southern California. Patients were identified by auditing individuals evaluated in the Pediatric Neuroimmunology and Demyelinating Disorders Program at Children's Hospital Los Angeles between July 2019 and December 2021 who had genetic testing. Inclusion criteria were (1) patients were < 21 years of age at the time of first neuroinflammatory attack or clinical presentation and (2) had a confirmed neuroinflammatory disorder per the senior author, a fellowship trained pediatric neuroimmunologist (JS). Diagnostic criteria varied for each condition (e.g., McDonald's 2017 or International Pediatric Multiple Sclerosis Study Group 2013 criteria for MS) although were considered standard of care for the condition assessed. Diagnosis was subsequently verified by a second pediatric-trained neuroimmunologist (NA). There were no exclusion criteria and all individuals with genetic testing as defined below were enrolled. As this study was retrospective in nature, consent and assent were waived.

Study design

Individuals meeting inclusion criteria had to have undergone genetic testing with either whole exome sequencing or a focused exome sequencing study (e.g., commercial autoinflammatory and autoimmunity syndromes panel) which was obtained for clinical purposes. Institutionally, all patients are advised to have genetic testing performed following confirmatory diagnosis of a neuroinflammatory condition, limiting severity bias. All studies were completed at the same laboratory.

Demographic data were obtained through chart review. Patient characteristics included age (at the time when results of genetic studies were obtained), sex, race, ethnicity (Hispanic/Latino vs. non-Hispanic/Latino), and clinical diagnosis.

Autoimmune and inflammatory CNS disorders include the following categories: demyelinating brain and spinal cord disorders, immune-mediated encephalopathies or encephalitis, systemic autoimmune conditions with CNS manifestations, CNS vasculitis, and neurodegenerative and genetic conditions with immune-mediated pathophysiology [1].

Next-generation sequencing and bioinformatic analysis

Next-generation sequencing was performed using a focused exome analysis targeting 155 genes associated with primary disorders of innate or adaptive immunity. In some patients, an additional 37 genes implicated in autoimmunity were tested when clinically indicated (atypical or severe presentations). Additional gene testing was never reflexive (added on when the initial panels were negative) and was only ordered at the time of the initial panel. These panels are designed to identify monogenic autoinflammatory syndromes, monogenic autoimmunity, periodic fever syndromes, familial cold autoinflammatory syndromes, familial Mediterranean fever, and monogenic inflammatory bowel disease. The list of genes included in the panels and relevant transcript(s) are included in the supplementary material (Appendix 1). Online Mendelian Inheritance in Man (OMIM®) database was used to identify the reported associated conditions and inheritance pattern.

Single nucleotide variants, exon-level deletions, coding exons duplications, and 10–20 base pair mutations of adjacent intronic sequences were reported [6]. The Single Nucleotide Polymorphism Database (dbSNP) reference SNP ID number (rs number) was reported when available. Variant frequencies were obtained using population frequency databases including the Genome Aggregation Database (gnomAD v.2.1.1) and Exome Aggregation Consortium (ExAC).

For in silico prediction of variant functional effects, we used Polymorphism Phenotyping v2 (PolyPhen-2), and

Sorting Intolerant from Tolerant (SIFT) with Genome Reference Consortium Human Build 37 (GRCh37/hg19) assembly input. Combined Annotation Dependent Depletion (CADD) scores were calculated using the GRCh37-v1.6 model.

Pathway analysis

To perform Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis using clinical diagnosis gene lists, lists of gene names were first imported into the NIAID/NIH Database for Annotation, Visualization and Integrated Discovery (DAVID) Bioinformatics Resources v.6.8 Analysis Wizard Tool. "OFFICIAL_GENE_SYMBOL" was selected in the Identifier field, Homo sapiens was inputted within the Species field, and "Gene List" was selected under List Type. Next, the imported gene list was analyzed using the DAVID Functional Annotation Tool set, specifically looking within the "Pathway" and "KEGG_Pathway" tools [7, 8].

Burden test analysis

This study assessed gene-based contribution of variants of unknown significance via weighted sum statistics (WSS) burden test[9] and the variance component C-alpha test [10], using previously established methods [11]. To assess the aggregate contribution of multiple rare genes in the disease processes studied, the authors performed burden testing analysis using high confidence variants and potentially pathogenic variants based on MAF or protein-prediction algorithms. Variants were identified by literature driven review in multiple sclerosis as other, more rare disorders, did not have sufficient genetic investigation to warrant phenotype/genotype differentiation [11–13]. Variants meeting criteria were considered qualifying variants and were applied in Test Rare vAriants with Public Data (TRAPD)[14] as a pathogenicity filter and subsequently analyzed against the gnomeAD database.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of patients included in this study. For KEGG pathway analysis, p values and Benjamini corrections were calculated. Benjamini values of < 0.05 were considered statistically significant. Analyses were performed using DAVID Bioinformatics Resources 6.8. For burden test analysis, the freely available TRAPD program was utilized. Data were reformatted to python format for conversion.

Results

We identified 54 patients with pediatric-onset autoimmune CNS disorders in whom autoimmune and autoinflammatory panels were obtained out of a total of 174 eligible patients (31%). The most frequent reasons for not having testing were: insurance denial ($n = 103/120$, 86%), family or patient declining testing ($n = 10/120$, 8%), and delays in obtaining testing at the time of study ($n = 7/120$, 6%). Of note, insurance denials were primarily commercial payors ($n = 69/103$, 67%) as opposed to state or federal payors ($n = 34/103$, 33%). Enrolled patients had higher rates of state or federal payors as a primary insurance ($n = 40/54$, 74%) which was significant different ($p < 0.001$, 95% CI 0.08–0.36) compared to excluded patients. The mean age was 13.4 ± 5.31 years and 55% were female. Demographics and clinical diagnosis of patients are listed in Table 1.

Table 1 Demographics and clinical diagnosis

Age	Mean (year)	13.4 ± 5.31
Sex (*n*, %)	Male	24 (44.4%)
	Female	30 (55.6%)
Ethnicity (*n*, %)	Hispanic/Latino	27 (50.0%)
	Not Hispanic/Latino	11 (20.4%)
	Not reported	16 (29.6%)
Diagnosis (*n*, %)	MS	15 (27.8%)
	MOGAD	13 (24.0%)
	Autoimmune encephalitis	5 (9.25%)
	CNS vasculitis	3 (5.56%)
	ADEM	2 (3.70%)
	Idiopathic transverse myelitis	2 (3.70%)
	Meningoencephalitis of unknown etiology	2 (3.70%)
	Post-infectious meningoencephalitis	2 (3.70%)
	CIS	1 (1.85%)
	Down syndrome regression disorder	1 (1.85%)
	Hemispheric inflammation	1 (1.85%)
	Inflammatory Stroke	1 (1.85%)
	MFS/Bickerstaff's brainstem encephalitis	1 (1.85%)
	Neuropychiatric SLE	1 (1.85%)
	Neurosarcoidosis	1 (1.85%)
	RIS	1 (1.85%)
	SLE cerebritis	1 (1.85%)
	Susac Syndrome	1 (1.85%)

ADEM acute disseminated encephalomyelitis, *CIS* clinically isolated syndrome, *CNS* central nervous system, *MFS* Miller Fisher syndrome, *MOGAD* myelin oligodendrocyte glycoprotein antibody-associated disease, *MS* multiple sclerosis, *RIS* radiographically isolated syndrome, *SLE* systemic lupus erythematous

Forty-two patients (77.8%) carried variant(s) in immune dysregulation genes, among which 12 (22.2%) had 3–8 variants (Appendix 2). Eighty-eight unique single-nucleotide variants of 55 genes were identified (all heterozygous). Twelve patients (22.2%) had negative results. All variants were unique to each individual, except for two variants of NOD2 (p.Arg702Trp and p.Gly908Arg) that were each shared among two different individuals. The highest number of variants were detected in *UNC13D* (6 variants); *LRBA, LYST,* and *NOD2* (4 variants); and *DOCK8, RNASEH2A, STAT5B,* and *AIRE* (3 variants).

Table 2 lists the gene variants categorized by clinical diagnosis. Two variants were deemed as increased risk alleles [*NOD2* c.2104C > T (p.Arg702Trp) and *NOD2* c.2722G > C (p.Gly908Arg)]. The rest of the variants (86, 97.7%) were classified as VUS. Seventy-seven (87.5%) variants were missense mutations in coding regions, four (4.5%) silent, three (3.4%) intronic, two (2.3%) in non-coding regions, and two (2.3%) resulted in a change in an RNA molecule that does not result in any protein product. Of note, no patients had any abnormalities on the 37 gene "add-on" testing that was performed in a minority (8/54, 15%) of patients.

Most of the variants (85, 96.5%) had an allele frequency of less than 0.1% (MAF < 0.001) in the gnomAD database, including 68 variants (77.2%) < 0.01% (MAF < 0.0001). Fourteen variants (15.9%) were not reported in the gnomAD database.

Mean CADD score was 17.3 ± 9.45 (median 21.4, IQR 9.63–24.6). The majority of variants (62, 70.4%) had CADD score > 10. For seventeen rare variants of 13 genes (*ACP5, ADAR, DEF6, LYST, NLRC4, NOD2, RAB27A, RFXANK, RNASEH2A, SLC7A7, TTC7A, UNC13D, and XIAP*) available results of all platforms were in agreement predicting detrimental effect [deleterious/damaging based on PolyPhen and SIFT, moderate to highly conserved, and CADD > 15 (median 25.9, IQ 25.9–27.5)] (Table 2).

From the KEGG pathway analysis of the aggregated gene lists, seven genes associated with primary immunodeficiency (Benjamini 1.40 $E-06$), six genes with NOD-like receptor signaling pathway (Benjamini 4.10 $E-04$), five genes with inflammatory bowel disease (IBD) (Benjamini 9.80 $E-03$), and five genes with NF-kappa B signaling pathway (Benjamini 1.90$E-02$) (Table 3).

Burden testing analysis of rare variants in our cohort were compared to the gnomAD control database. No single gene in burden testing analysis was noted to be significant after multiple testing corrections ($p = 0.38$) with a similar non-statistically significant c-alpha score ($p = 0.66$).

Discussion

To our knowledge, this is the first study of rare variants of immune regulation genes in a relatively large sample of pediatric patients with autoimmune CNS diseases. Using next-generation sequencing provides insight into rare variants that are not identified by GWAS.

We observed a high rate (77.4%) of identification of rare and low-frequency variants within immune dysregulation genes among pediatric patients with autoimmune CNS disorders. The majority of identified variants had a CADD score > 10, indicating the likelihood to be function-altering. The findings could shed light on pathophysiologic mechanisms of these conditions. Although the cohort-based gene test did not achieve statistical significance after correcting for multiple gene testing, the heterogeneity and small "*n*" in this inception cohort likely limited the ability to detect genes that may have contributed to the phenotypes recorded.

Table 4 lists immune dysregulation conditions associated with the 55 genes harboring the rare variants identified in our study. Several of these genes have been reported to be associated with neurological manifestations. Notably, *TREX1*, *RNASEH2A, ADAR, and IFIH* are among the genes associated with Aicardi–Goutieres syndrome [15]; *STXBP2, UNC13D* are associated with familial hemophagocytic lymphohistiocytosis (FHL) [16], which can cause neuroinflammation in up to 50% of patients [17]. Variants of *NOD2* are most notably known for increased risk of Crohn's disease [18], but are also reported in association with Rasmussen syndrome with CNS granulomatosis [19]. *TNFAIP3* has been reported in association with a granulomatous neuroinflammatory disorder of CNS [20], neuropsychiatric Systemic Lupus Erythematous (SLE) [21], and Neuromyelitis Optica (NMO) [22]. Decreased *TNFAIP3* gene expression was associated with Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) relapse [23]. *LYST* is associated with Chediak-Higashi syndrome, learning disorders, cerebellar deficits, polyneuropathies, spasticity, cognitive decline, and parkinsonism [24]. *RAG1*, one of the genes involved in Severe Combined Immunodeficiency (SCID) [25], is also reported in association with refractory status epilepticus [26] and optic neuropathy [27]. Other associations include *AIRE* with autoimmune cerebellar degeneration [28]; *RAB27A* with developmental regression and seizures [29]; *RTEL1* with microcephaly, developmental delay, spastic diplegia, and cerebellar dysfunction [30]; *STAT1* with CNS aneurysms and inflammatory spinal cord lesions [31]; *SMARCAL1* with microcephaly, developmental delays, and neuronal migration disorders [32]. *TTC7A*

Table 2 List of rare variants, allele frequency, and results of in silico predictions categorized by diagnosis

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
ADEM	***ADAR***	**c.577C > G (p.Pro193Ala)**	**rs145588689**	**0.003**	**NA**	**NA**	**Mod**	**23.5**
	AIRE	c.722G > T (p.Ser241Ile)	rs1260665653	NA	Probably damaging	Deleterious	Weak	5.897
	DEF6	**c.1745 T > A (p.Leu582Gln)**	**rs751075162**	**0.0001**	**Possibly damaging**	**Deleterious**	**High**	**27.7**
	ITGB2	c.1358G > A (p.Ser453Asn)	rs138659490	0.0008	NA	NA	High	9.234
	NOD2	c.1151 T > A (p.Phe384Tyr)	rs777343284	0.0003	Probably damaging	Tolerated	High	25.9
Autoimmune encephalitis	*AIRE*	c.1256G > A (p.Cys419Tyr)	rs756933733	NA	Possibly damaging	Tolerated	Mod	19.08
	IL21R	c.585C > G (p.Ser195Arg)	rs773814550	NA	Possibly damaging	Tolerated	Mod	24.6
	RNASEH2A	**c.871C > T (p.Arg291Cys)**	**rs771858022**	**0.00006**	**Probably damaging**	**Deleterious**	**High**	**24.6**
	STAT1	c.1632 + 6G > A (Intronic)	rs185216067	0.0008	NA	NA	NA	5.658
	TNFRSF1A	c.271G > A (p.Ala91Thr)		NA	Possibly damaging	Tolerated	Mod	21.7
	XIAP	**c.844G > C (p.Glu282Gln)**		**NA**	**Probably damaging**	**Deleterious**	**High**	**37**
CIS	*CYBA*	c.553G > A (p.Val185Ile)	rs1158937022	NA	Tolerated	Tolerated	Weak	15.57
CNS vasculitis	*DOCK8*	c.4276A > G (p.Ser1426Gly)	rs755182322	0.00009	Tolerated	Tolerated	High	23.6
	IL21	c.470A > T (p.His157Leu)	rs1326239267	NA	Tolerated	Tolerated	Weak	12.68
	SLC7A7	**c.187C > T (p.Leu63Phe)**		**NA**	**Probably damaging**	**Deleterious**	**High**	**26**
	UNC13D	**c.652G > T (p.Gly218Trp)**	**rs775666284**	**0.00001**	**Possibly damaging**	**Deleterious**	**Mod**	**26.1**
Down syndrome regression disorder	*CTLA4*	c.23G > A (p.Arg8Gln)	rs138279736	0.0005	Tolerated	Tolerated`	Mod	17.97
	IRF7	c.1405 T > C (p.Trp469Arg)	rs746725871	0.00009	Benign	Tolerated	Mod	4.558
	LYST	c.1676G > A (p.Arg559His)	rs138011756	0.0008	Benign	Tolerated	Mod	16.15
	SMARCAL1	c.488C > A (p.Thr163Asn)	rs748188404	0.0003	Tolerated	Tolerated	Weak	6.197
Hemispheric inflammation	*RBCK1*	c.69 T > G (p.Asp23Glu)	rs748386516	0.0007	Possibly damaging	Tolerated	High	13.08
	UNC13D	**c.419 T > C (p.Ile140Thr)**	**rs1181554837**	**NA**	**Probably damaging**	**Deleterious**	**Mod**	**25.9**
Meningoencephalitis of unknown etiology	*CARD14*	c.652C > T (p.Arg218Cys)		NA	NA	NA	Weak	24.7
	CYBA	c.274G > A (p.Val92Ile)	rs202179890	0.0002	Benign	Tolerated	Weak	7.442
	DOCK8	c.1817G > A (p.Ser606Asn)	rs778451048	0.0003	Benign	Tolerated	High	21.3
	PLCG2	c.3092A > G (p.Asn1031Ser)	rs747605077	0.00001	Benign	Deleterious	High	2.114

Table 2 (continued)

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
	PSTPIP1	c.831G > T (p.Glu277Asp)	rs990986006	NA	Tolerated	Tolerated	Mod	6.831
	RMRP	n.189C > T (RNA change)		NA			NA	
	STAT5B	c.799C > T (p.Pro267Ser)		NA	Probably damaging	Tolerated	Mod	24.3
	TNFRSF13B	c.41G > A (p.Arg14His)	rs200309474	0.002	Tolerated	Tolerated	Weak	0.258
	TNFSF12	c.610G > A (p.Gly204Arg)	rs746979506	0.00009	Probably damaging	Tolerated	Weak	14.18
	TREX1	c.24G > A (Silent)	rs147463121	0.0001	NA	NA	NA	3.279
MOGAD	***ACP5***	**c.249C > G (p.Asp83Glu)**	**rs563929774**	**0.0001**	**Probably damaging**	**Deleterious**	**High**	**24.3**
	ADA2	c.1033G > A (p.Ala345Thr)	rs752798667	0.0002	Benign	Tolerated	Mod	26.6
	AIRE	c.1438A > G (p.Thr480Ala)		NA	Benign	Tolerated	Mod	21.6
	CTLA4	c.309C > T (Silent)		NA	NA	NA	NA	35
	IFIH1	c.1745C > T (p.Ala582Val)	rs889262310	NA	Benign	Tolerated	Weak	12.41
	LRBA	c.40A > G (p.Thr14Ala)	rs1200143430	NA	Probably damaging	Tolerated	Weak	21.4
	LRBA	c.8479A > G (p.Met2827Val)	rs1276578449	NA	Probably damaging	Tolerated	Mod	19.67
	LRBA	c.8476G > A (p.Ala2826Thr)	rs779604273	0.00009	Probably damaging	Tolerated	Weak	23.7
	MEFV	c.828A > C (p.Glu276Asp)	rs775020273	0.0005	NA	NA	Weak	0.1
	NOD2	c.2104C > T (p.Arg702Trp)	rs2066844	0.03	Probably damaging	Deleterious	Mod	8.082
	RAG1	c.656G > A (p.Arg219Gln)	rs764179803	0.0001	Benign	Tolerated	Mod	10.03
	RBCK1	c.700G > C (p.Glu234Gln)	rs756811010	0.0001	Benign	NA	High	40
	STAT5B	c.2348C > T (p.Pro783Leu)		NA	Possibly damaging	Tolerated	Mod	23.6
	STIM1	c.1367 T > C (p.Ile456Thr)		NA	Benign	Deleterious	Mod	5.025
	STXBP2	c.1453-9G > A (Intronic)	rs372742473	0.00002	NA	NA	NA	6.059
	TNFRSF13B	c.21C > G (p.Ser7Arg)	rs780461208	0.00002	NA	Tolerated	Weak	13.14
	UNC13D	c.3022A > C (p.Thr1008Pro)	rs753816739	0.0002	Probably damaging	Tolerated	Weak	24.5
	UNC13D	c.2783G > A (p.Arg928His)	rs113461073	0.002	Benign	Tolerated	Weak	0.44
	ZAP70	c.790 + 5C > T (Intronic)	rs56133341	0.0004	NA	NA	NA	0.239

Table 2 (continued)

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
MS	*ACP5*	c.131C > T (p.Thr44Met)	rs369804864	0.00003	Probably damaging	NA	High	7.842
	ADAM17	c.53C > T (p.Pro18Leu)	rs144458353	0.0006	Benign	Tolerated	Mod	21.4
	BACH2	c.2230A > G (p.Ile744Val)	rs1321699864	NA	Benign	Tolerated	Weak	13.41
	CARD14	c.2140G > A (p.Gly714Ser)	rs151150961	0.0007	NA	NA	Weak	6.068
	DOCK8	c.268_270del (p.Asp90del)	rs776468911	0.0003	NA	NA	NA	26.2
	DUOX2	c.1295G > A (p.Arg432His)	rs530736554	0.0007	NA	NA	High	24.3
	DUOX2	c.1825C > T (p.Pro609Ser)	rs201221237	0.0009	NA	NA	High	25.6
	G6PC3	c.1001 T > C (p.Met334Thr)	rs746741551	0.0002	Benign	Tolerated	Weak	1.205
	G6PC3	c.413G > A (p.Arg138His)	rs763535974	0.0001	Benign	Tolerated	Mod	15.17
	IL10	c.434C > T (p.Ala145Val)	rs774072665	0.00001	Benign	Tolerated	Weak	14.84
	IL1RN	c.28G > C (p.Gly10Arg)	rs770976676	0.0002	Benign	Deleterious	Weak	33
	LRBA	c.5149G > A (p.Val1717Met)	rs143003767	0.0007	Benign	Tolerated	Weak	16
	LYST	**c.2465C > T (p.Thr822Ile)**	**rs199746236**	**0.0003**	**Probably damaging**	**Deleterious**	**Mod**	**26.4**
	LYST	c.6454A > C (p.Ser2152Arg)	rs201317160	0.0003	Tolerated	Tolerated	Mod	14.68
	NLRC4	**c.443G > T (p.Arg148Leu)**	**rs377088692**	**NA**	**Possibly damaging**	**Deleterious**	**High**	**15.23**
	NOD2	**c.1295C > T (p.Ala432Val)**	**rs2076754**	**0.0002**	**Probably damaging**	**Deleterious**	**High**	**16.34**
	ORAI1	c.14C > T (p.Pro5Leu)	rs549883296	NA	Tolerated	Tolerated	Weak	24.7
	RAB27A	**c.543A > G (p.Ile181Met)**	**rs139025012**	**0.0001**	**Possibly damaging**	**Deleterious**	**High**	**22.4**
	RFXANK	**c.661G > A (p.Asp221Asn)**		**NA**	**Possibly damaging**	**Deleterious**	**Mod**	**NA**
	RMRP	n.*70G > A (Non-coding)		NA	NA	NA	NA	NA
	SH3BP2	c.1135C > T (p.Pro379Ser)	rs759054470	0.00003	Benign	Tolerated	High	23.4
	STAT5B	c.2358A > G (Silent)	rs568497349	0.0002	NA	NA	NA	23.6
	STIM1	c.1773C > G (p.Asp591Glu)	rs776241052	0.0002	Benign	Tolerated	Weak	13.73
	TBX1	c.1039C > A (p.Arg347Ser)		NA	Possibly damaging	Tolerated	Mod	NA

Table 2 (continued)

Dx	Gene	Variant	dbSNP	ExAC AF	PolyPhen	SIFT	Conserv	CADD
	TNFAIP3	c.2117G > A (p.Arg706Gln)	rs3734553	0.0001	Benign	Deleterious	High	22.4
	UNC13D	**c.2795 T > C (p.Leu932Pro)**	**rs760552006**	**0.003**	**Probably damaging**	**Deleterious**	**High**	**26.4**
	UNC13D	c.681C > T (Silent)	rs779543680	0.0003	NA	NA	NA	11.53
Neuropychiatric SLE	*SLC29A3*	c.146G > C (p.Arg49Pro)	rs201610819	0.001	Probably damaging	Tolerated	Weak	24.3
Neurosarcoidosis	***RNASEH2A***	**c.101A > G (p.Asp34Gly)**	**rs762516714**	**0.001**	**Probably damaging**	**Deleterious**	**High**	**27.5**
Inflammatory stroke	***NOD2***	**c.2722G > C (p.Gly908Arg)**	**rs2066845**	**0.014**	**Probably damaging**	**Deleterious**	**Mod**	**29.7**
	RTEL1	c.2306G > A (p.Arg769His)		0.0001	Tolerated	Tolerated	Weak	11.48
RIS	*NOD2*	c.2722G > C (p.Gly908Arg)	rs2066845	0.014	NA	NA	Mod	29.7
	TTC7A	**c.563G > A (p.Arg188His)**	**rs147471840**	**0.0002**	**Probably damaging**	**Deleterious**	**Mod**	**25.2**
SLE cerebritis	*CARD8*	c.803A > G (p.Asn268Ser)		NA	Tolerated	Tolerated	Mod	NA
	LYST	c.7157A > G (p.His2386Arg)	rs758888571	0.0002	Probably damaging	Tolerated	High	23.2
	NOD2	c.2104C > T (p.Arg702Trp)	rs2066844	0.03	NA	NA	Mod	8.082
Susac syndrome	*DCLRE1C*	c.212C > T (p.Thr71Met)	rs147013097	0.0003	Tolerated	Tolerated	Mod	24.6
Transverse myelitis	*IFIH1*	c.2973C > A (p.Phe991Leu)	rs763358277	NA	Possibly damaging	Tolerated	Mod	21.6
	RNASEH2A	c.821A > G (p.Asn274Ser)	rs373169862	0.0007	Benign	Tolerated	Weak	2.817

Variants for which available results of all platforms were in agreement predicting detrimental effect are bolded

ADEM acute disseminated encephalomyelitis, *CIS* clinically isolated syndrome, *CNS* central nervous system, *MOGAD* myelin oligodendrocyte glycoprotein antibody-associated disease, *MS* multiple sclerosis, *RIS* radiographically isolated syndrome, *SLE* systemic lupus erythematous

with perisylvian polymicrogyria, cerebellar hypoplasia and arthrogryposis, severe microcephaly, refractory epilepsy, developmental delay, and hypomyelinating leukodystrophy [33]; and ZAP70 with silent brain infarcts [34].

Our analysis of KEGG-enriched pathways both reflects the nature of the screening tests used and provides mechanistic insights into the pathophysiology of these conditions. The most significantly enriched term was "Primary Immunodeficiency," potentially a result of the autoinflammatory and autoimmunity syndrome screening panels used in the study. By definition, autoimmune neurologic diseases represent disorders of immune regulation. Inflammatory pathways have already been linked to neural dysfunction; examples in epilepsy alone include the IL-1 receptor/Toll-like receptor (TLR) 4 axis, the arachidonic acid–prostanoid cascade, oxidative stress, and transforming growth factor-β (TGFβ) signaling associated with blood–brain barrier dysfunction, among others [82]. It is, therefore, not surprising that genes involved with immune development and regulation may also be involved with diseases of neuroinflammation.

What is surprising from these data is an identified enrichment in specific arms of the immune response, notably the Nucleotide Oligomerization Domain (NOD)-like Receptor

Table 3 Results of KEGG pathway analysis of the aggregated gene lists

KEGG Pathway	Genes	Count	%	*p* value	Benjamini
Primary immunodeficiency	*DCLRE1C* *ORAI* *TNFRSF13B* *AIRE* *RAG1* *RFXANK* *ZAP70*	7	13	1.30*E* − 08	1.40*E* − 06
NOD-like receptor signaling pathway	*MEFV* *NLRC4* *TNFAIP3* *CARD8* *NOD2* *PSTPIP1*	6	11.1	8.00*E* − 06	4.10*E* − 04
Inflammatory bowel disease (IBD)	*IL10* *IL21R* *IL21* *NOD2* *STAT1*	5	9.3	2.90*E* − 04	9.80*E* − 03
NF-kappa B signaling pathway	*TNFAIP3* *TNFRSF1A* *XIAP* *PLCG2* *ZAP70*	5	9.3	9.30*E* − 04	1.90*E* − 02

signaling pathway. The NOD-like Receptor protein family is one of several classes of germline-encoded pattern recognition receptors (PRR) used within the innate immune system [83]. Other example PRRs include TLRs and C-type lectin receptors, which interact with microbial ligands such as bacterial lipopolysaccharide and peptidoglycan or yeast β-glucans. In contrast to membrane-bound PRRs, NOD-like receptors are known to detect pathogen and danger-associated patterns within the cytoplasmic compartment and are involved with initial innate immune responses to cellular injury and stress [83].

NOD2 in particular is stimulated by bacterial peptidoglycan-related products to oligomerize, recruit receptor-interacting serine/threonine-protein kinase 2 (RIPK2), and ultimately activate downstream NF-κB and MAPK signaling to promote production of proinflammatory molecules [84] (Fig. 1). NOD2 has already been linked to conditions of immune dysregulation; NOD2 polymorphisms are the strongest genetic risk factors for the development of Crohn's Disease, although the exact mechanisms by which are not yet clear [18]. In addition to Crohn's disease, *NOD2* mutations are associated with systemic and CNS inflammatory granulomatous diseases, such as Blau Syndrome, early-onset sarcoidosis [85], and CNS granulomatosis [19]. Moreover, expression of NOD is increased in astrocytes after exposure to bacterial pathogens of the CNS [86], promoting microglial inflammation in murine models of pneumococcal meningitis [87], as well as dopaminergic degeneration in a murine model of Parkinson's Disease [88]. Our data suggest NOD2-receptor signaling may be an attractive candidate for further investigation and targeting in pediatric autoimmune-neuroinflammatory conditions.

This study is not without limitations. This study evaluated a population of children with heterogenous rare and ultra-rare diseases making broad generalization of the results difficult. Accordingly, this study has a low total *n*. This undoubtedly contributed to the lack of statistical significance during burden testing analysis. In addition, there are several limitations to burden testing that affect its utility particularly in more modest sample sizes. Some of the well-known barriers include locus heterogeneity (several contributing genes each accounting for only a small percentage of cases), and high background rate of rare variants in the candidate genes [14]. Using a public sequencing database (e.g., gnomAD) as control imposes additional challenges. There is possibility of "contamination" of the control group, as these datasets might contain individuals with neurological and/or immune dysregulation conditions. Another important consideration is that the aggregate datasets include multiple different sequencing platforms and variant-calling processes that might be different from which was used for cases, affecting the validity of the comparison between the two groups. Moreover, due to lack of individual-level data in the aggregate datasets, an approximation is used, resulting in a more conservative test which overestimates the sum of variants in the population-based datasets, in turn underestimating the difference between cases and controls.

Our results highlight the need for more expansive testing of this population to further assess if the high frequency of

Table 4 Immune dysregulation conditions and neurologic manifestations associated with the 55 genes harboring rare variants

Gene	Associated immune dysregulation conditions	Neurologic manifestations
ACP5	Spondyloenchondrodysplasia with immune dysregulation (MIM: 607,944), monogenic SLE, Sjögren's syndrome, hemolytic anemia, thrombocytopenia, hypothyroidism, inflammatory myositis, Raynaud's disease, vitiligo [35]	Childhood-onset spastic diplegia, developmental delay, calcification of the basal ganglia [42, 43]
ADA2	Sneddon syndrome (livedo reticularis and onset of cerebrovascular disease in early adulthood) (MIM:182,410), Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome (MIM:615,688)	Early onset recurrent strokes [44]
ADAM17	Neonatal inflammatory skin and bowel disease (MIM: 614,328)	
ADAR	AGS 6 [36] (MIM: 615,010), Dyschromatosis symmetrica hereditaria (MIM: 127,400)	AGS, Torsion dystonia [45], Bilateral striatal necrosis and spastic paraplegia [46]
AIRE	Autoimmune Polyendocrinopathy Syndrome type 1 (MIM: 240,300)	Autoimmune cerebellar degeneration [47]
BACH2	Immunodeficiency-60 and autoimmunity (inflammatory bowel disease and recurrent sinopulmonary infections) (MIM: 618,394)	
CARD14	Pityriasis rubra pilaris (MIM: 173,200), Psoriasis 2 (MIM:602,723)	
CARD8	Crohn's disease 30 (MIM 619,079)	
CTLA4	Immune dysregulation with autoimmunity, immunodeficiency, and lymphoproliferation (MIM: 616,100). Susceptibility to Celiac disease, DM1, Hashimoto thyroiditis, SLE	Lymphocytic infiltration of brain, seizures and headache [48]
CYBA	CGD4 (MIM: 233,690)	
DCLRE1C	Omenn syndrome (SCID associated with erythrodermia, hepatosplenomegaly, lymphadenopathy, and alopecia) (MIM: 603,554, 602,450)	
DEF6	Immunodeficiency 87 and autoimmunity, increased susceptibility to EBV, hemolytic anemia (MIM: 619,573)	
DOCK8	Hyper-IgE recurrent infection syndrome (MIM: 243,700)	Hemiplegia, ischemic infarction, and subarachnoid hemorrhages [49]
DUOX2	Partial iodide organification defect, thyroid dyshormonogenesis (MIM: 607,200)	
G6PC3	Dursun Syndrome, severe congenital neutropenia(MIM: 612,541)	
IFIH1	AGS7 (MIM: 615,846), Singleton-Merton syndrome (MIM:182,250)	AGS, rapid neuroregression, spastic-dystonic syndrome, spastic paraparesis [50]
IL10	Progression of RA (MIM: 180,300)	
IL1RN	Osteomyelitis, sterile multifocal, with periostitis and pustulosis (MIM: 612,852)	
IL21	CVID 11(MIM:615,767)	
IL21R	Combined immunodeficiency due to interleukin 21 receptor deficiency (MIM: 615,207)	
IRF7	Severe influenza disease (MIM: 616,345)	
ITGB2	Leukocyte adhesion deficiency type 3 (MIM: 612,840)	
LRBA	CVID 8 with autoimmunity (MIM: 614,700), idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and inflammatory bowel disease	IIH [51]
LYST	Chediak-Higashi syndrome (MIM:214,500)	Learning difficulties, cerebellar deficits, polyneuropathies, spasticity, cognitive decline, and parkinsonism [52]
MEFV	FMF (MIM: 134,610, 249,100), acute febrile neutrophilic dermatosis (MIM: 608,068)	Vertigo, paresthesia, seizures [53, 54]
NLRC4	Familial cold autoinflammatory syndrome (MIM: 616,115), Autoinflammation with infantile enterocolitis (MIM: 616,050)	
NOD2	Increased risk Crohn's disease, granulomatous diseases (Blau syndrome, early-onset sarcoidosis)[37], NOD2-associated autoinflammatory disease [38]	Rasmussen syndrome with CNS granulomatosis [55], Multiple system atrophy [56]

Table 4 (continued)

Gene	Associated immune dysregulation conditions	Neurologic manifestations
ORAI1	Tubular aggregate myopathy 2 (MIM: 615,883), Immunodeficiency 9 (MIM: 612,782), Immunodeficiency 9 (MIM: 612,782)	
PLCG2	Familial cold autoinflammatory syndrome, autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation (MIM: 614,878)	
PSTPIP1	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome (MIM:604,416)	
RAB27A	Griscelli syndrome type 2 (affecting skin, hair, immune system) (MIM:607,624)	Developmental regression, seizure [57–59]
RAG1	Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity (MIM: 609,889), Combined cellular and humoral immune defects with granulomas (MIM: 233,650), Omenn syndrome (SCID with hypereosinophilia) (MIM:603,554), SCID, B cell-negative (MIM:601,457)	Facial nerve palsy, seizure, and decreased consciousness [60], Optic neuropathy [61]
RBCK1	Polyglucan body myopathy with or without immunodeficiency (MIM: 615,895)	
RFXANK	Hereditary MHC class II deficiency (MIM: 209,920)	
RMRP	Cartilage-hair hypoplasia (MIM: 250,250), Anauxetic (spondylopmetaepiphysieal) dysplasia (MIM:607,095)	
RNASEH2A	AGS4 (MIM: 610,333)	AGS, Developmental delay, intellectual disability, seizures and epileptic encephalopathy [62]
RTEL1	Dyskeratosis congenita (MIM: 615,190)	Microcephaly, developmental delay, spastic diplegia, cerebellar dysfunction [63]
SH3BP2	Cherubism (MIM: 118,400)	
SLC29A3	Histiocytosis-lymphadenopathy plus syndrome (MIM: 602,782)	
SLC7A7	Lysinuric protein intolerance (MIM:222,700)	Hypotonia, lethargy, ataxia, behavioral disorders, seizures, and coma due to hyperammonemia [64]
SMARCAL1	Schimke immunoosseous dysplasia (SIOD)(MIM: 242,900)	Microcephaly, developmental delays, neuronal migration disorders such as heterotopia, irregular cortical thickness, incomplete gyral formation, and poor definition of cortical layers [65], early-onset cerebral infarction [66]
STAT1	STAT1 Immunodeficiencies (MIM: 614,892, 613,796, 614,162)	CNS aneurysms, inflammatory spinal cord lesions [67], microglial activation, [68] exacerbation of pathophysiological actions of IFN-α in the CNS [69]
STAT5B	Growth hormone insensitivity with immune dysregulation (MIM:245,590, 618,985)	Epileptogenic GBM [70]
STIM1	Tubular aggregate myopathy (MIM: 160,565), Stormorken syndrome (thrombocytopenia, asplenia, skin rash, deep-set eyes with miosis, muscle weakness) (MIM: 185,070), STIM1 immunodeficiency (MIM:612,783)	Learning disorders
STXBP2	FHL5(MIM: 613,101)	Neuro HLH [71–73]
TBX1	DiGeorge/Velocardiofacial syndrome (MIM: 217,095, 188,400, 187,500, 192,430)	
TNFAIP3	familial Behcet-like autoinflammatory syndrome (MIM: 616,744)	Relapse biomarker in MOGAD [74], Neuropsychiatric SLE [75], Unclassified granulomatous neuroinflammatory disorder reminiscent of neurosarcoidosis [76]
TNFRSF13B	SCID (MIM: 240,500), autoinflammatory disorder associated with COVID-19 [39]	
TNFRSF1A	Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	
TNFSF12	CVID	GBM prognosis [77]
TREX1	AGS1(MIM:225,750), Chilblain lupus (MIM: 610,448), susceptibility to SLE (MIM: 152,700), Retinal vasculopathy with cerebral leukodystrophy [40, 41](MIM: 192,315)	AGS, white matter ring-enhancing lesions, stroke [78], tumor like lesions of the brain [79]

Table 4 (continued)

Gene	Associated immune dysregulation conditions	Neurologic manifestations
TTC7A	Gastrointestinal defects and immunodeficiency syndrome (MIM: 243,150)	Perisylvian polymicrogyria, cerebellar hypoplasia and arthrogryposis, severe microcephaly, refractory epilepsy, developmental delay, hypomyelinating leukodystrophy [80]
UNC13D	FHL3 (MIM: 608,898)	Neuro HLH [71–73]
XIAP	X-linked lymphoproliferative syndrome 2 (MIM:300,653)	
ZAP70	Infantile-onset autoimmunity (MIM: 617,006), Immunodeficiency due to ZAP70 deficiency (MIM:269,840)	Silent brain infarct, facial palsies [81]

AGS Aicardi–Goutieres syndrome, *CGD* chronic granulomatous disease, *CNS* central nervous system, *CVID* common variable immunodeficiency, *COVID-19* coronavirus disease 2019, *DM* diabetes mellitus, *EBV* Epstein–Barr virus, *FHL* familial hemophagocytic lymphohistiocytosis, *FMF* familial Mediterranean fever, *GBM* glioblastoma multiforme, *HLH* hemophagocytic lymphohistiocytosis, *IFN-α* Interferon-α, *IgE* Immunoglobulin E, *IIH* idiopathic intracranial hypertension, *MHC* major histocompatibility complex, *MOGAD* myelin oligodendrocyte glycoprotein antibody-associated disease, *NOD2* nucleotide binding oligomerization domain containing 2, *PLCG2* Phospholipase C Gamma 2, *RA* rheumatoid arthritis, *SCID* severe combined immunodeficiency, *SLE* systemic lupus erythematous, *STAT1* signal transducer and activator of transcription 1, *ZAP70* Zeta chain of T Cell receptor-associated protein kinase 70

rare and ultra-rare variants is contributory. However, the broad overlap of the dysfunctional pathways associated with identified gene abnormalities does shed light on the possibility of shared pathology among these disorders. The authors hope that these data serve as a proof of concept for the need for additional next-generation exome sequencing in individuals with pediatric neuroinflammatory disorders. Further study of more homogenous populations within this broad category (e.g., multiple sclerosis) would be particularly beneficial to best evaluate the nuances of the role of genes. There is a potential for severity bias in this study as well as not all patients at our center were able to obtain genetic testing and those who did have this testing may have had more significant or severe disease phenotypes. An important consideration in these data are that it was derived out of a focused exome panel which was limited to only genes already associated with inflammatory disease. Thus, pathway analysis is anticipated to be heavily influenced by the focused selection of genes that were analyzed, even beyond the variant level. Further study, with more broad, whole exome-based analysis, would be greatly beneficial for determining how enriched these pathways truly are. An additional limitation was that there was a statistically significant difference in the rate of commercial versus state/federal insurance for patients in the enrolled versus unenrolled groups, potentially skewing our results towards individuals who were more likely to come from lower socio-economic statuses although this was not assessed in this study. Additionally, given the geographic location of our center, there is a much higher rate of individuals of Hispanic or LatinX descent than at other centers nationally and this is of particular importance when assessing generalizability of these data. Finally, the potentially for epigenetic phenomenon or the interplay of environment, early childhood stress, and/or diet, was not assessed in this study and may be of use in future research.

Conclusions

The genetic basis of autoimmune and neuroinflammatory CNS disorders remains largely unknown, particularly in pediatric patient populations. We observed a high rate (77.4%) of identification of rare and low-frequency variants in immune regulatory genes in pediatric neuroinflammatory CNS disorders. We identified 88 unique single-nucleotide variants of 55 genes, including *UNC13D, LRBA, LYST, NOD2, DOCK8, RNASEH2A, STAT5B, and AIRE*. Finally, pathway analysis revealed an enrichment of NOD2-receptor signaling within this patient cohort, consistent with involvement of the pathway within other autoinflammatory conditions and warranting further investigation. This study provides the field a first glance at the genetic underpinning of pediatric autoimmune and inflammatory CNS disorders. The above gene variants, implicated in disorders of immune regulation, may play a role in pathogenesis of or predilection for autoimmune CNS disorders.

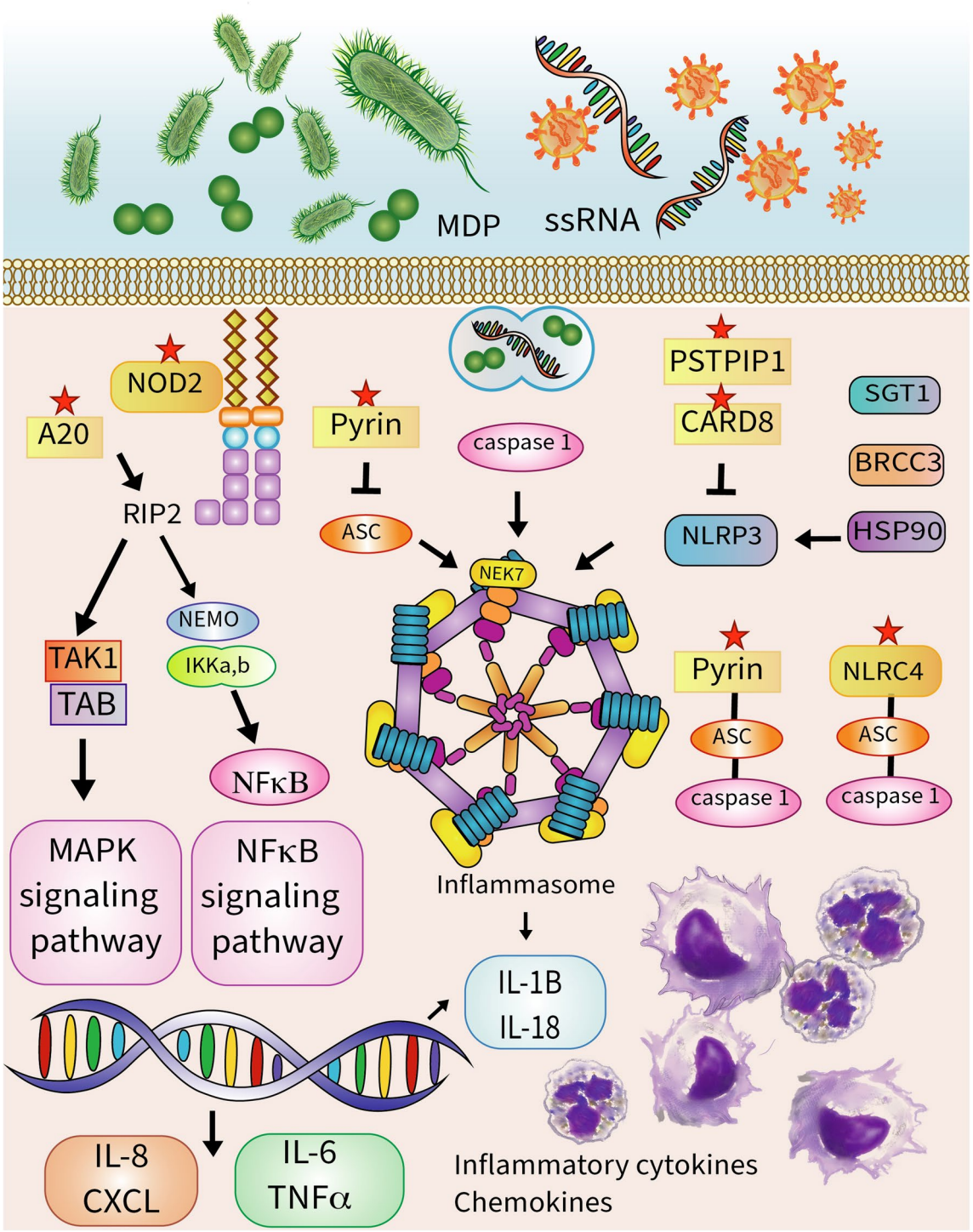

Fig. 1 **A** NOD2 and **B** Inflammatory bowel disease signaling pathways. Genes harboring rare variants are marked with a red star

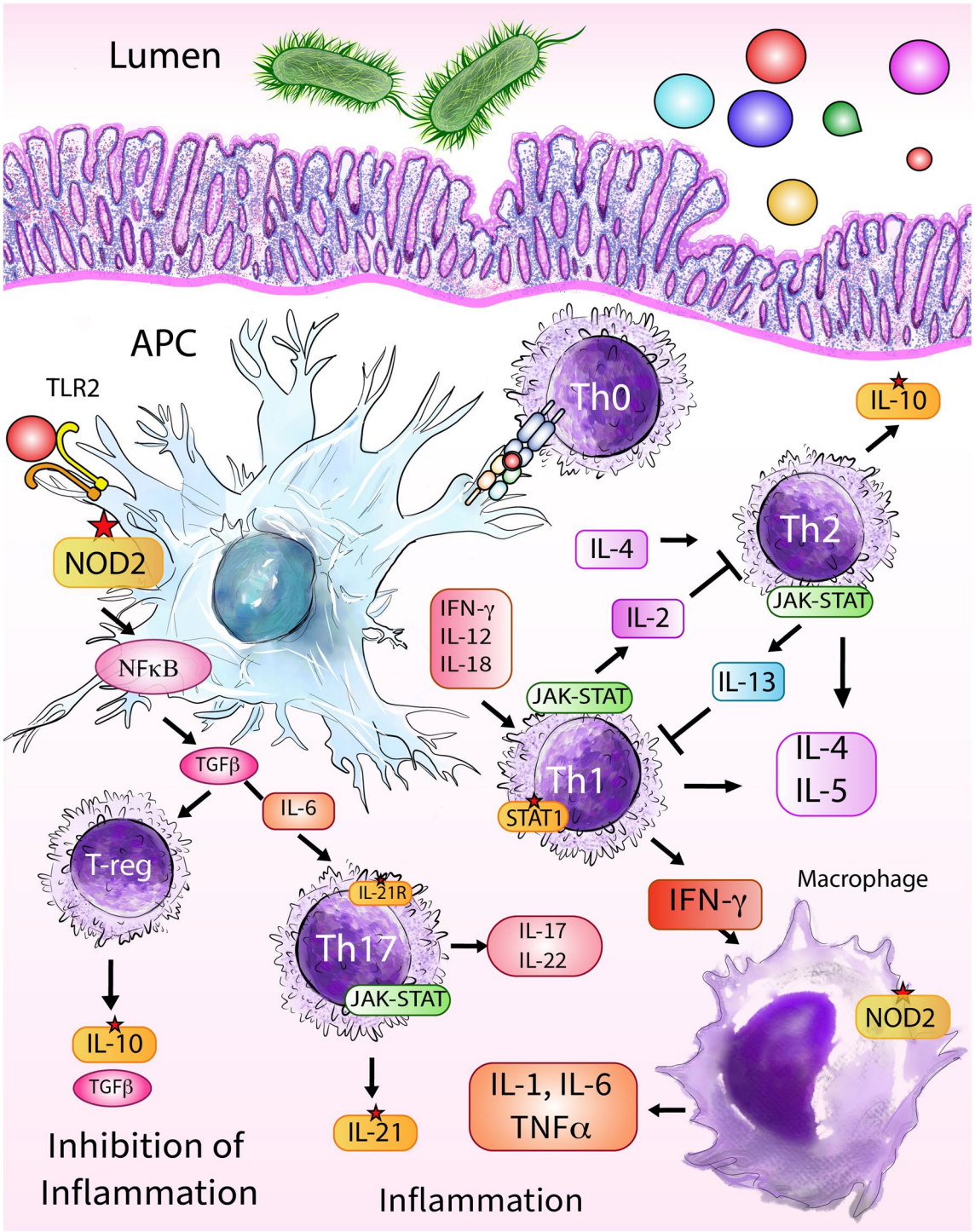

Fig. 1 (continued)

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-022-11325-2.

Declarations

Conflicts of interest The authors declare that they have no conflicts of interest.

References

1. Malani Shukla N, Lotze TE, Muscal E (2021) Inflammatory diseases of the central nervous system. Neurol Clin 39:811–828
2. International Multiple Sclerosis Genetics C, Patsopoulos NA, Baranzini SE, Santaniello A, Shoostari P, Cotsapas C, Wong G, Beecham AH, James T, Replogle J, Vlachos I, McCabe C, Pers T, Brandes A, White C, Keenan B, Cimpean M, Winn P, Panteliadis IP, Robbins A, Andlauer TFM, Zarzycki O, Dubois B, Goris A, Sondergaard HB, Sellebjerg F, Sorensen PS, Ullum H, Thoerner LW, Saarela J, Rebeix IC, Damotte V, Fontaine B, Noel LG, Lathrop M, Vukusik S, Berthele A, Biberacher V, Buck D, Gasperi C, Graetz C, Grummel V, Hemmer B, Hoshi M, Knier B, Korn T, Lill CM, Luessi F, Mühlau M, Zipp F, Dardiotis E, Agliardi C, Amoroso A, Barizzone N, Benedetti MD, Bernardinelli L, Cavalla P, Clarelli F, Comi G, Cusi D, Esposito F, Ferrè L, Galimberti D, Guaschino C, Leone MA, Martinelli V, Moiola L, Salvetti M, Sorosina M, Vecchio D, Zauli A, Santoro S, Zuccalà M, Mescheriakova J, Duijn Cv, Bos SD, Celius EG, Spurkland A, Comabella M, Montalban X, Alfredsson L, Bomfim I, Gomez-Cabrero D, Hillert J, Jagodic M, Lindén M, Piehl F, Jelčić I, Martin R, Sospedra M, Baker A, Ban M, Hawkins C, Hysi P, Kalra S, Karpe F, Khadake J, Lachance G, Molyneux P, Neville M, Thorpe J, Bradshaw E, Caillier SJ, Calabresi P, Cree BAC, Cross A, Davis M, Bakker PWId, Delgado S, Dembele M, Edwards K, Fitzgerald K, Frohlich IY, Gourraud PA, Haines JL, Hakonarson H, Kimbrough D, Isobe N, Konidari I, Lathi E, Lee MH, Li T, An D, Zimmer A, Lo A, Madireddy L, Manrique CP, Mitrovic M, Olah M, Patrick E, Pericak-Vance MA, Piccio L, Schaefer C, Weiner H, Lage K, Compston A, Hafler D, Harbo HF, Hauser SL, Stewart G, D'Alfonso S, Hadjigeorgiou G, Taylor B, Barcellos LF, Booth D, Hintzen R, Kockum I, Martinelli-Boneschi F, McCauley JL, Oksenberg JR, Oturai A, Sawcer S, Ivinson AJ, Olsson T, Jager PLD, Barclay M, Peyrin-Biroulet L, Chamaillard M, Colombe J-F, Cottone M, Croft A, D'Incà R, Halfvarson J, Hanigan K, Henderson P, Hugot J-P, Karban A, Kennedy NA, Khan MA, Lémann M, Levine A, Massey D, Milla M, Montgomery GW, Evelyn Ng SM, Oikonomou I, Peeters H, Proctor DD, Rahier J-F, Roberts R, Rutgeerts P, Seibold F, Stronati L, Taylor KM, Törkvist L, Ublick K, Limbergen JV, Gossum AV, Vatn MH, Zhang H, Zhang W, Australia, New Zealand I, Belgium Genetic C, Initiative on C, Colitis, Niddk I, United Kingdom I, Wellcome Trust Case Control C (2017) The Multiple Sclerosis Genomic Map: role of peripheral immune cells and resident microglia in susceptibility. bioRxiv:143933
3. Mitrovič M, Patsopoulos NA, Beecham AH, Dankowski T, Goris A, Dubois B, D'hooghe MB, Lemmens R, Van Damme P, Søndergaard HB, Sellebjerg F, Sorensen PS, Ullum H, Thørner LW, Werge T, Saarela J, Cournu-Rebeix I, Damotte V, Fontaine B, Guillot-Noel L, Lathrop M, Vukusik S, Gourraud P-A, Andlauer TFM, Pongratz V, Buck D, Gasperi C, Bayas A, Heesen C, Kümpfel T, Linker R, Paul F, Stangel M, Tackenberg B, Bergh FT, Warnke C, Wiendl H, Wildemann B, Zettl U, Ziemann U, Tumani H, Gold R, Grummel V, Hemmer B, Knier B, Lill CM, Luessi F, Dardiotis E, Agliardi C, Barizzone N, Mascia E, Bernardinelli L, Comi G, Cusi D, Esposito F, Ferrè L, Comi C, Galimberti D, Leone MA, Sorosina M, Mescheriakova J, Hintzen R, van Duijn C, Teunissen CE, Bos SD, Myhr K-M, Celius EG, Lie BA, Spurkland A, Comabella M, Montalban X, Alfredsson L, Stridh P, Hillert J, Jagodic M, Piehl F, Jelčić I, Martin R, Sospedra M, Ban M, Hawkins C, Hysi P, Kalra S, Karpe F, Khadake J, Lachance G, Neville M, Santaniello A, Caillier SJ, Calabresi PA, Cree BAC, Cross A, Davis MF, Haines JL, de Bakker PIW, Delgado S, Dembele M, Edwards K, Fitzgerald KC, Hakonarson H, Konidari I, Lathi E, Manrique CP, Pericak-Vance MA, Piccio L, Schaefer C, McCabe C, Weiner H, Goldstein J, Olsson T, Hadjigeorgiou G, Taylor B, Tajouri L, Charlesworth J, Booth DR, Harbo HF, Ivinson AJ, Hauser SL, Compston A, Stewart G, Zipp F, Barcellos LF, Baranzini SE, Martinelli-Boneschi F, D'Alfonso S, Ziegler A, Oturai A, McCauley JL, Sawcer SJ, Oksenberg JR, De Jager PL, Kockum I, Hafler DA, Cotsapas C (2018) Low-frequency and rare-coding variation contributes to multiple sclerosis risk. Cell 175:1679–1687 (**e1677**)
4. Patsopoulos NA (2018) Genetics of multiple sclerosis: an overview and new directions. Cold Spring Harb Perspect Med 8(7):a028951
5. Farh KK, Marson A, Zhu J, Kleinewietfeld M, Housley WJ, Beik S, Shoresh N, Whitton H, Ryan RJ, Shishkin AA, Hatan M, Carrasco-Alfonso MJ, Mayer D, Luckey CJ, Patsopoulos NA, De Jager PL, Kuchroo VK, Epstein CB, Daly MJ, Hafler DA, Bernstein BE (2015) Genetic and epigenetic fine mapping of causal autoimmune disease variants. Nature 518:337–343
6. Then Bergh F, Kümpfel T, Trenkwalder C, Rupprecht R, Holsboer F (1999) Dysregulation of the hypothalamo-pituitary-adrenal axis is related to the clinical course of MS. Neurology 53:772–777
7. da Huang W, Sherman BT, Lempicki RA (2009) Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. Nucleic Acids Res 37:1–13
8. Huang DW, Sherman BT, Lempicki RA (2009) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 4:44–57
9. Madsen BE, Browning SR (2009) A groupwise association test for rare mutations using a weighted sum statistic. PLoS Genet 5:e1000384
10. Neale BM, Rivas MA, Voight BF, Altshuler D, Devlin B, Orho-Melander M, Kathiresan S, Purcell SM, Roeder K, Daly MJ (2011) Testing for an unusual distribution of rare variants. PLoS Genet 7:e1001322
11. Clarelli F, Barizzone N, Mangano E, Zuccalà M, Basagni C, Anand S, Sorosina M, Mascia E, Santoro S, Guerini FR, Virgilio E, Gallo A, Pizzino A, Comi C, Martinelli V, Comi G, De Bellis G, Leone M, Filippi M, Esposito F, Bordoni R, Martinelli Boneschi F, D'Alfonso S (2021) Contribution of rare and low-frequency variants to multiple sclerosis susceptibility in the Italian continental population. Front Genet 12:800262
12. Mascia E, Clarelli F, Zauli A, Guaschino C, Sorosina M, Barizzone N, Basagni C, Santoro S, Ferrè L, Bonfiglio S, Biancolini D, Pozzato M, Guerini FR, Protti A, Liguori M, Moiola L, Vecchio D, Bresolin N, Comi G, Filippi M, Esposito F, D'Alfonso S, Martinelli-Boneschi F (2022) Burden of rare coding variants in an Italian cohort of familial multiple sclerosis. J Neuroimmunol 362:577760
13. Rhead B, Shao X, Graves JS, Chitnis T, Waldman AT, Lotze T, Schreiner T, Belman A, Krupp L, Greenberg BM, Weinstock-Guttman B, Aaen G, Tillema JM, Rodriguez M, Hart J, Caillier S, Ness J, Harris Y, Rubin J, Candee MS, Gorman M, Benson L, Mar S, Kahn I, Rose J, Casper TC, Quach H, Quach D, Schaefer C, Waubant E, Barcellos LF (2019) miRNA contributions to pediatric-onset multiple sclerosis inferred from GWAS. Ann Clin Transl Neurol 6:1053–1061
14. Guo MH, Plummer L, Chan YM, Hirschhorn JN, Lippincott MF (2018) Burden testing of rare variants identified through exome sequencing via publicly available control data. Am J Hum Genet 103:522–534
15. Crow YJ, Chase DS, Lowenstein Schmidt J, Szynkiewicz M, Forte GM, Gornall HL, Oojageer A, Anderson B, Pizzino A, Helman G, Abdel-Hamid MS, Abdel-Salam GM, Ackroyd S, Aeby A, Agosta G, Albin C, Allon-Shalev S, Arellano M, Ariaudo G, Aswani V, Babul-Hirji R, Baildam EM,

Bahi-Buisson N, Bailey KM, Barnerias C, Barth M, Battini R, Beresford MW, Bernard G, Bianchi M, Billette de Villemeur T, Blair EM, Bloom M, Burlina AB, Carpanelli ML, Carvalho DR, Castro-Gago M, Cavallini A, Cereda C, Chandler KE, Chitayat DA, Collins AE, Sierra Corcoles C, Cordeiro NJ, Crichiutti G, Dabydeen L, Dale RC, D'Arrigo S, De Goede CG, De Laet C, De Waele LM, Denzler I, Desguerre I, Devriendt K, Di Rocco M, Fahey MC, Fazzi E, Ferrie CD, Figueiredo A, Gener B, Goizet C, Gowrinathan NR, Gowrishankar K, Hanrahan D, Isidor B, Kara B, Khan N, King MD, Kirk EP, Kumar R, Lagae L, Landrieu P, Lauffer H, Laugel V, La Piana R, Lim MJ, Lin JP, Linnankivi T, Mackay MT, Marom DR, Marques Lourenço C, McKee SA, Moroni I, Morton JE, Moutard ML, Murray K, Nabbout R, Nampoothiri S, Nunez-Enamorado N, Oades PJ, Olivieri I, Ostergaard JR, Pérez-Dueñas B, Prendiville JS, Ramesh V, Rasmussen M, Régal L, Ricci F, Rio M, Rodriguez D, Roubertie A, Salvatici E, Segers KA, Sinha GP, Soler D, Spiegel R, Stödberg TI, Straussberg R, Swoboda KJ, Suri M, Tacke U, Tan TY, te Water Naude J, Wee Teik K, Thomas MM, Till M, Tonduti D, Valente EM, Van Coster RN, van der Knaap MS, Vassallo G, Vijzelaar R, Vogt J, Wallace GB, Wassmer E, Webb HJ, Whitehouse WP, Whitney RN, Zaki MS, Zuberi SM, Livingston JH, Rozenberg F, Lebon P, Vanderver A, Orcesi S, Rice GI (2015) Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. Am J Med Genet A 167:296–312

16. Sieni E, Cetica V, Hackmann Y, Coniglio ML, Da Ros M, Ciambotti B, Pende D, Griffiths G, Aricò M (2014) Familial hemophagocytic lymphohistiocytosis: when rare diseases shed light on immune system functioning. Front Immunol 5:167
17. Benson LA, Li H, Henderson LA, Solomon IH, Soldatos A, Murphy J, Bielekova B, Kennedy AL, Rivkin MJ, Davies KJ, Hsu AP, Holland SM, Gahl WA, Sundel RP, Lehmann LE, Lee MA, Alexandrescu S, Degar BA, Duncan CN, Gorman MP (2019) Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. Neurology 6:e560
18. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G (2001) Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature 411:599–603
19. Goyal M, Cohen ML, Bangert BA, Robinson S, Singer NG (2007) Rasmussen syndrome and CNS granulomatous disease with NOD2/CARD15 mutations. Neurology 69:640–643
20. Mulhern CM, Hong Y, Omoyinmi E, Jacques TS, D'Arco F, Hemingway C, Brogan PA, Eleftheriou D (2019) Janus kinase 1/2 inhibition for the treatment of autoinflammation associated with heterozygous TNFAIP3 mutation. J Allergy Clin Immunol 144:863-866.e865
21. Duan R, Liu Q, Li J, Bian X, Yuan Q, Li Y, Long F, Gao S, Wei S, Li P, Gao F, Sun W, Li X, Liu Q (2019) A De Novo frameshift mutation in TNFAIP3 impairs A20 deubiquitination function to cause neuropsychiatric systemic Lupus Erythematosus. J Clin Immunol 39:795–804
22. Calame DG, Herman I, Fatih JM, Fisher KS, Coban-Akdemir Z, Du H, Jhangianis SN, Gibbs RA, Pehlivan D, Shukla N, Lotze T, Posev JE, Chinns IK, Lupski JR (2021) Evidence for different gene rare variants contributing to early onset neurological autoimmune disease. In: Child Neurology Society Annual Meeting. Boston
23. Saxena S, Lokhande H, Gombolay G, Raheja R, Rooney T, Chitnis T (2020) Identification of TNFAIP3 as relapse biomarker and potential therapeutic target for MOG antibody associated diseases. Sci Rep 10:12405
24. Introne WJ, Westbroek W, Cullinane AR, Groden CA, Bhambhani V, Golas GA, Baker EH, Lehky TJ, Snow J, Ziegler SG, Adams DR, Dorward HM, Hess RA, Huizing M, Gahl WA, Toro C (2016) Neurologic involvement in patients with atypical Chediak-Higashi disease. Neurology 86:1320–1328
25. Li W, Chang FC, Desiderio S (2001) Rag-1 mutations associated with B-cell-negative scid dissociate the nicking and transesterification steps of V(D)J recombination. Mol Cell Biol 21:3935–3946
26. Melika S, Hossein E, Mona S, Elham R, Samaneh Z, Sepideh S, Raul Jimenez H, Ana K, Kaan B, Nima R (2021) A novel homozygous RAG1 mutation is associated with severe combined immunodeficiency and neurological presentations. Allergol Immunopathol (Madr) 49:91–97
27. Hirano T, Murata T, Hayashi T (2015) Physiological significance of recombination-activating gene 1 in neuronal death, especially optic neuropathy. Febs j 282:129–141
28. Berger JR, Weaver A, Greenlee J (2008) Neurologic consequences of autoimmune polyglandular syndrome type 1. Neurology 70:2248–2251
29. Al-Sulaiman R, Othman A, El-Akouri K, Fareed S, AlMulla H, Sukik A, Al-Mureikhi M, Shahbeck N, Ali R, Al-Mesaifri F, Musa S, Al-Mulla M, Ibrahim K, Mohamed K, Al-Nesef MA, Ehlayel M, Ben-Omran T (2020) A founder RAB27A variant causes Griscelli syndrome type 2 with phenotypic heterogeneity in Qatari families. Am J Med Genet A 182:2570–2580
30. Touzot F, Kermasson L, Jullien L, Moshous D, Ménard C, Ikincioğullari A, Doğu F, Sari S, Giacobbi-Milet V, Etzioni A, Soulier J, Londono-Vallejo A, Fischer A, Callebaut I, de Villartay JP, Leblanc T, Kannengiesser C, Revy P (2016) Extended clinical and genetic spectrum associated with biallelic RTEL1 mutations. Blood Adv 1:36–46
31. Kranick S, Holland S, Uzel G, Nath A (2012) CNS complications in immunodeficiency syndromes due to mutations in transcription factors STAT-1 and GATA-2 (S57.003). Neurology 78:S57.003
32. Deguchi K, Clewing JM, Elizondo LI, Hirano R, Huang C, Choi K, Sloan EA, Lücke T, Marwedel KM, Powell RD Jr, Santa Cruz K, Willaime-Morawek S, Inoue K, Lou S, Northrop JL, Kanemura Y, van der Kooy D, Okano H, Armstrong DL, Boerkoel CF (2008) Neurologic phenotype of Schimke immuno-osseous dysplasia and neurodevelopmental expression of SMARCAL1. J Neuropathol Exp Neurol 67:565–577
33. Salter CG, Cai Y, Lo B, Helman G, Taylor H, McCartney A, Leslie JS, Accogli A, Zara F, Traverso M, Fasham J, Lees JA, Ferla MP, Chioza BA, Wenger O, Scott E, Cross HE, Crawford J, Warshawsky I, Keisling M, Agamanolis D, Ward Melver C, Cox H, Elawad M, Marton T, Wakeling MN, Holzinger D, Tippelt S, Munteanu M, Valcheva D, Deal C, Van Meerbeke S, Walsh Vockley C, Butte MJ, Acar U, van der Knaap MS, Korenke GC, Kotzaeridou U, Balla T, Simons C, Uhlig HH, Crosby AH, De Camilli P, Wolf NI, Baple EL (2021) Biallelic PI4KA variants cause neurological, intestinal and immunological disease. Brain 144:3597–3610
34. Sharifinejad N, Jamee M, Zaki-Dizaji M, Lo B, Shaghaghi M, Mohammadi H, Jadidi-Niaragh F, Shaghaghi S, Yazdani R, Abolhassani H, Aghamohammadi A, Azizi G (2020) Clinical, immunological, and genetic features in 49 patients with ZAP-70 deficiency: a systematic review. Front Immunol 11:831
35. Briggs TA et al (2011) Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. Nat Genet 43(2):127–131
36. Rice GI et al (2012) Mutations in ADAR1 cause Aicardi-Goutières syndrome associated with a type I interferon signature. Nat Genet 44(11):1243–1248
37. La Torre F et al (2015) Early-onset sarcoidosis caused by a rare CARD15/NOD2 de novo mutation and responsive to infliximab: a

case report with long-term follow-up and review of the literature. Clin Rheumatol 34(2):391–395
38. Caso F et al (2015) Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. RMD Open 1(1):e000097
39. Schmidt A et al (2021) TBK1 and TNFRSF13B mutations and an autoinflammatory disease in a child with lethal COVID-19. NPJ Genom Med 6(1):55
40. Dhamija R et al (2015) Evolution of brain lesions in a patient with *TREX1* cerebroretinal vasculopathy. Neurology 85(18):1633
41. Saito R et al (2019) Retinal vasculopathy with cerebral leukodystrophy: clinicopathologic features of an autopsied patient with a heterozygous TREX 1 mutation. J Neuropathol Exp Neurol 78(2):181–186
42. Lausch E et al (2011) Genetic deficiency of tartrate-resistant acid phosphatase associated with skeletal dysplasia, cerebral calcifications and autoimmunity. Nat Genet 43(2):132–137
43. Renella R et al (2006) Spondyloenchondrodysplasia with spasticity, cerebral calcifications, and immune dysregulation: clinical and radiographic delineation of a pleiotropic disorder. Am J Med Genet A 140(6):541–550
44. Zhou Q et al (2014) Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med 370(10):911–920
45. Patrizi A et al (1994) Dyschromatosis symmetrica hereditaria associated with idiopathic torsion dystonia. A case report. Acta Derm Venereol 74(2):135–137
46. Yang Y, Okada S, Sakurai M (2021) Adenosine-to-inosine RNA editing in neurological development and disease. RNA Biol 18(7):999–1013
47. Berger JR, Weaver A, Greenlee J (2008) Neurologic consequences of autoimmune polyglandular syndrome type 1. Neurology 70(23):2248–2251
48. Schwab C et al (2018) Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol 142(6):1932–1946
49. Renner ED et al (2004) Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr 144(1):93–99
50. Rice GI et al (2020) Genetic and phenotypic spectrum associated with IFIH1 gain-of-function. Hum Mutat 41(4):837–849
51. Yildirim M et al (2018) Neurologic Involvement in Primary Immunodeficiency Disorders. J Child Neurol 33(5):320–328
52. Introne WJ et al (2016) Neurologic involvement in patients with atypical Chediak-Higashi disease. Neurology 86(14):1320–1328
53. Ahmed MH et al (2022) Musculoskeletal and neurological manifestations in a cohort of Egyptian Familial Mediterranean fever patients: genotype-phenotype correlation. Egypt Rheumatol Rehabil 49(1):6
54. Canpolat M et al (2017) Neurological Manifestations in Familial Mediterranean Fever: Results of 22 Children from a Reference Center in Kayseri, an Urban Area in Central Anatolia, Turkey. Neuropediatrics 48(2):79–85
55. Goyal M et al (2007) Rasmussen syndrome and CNS granulomatous disease with NOD2/CARD15 mutations. Neurology 69(7):640–643
56. Cao B et al (2018) Functional variant rs3135500 in NOD2 increases the risk of multiple system atrophy in a Chinese population. Frontiers in Aging Neuroscience. https://doi.org/10.3389/fnagi.2018.00150
57. Ortiz JF et al (2021) Refractory seizure in a patient with Griscelli syndrome: a unique case with one mutation and a novel deletion. Cureus 13(4):e14402
58. Al-Sulaiman R et al (2020) A founder RAB27A variant causes Griscelli syndrome type 2 with phenotypic heterogeneity in Qatari families. Am J Med Genet A 182(11):2570–2580
59. Panigrahi I et al (2015) Seizure as the presenting manifestation in Griscelli syndrome type 2. Pediatr Neurol 52(5):535–538
60. Melika S et al (2021) A novel homozygous RAG1 mutation is associated with severe combined immunodeficiency and neurological presentations. Allergol Immunopathol (Madr) 49(4):91–97
61. Hirano T, Murata T, Hayashi T (2015) Physiological significance of recombination-activating gene 1 in neuronal death, especially optic neuropathy. Febs j 282(1):129–141
62. Al Mutairi F et al (2018) Phenotypic and molecular spectrum of Aicardi-Goutières syndrome: a study of 24 patients. Pediatr Neurol 78:35–40
63. Touzot F et al (2016) Extended clinical and genetic spectrum associated with biallelic RTEL1 mutations. Blood Adv 1(1):36–46
64. Alqarajeh F et al (2020) Lysinuric protein intolerance: pearls to detect this otherwise easily missed diagnosis. Transl Sci Rare Dis 5(1–2):81–86
65. Deguchi K et al (2008) Neurologic phenotype of Schimke immuno-osseous dysplasia and neurodevelopmental expression of SMARCAL1. J Neuropathol Exp Neurol 67(6):565–577
66. Hossein Babaei A et al (2018) Early onset cerebral infarction in schimke immuno-osseous dysplasia. Iran J Child Neurol 12(3):126–132
67. Kranick S et al (2012) CNS complications in immunodeficiency syndromes due to mutations in transcription factors STAT-1 and GATA-2 (S57.003). Neurology 78(1 Supplement):S57.003
68. Butturini E et al (2019) STAT1 drives M1 microglia activation and neuroinflammation under hypoxia. Arch Biochem Biophys 669:22–30
69. Wang J, Schreiber Robert D, Campbell Iain L (2002) STAT1 deficiency unexpectedly and markedly exacerbates the pathophysiological actions of IFN-α in the central nervous system. Proc Natl Acad Sci 99(25):16209–16214
70. Berendsen S et al (2019) Epilepsy associates with decreased HIF-1α/STAT5b Signaling in Glioblastoma. Cancers (Basel) 11(1):41
71. Giardino G et al (2017) Two brothers with atypical UNC13D-related hemophagocytic lymphohistiocytosis characterized by massive lung and brain involvement. Front Immunol 8:1892
72. Amirifar P et al (2021) Clinical, immunological and genetic findings in patients with UNC13D deficiency (FHL3): a systematic review. Pediatr Allergy Immunol 32(1):186–197
73. Benson LA et al (2019) Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. Neurology 6(3):e560
74. Saxena S et al (2020) Identification of TNFAIP3 as relapse biomarker and potential therapeutic target for MOG antibody associated diseases. Sci Rep 10(1):12405
75. Duan R et al (2019) A De Novo frameshift mutation in TNFAIP3 impairs A20 deubiquitination function to cause neuropsychiatric systemic lupus erythematosus. J Clin Immunol 39(8):795–804
76. Mulhern CM et al (2019) Janus kinase 1/2 inhibition for the treatment of autoinflammation associated with heterozygous TNFAIP3 mutation. J Allergy Clin Immunol 144(3):863-866.e5
77. Xie H et al (2021) Potential molecular mechanism of TNF superfamily-related genes in glioblastoma multiforme based on transcriptome and epigenome. Front Neurol. https://doi.org/10.3389/fneur.2021.576382
78. Cimino M, Soo S, Morrow M (2018) Ring-enhancing lesions, stroke and vascular retinopathy associated with a novel TREX1 mutation (P2.246). Neurology 90(15 Supplement):P2.246
79. Mateen FJ et al (2010) Evolution of a tumor-like lesion in cerebroretinal vasculopathy and TREX1 mutation. Neurology 75(13):1211–1213
80. Salter CG et al (2021) Biallelic PI4KA variants cause neurological, intestinal and immunological disease. Brain 144(12):3597–3610

81. Sharifinejad N et al (2020) Clinical, immunological, and genetic features in 49 patients with ZAP-70 deficiency: a systematic review. Front Immunol 11:831
82. Vezzani A, Maroso M, Balosso S, Sanchez MA, Bartfai T (2011) IL-1 receptor/Toll-like receptor signaling in infection, inflammation, stress and neurodegeneration couples hyperexcitability and seizures. Brain Behav Immun 25:1281–1289
83. Broz P, Monack DM (2013) Newly described pattern recognition receptors team up against intracellular pathogens. Nat Rev Immunol 13:551–565
84. Philpott DJ, Sorbara MT, Robertson SJ, Croitoru K, Girardin SE (2014) NOD proteins: regulators of inflammation in health and disease. Nat Rev Immunol 14:9–23
85. Kambe N, Nishikomori R, Kanazawa N (2005) The cytosolic pattern-recognition receptor Nod2 and inflammatory granulomatous disorders. J Dermatol Sci 39:71–80
86. Sterka D Jr, Rati DM, Marriott I (2006) Functional expression of NOD2, a novel pattern recognition receptor for bacterial motifs, in primary murine astrocytes. Glia 53:322–330
87. Wang G, Fu Y, Ma K, Liu J, Liu X (2020) NOD2 regulates microglial inflammation through the TAK1-NF-κB pathway and autophagy activation in murine pneumococcal meningitis. Brain Res Bull 158:20–30
88. Cheng L, Chen L, Wei X, Wang Y, Ren Z, Zeng S, Zhang X, Wen H, Gao C, Liu H (2018) NOD2 promotes dopaminergic degeneration regulated by NADPH oxidase 2 in 6-hydroxydopamine model of Parkinson's disease. J Neuroinflamm 15:243