



# Understanding the genetics of rare neuroimmune disorders

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## DISCLOSURES

NO FINANCIAL DISCLOSURES TO DISCLOSE

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RESEARCH FUND



# AGENDA

Prevalence

Overview of Genetics

Genetics of each rare  
neuroimmune disorder

Current Research

Ongoing Projects and Conclusion

## PREVALENCE OF RARE NEUROIMMUNE DISORDERS

Idiopathic optic neuritis (ION): 4-8 per 100,000 per year

Acute demyelinating encephalomyelitis (ADEM): 1 per 125,000-250,000 per year (0.07-0.09 per 100,000 in children)

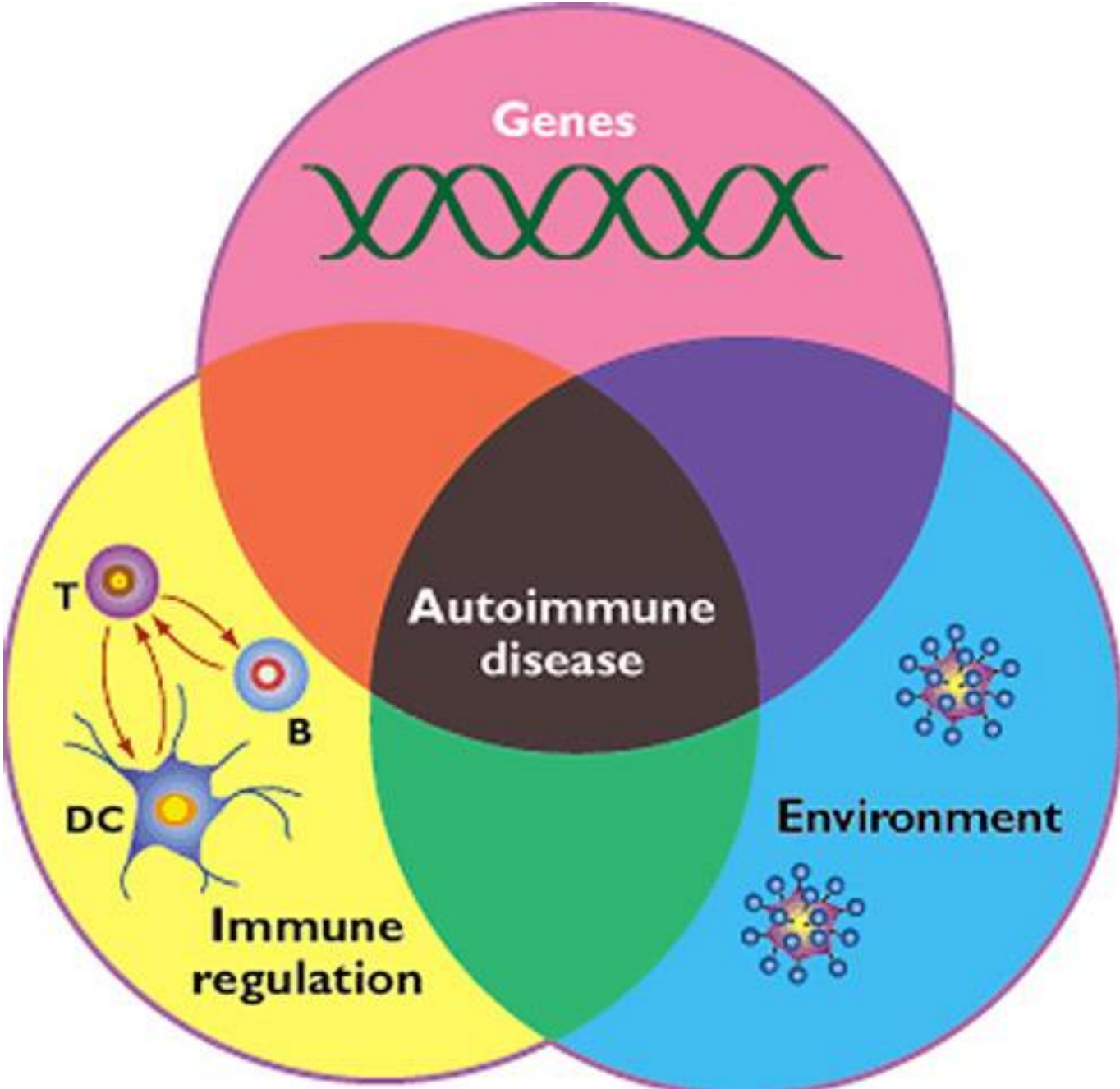
MOGAD: prevalence of 1.3-2.5 per 100,000

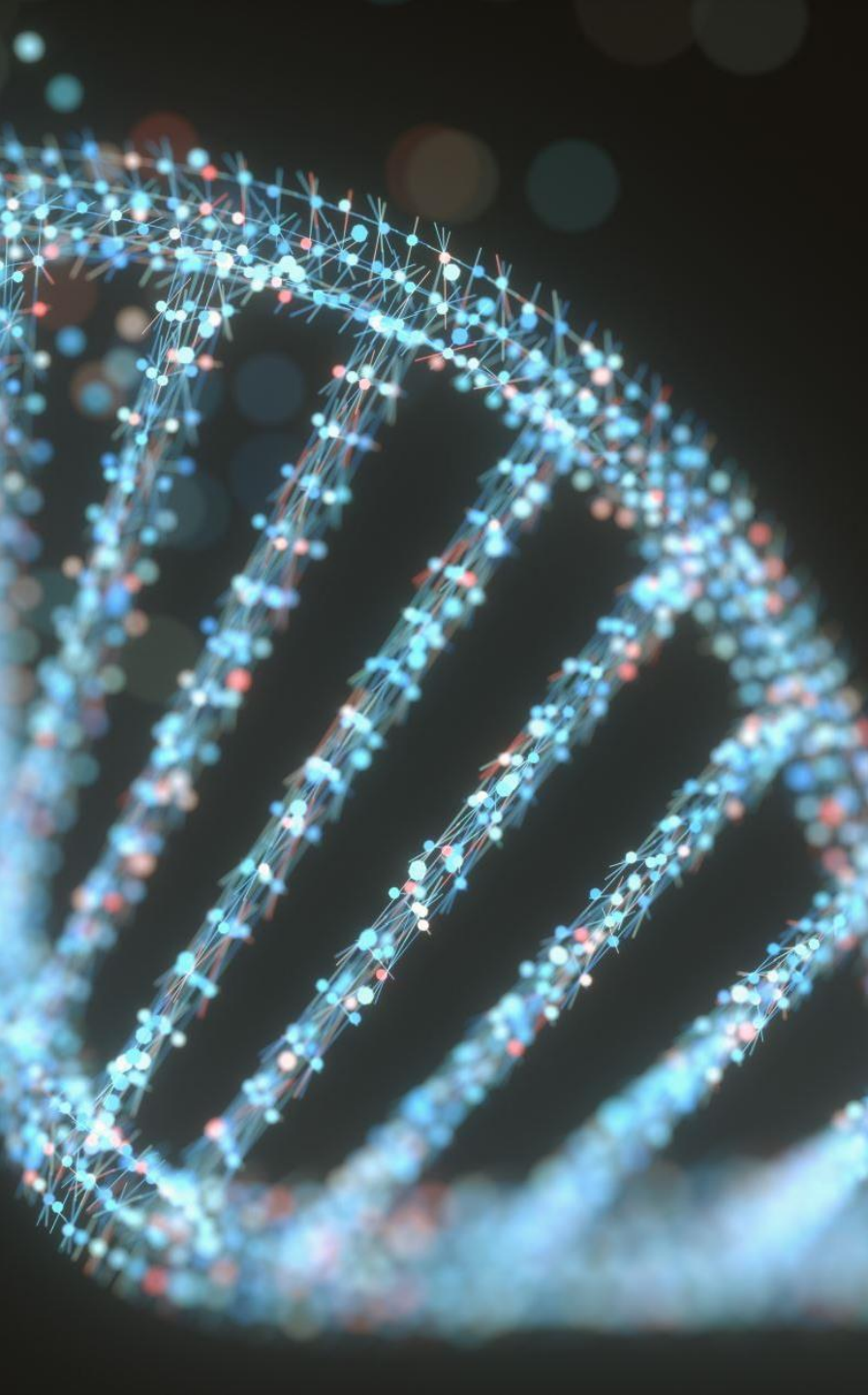
Acute Flaccid Myelitis (AFM): <1 per million per year

Idiopathic Transverse Myelitis (ITM): up to 7.9 per 100,000

NMOSD: 1-5 per 100,000 (worldwide), 6.88 per 100,000 (US)

# UNDERLYING FACTORS OF DISEASE



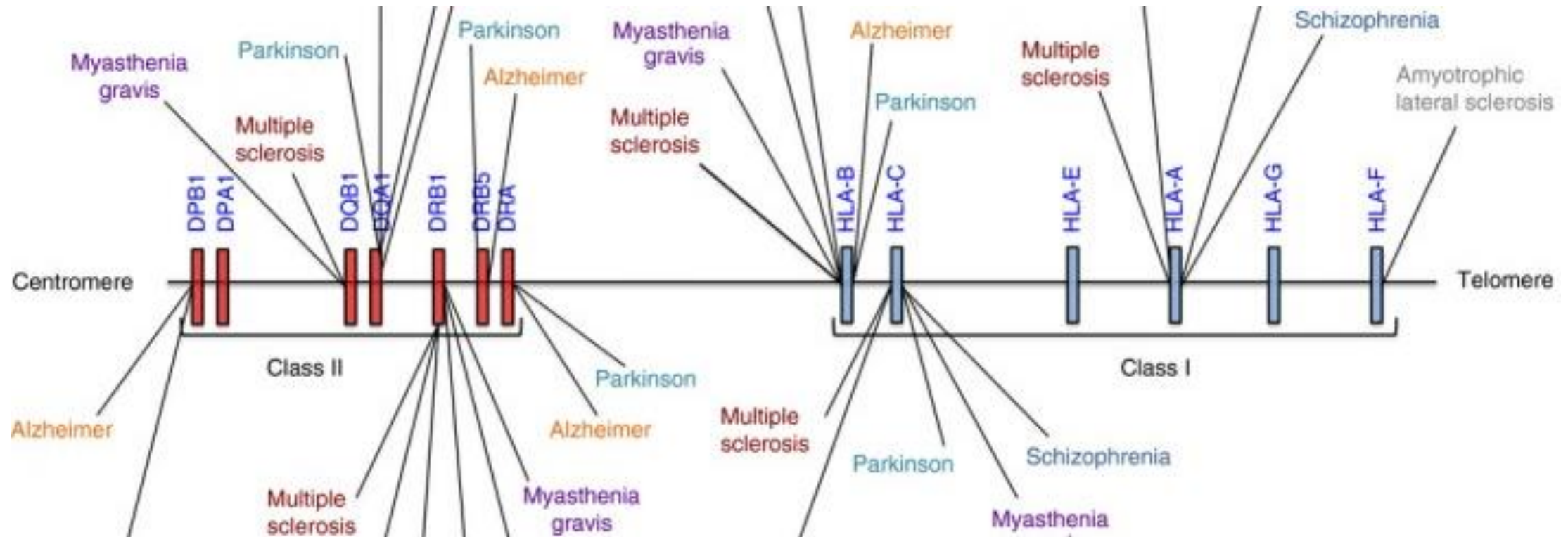


# Genetics

- Types of genetic mutations: Point mutations, insertions, deletions, duplications, translocations, inversions
- Germline vs somatic mutations
- De novo vs inherited
- Can increase or decrease likelihood of developing a disease
- Can impact how well you recover from injury and/or affect disease severity or likelihood of relapse



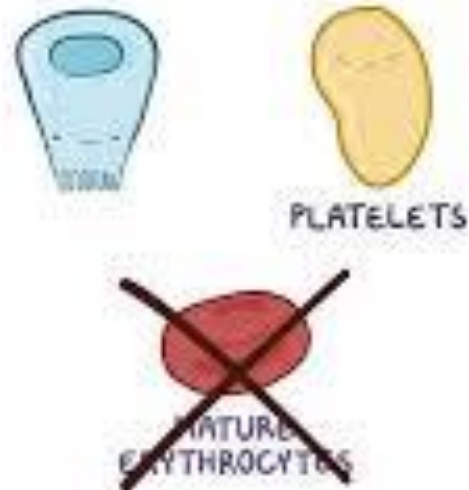
# HISTORY OF GENOME WIDE ASSOCIATION STUDIES IN NEUROLOGY



# HUMAN LEUKOCYTE ANTIGEN (HLA)

- Located on chromosome 6
- approximately 165 different protein-coding genes, most of which are immune related
- Class I: HLA-A, HLA-B and HLA-C, along with three nonclassical loci: HLA-G, HLA-E and HLA-F.
- Class II: HLA-DP, HLA-DQ and HLA-DR, along with two non-classical loci, HLA-DO and HLA-DM.

MHC CLASS I MOLECULES



MHC CLASS II MOLECULES

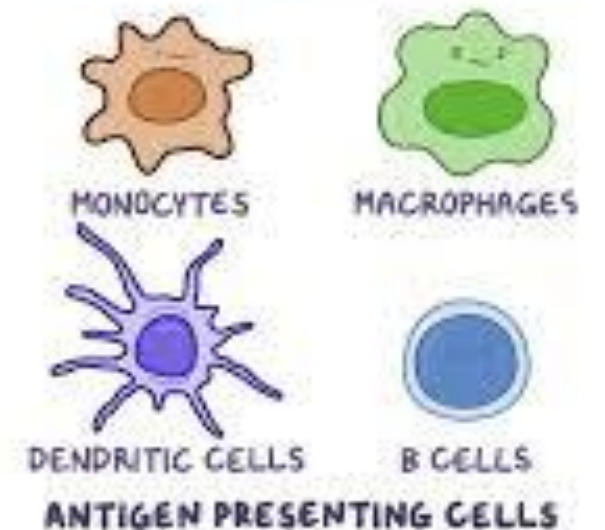


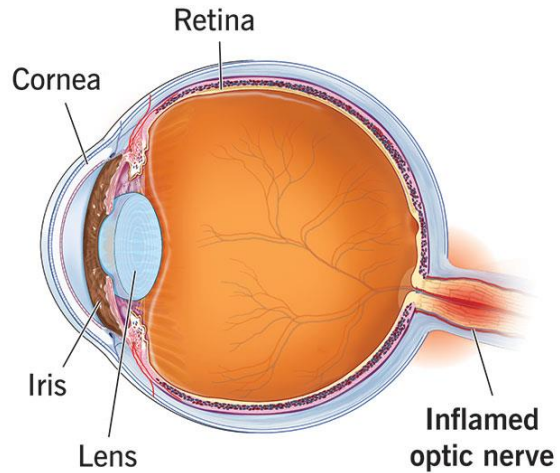


Table 1. Summary of HLA class I and II associated susceptible or protective alleles in neurological diseases

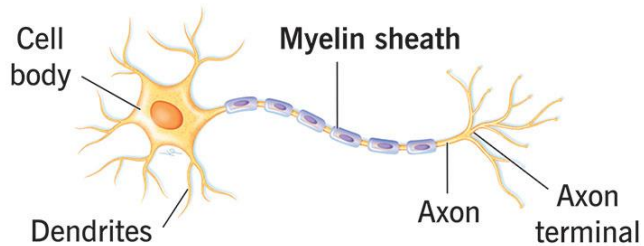
Neurological diseases	MHC class II		MHC class I		References
	Predisposing	Protective	Predisposing	Protective	
Multiple sclerosis	<i>DRB1*15:01, DRB1*15, DRB1*08:01, DRB1*04:05, DRB1*03:01; DRB1*13:03; DRB1*13 ~ DQA1*05:01 ~ DQB1*03:01</i>	<i>DRB1*14:01, DRB1*11, DRB1*13-DQB1*06:03, DQA1*01:01-DRB1*15:01, DQB1*03:01- DQB1*03:02</i>	<i>A*03, *0301; B*07</i>	<i>A*02:01; B*44:02, *44, *38:01, *55:01; C*07, *05</i>	5,29,30, 35-41, 50-55,57-64
Neuromyelitis optica	<i>DPB1*05:01, DPB1*03:01, DRB1*12, DRB1*16:02, DRB1*03</i>	<i>DRB1*09:01</i>	-	-	66-76
Parkinson	<i>DRA, DRB5, DRB1, DRB1*04, DRB1*04:03, DRB1*03, DRB1*03:01</i>	<i>DRB1*04:06, DRB1*04:04, DQA1*03:01</i>	<i>B*07:02, *17, *18; C*07:02</i>	<i>C*03:04</i>	4,77,78,84, 86,87,89
Alzheimer's	<i>DR1, DR2, DR3, DRB1*03, DPB1, DRB5-DRB1, DRA</i>	<i>DR4, DR6</i>	<i>A*02</i>	<i>B*07:02, A*03:01</i>	8,94-101,104
Schizophrenia	<i>DRB1*01:01, DRB1*03:01:01, DRB1*03:01:02, DQA1</i>	<i>DRB1*03:01, DRB1*04, DRB1*06</i>	<i>B*08:01, C*01:02</i>	<i>A*03, *011, *02; B*27, *51</i>	107,108,111, 114,117,118
Myasthenia gravis	<i>DQB1*05:02, DRB1*03, DRB1*04, DQB1*02, DQB1*03, DRB1*09, DRB1*15:01, DQB1*05:02, DRB1*16, DQA1*03:02/DQB1*03:03:02</i>	<i>DRB1*08, DRB1*13:01, DQA1*05:01</i>	<i>B*08, C*07:01</i>	-	63,121-125, 130,132, 133,138
Amyotrophic lateral sclerosis	-	-	<i>A*03, A*02, A*28; B*40, B*35, C*04</i>	<i>A*09, HLA-F</i>	7,140-142, 145,146

## Optic neuritis

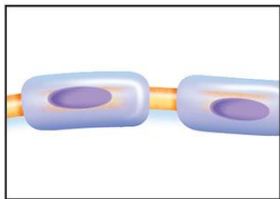
### Anatomy of the eye



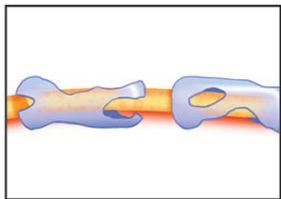
### Anatomy of a neuron



Healthy myelin sheath



Unhealthy myelin sheath



# Genetics of ION

- Momkute et al showed an increased risk of ON with  $APO\epsilon_4$  in males
- Increased APOE levels found in ON compared to controls
- Genotypes T/C and C/C of vascular endothelial growth factor A (VEGFA) rs1413711 were increased in ON subjects compared to controls (Punye et al)
- Another VEGFA, allele C of VEGFA rs833068 was associated with a 1.7 fold increased risk of ON



# ADDITIONAL GENES ASSOCIATED WITH ON RISK

IL-6

IL-1

RAGE

Matrix

metalloproteinase  
(MMP)

HLA-DR2 (assoc w/  
MS)

Cholesterol ester  
transfer protein  
(CETP)

# ADDITIONAL GENES ASSOCIATED WITH ON RISK

ADDITIONALLY, HABEK ET AL PERFORMED GWAS ON PATIENTS WITH ON, RULING OUT SECONDARY CAUSES, AND FOUND DIFFERENTIAL EXPRESSION OF OVER 722 GENES COMPARED TO CONTROLS. THE PROTEINS THAT APPEARED TO BE OF GREATEST SIGNIFICANCE WERE:

- SLP1 (AKA VPS33, sorts proteins from golgi to vacuole)
- CR3 (complement receptor 3)
- ITGA4 (integrin subunit alpha 4)

# ACUTE DEMYELINATING ENCEPHALOMYELITIS (ADEM)

- Alvez-Leon et al found HLA DQB1\*0602, DRB1\*1501 and DRB1\*1503 alleles to be slightly associated (<0.05) in monophasic ADEM.
- Cui et al demonstrated increased variations in NAC, GOLGA5 and CTLA4 in pediatric patients with MOG+ ADEM

**TABLE 3.**  
Significant Association Between Candidate SNPs and MOG-IgG+ ADEM

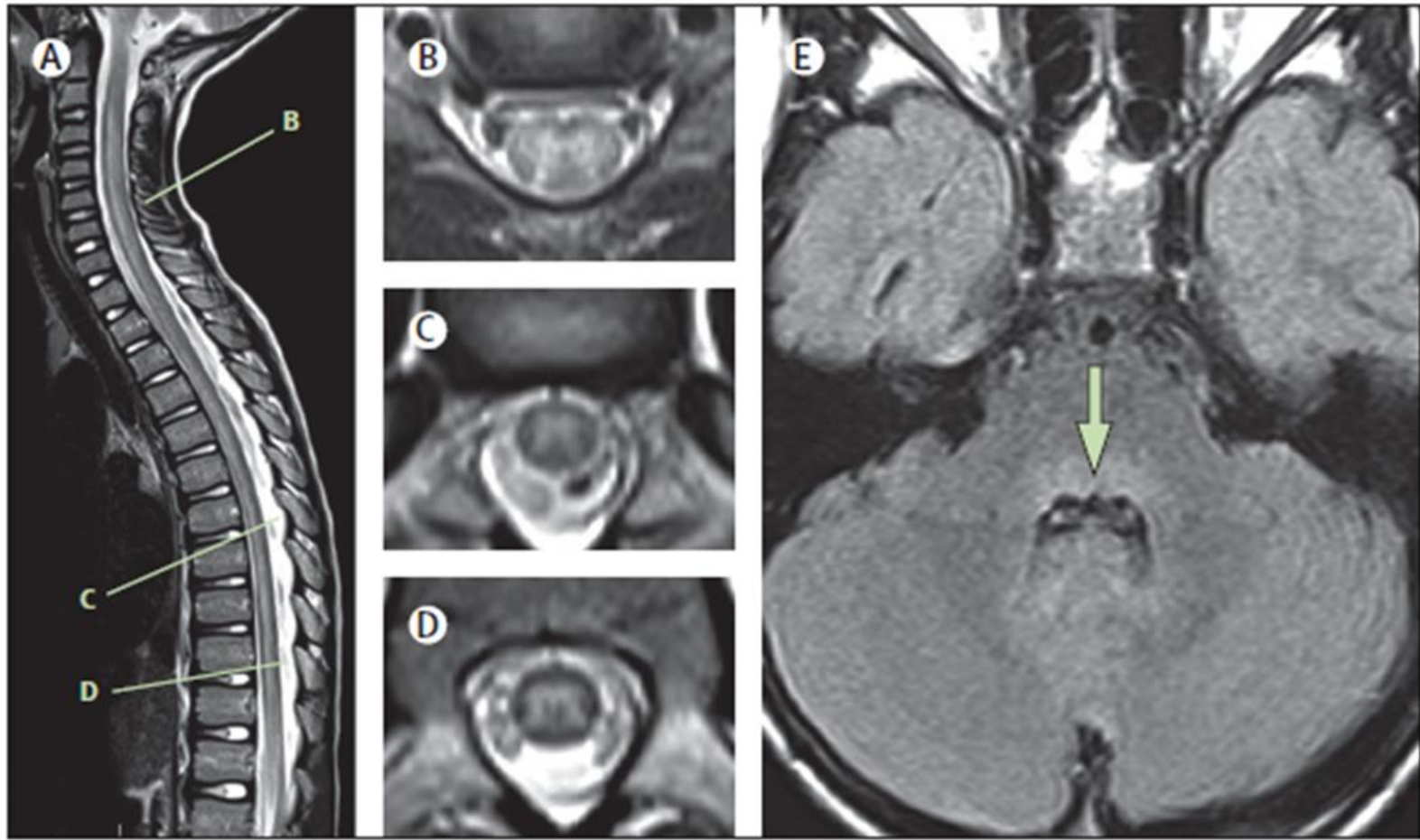
Gene	SNP	ADEM group	Aa+aa*	AA*	P	OR [95%CI]	P <sub>adj</sub>
NAC $\alpha$	rs11171951 (c.1864+684 G>A)	MOG-IgG+	28	2	<0.001 <sup>†</sup>	15.39[3.06-77.39]	<0.001 <sup>†</sup>
		MOG-IgG-	8	19			
GOLGA5	rs1040835 ( c.1048 T>C)	MOG-IgG+	27	2	0.027 <sup>†</sup>	3.84[1.13-13.09]	0.81
		MOG-IgG-	26	1			
CTLA4	rs231775 (c.49 A>G)	MOG-IgG+	23	6	0.019 <sup>†</sup>	4.11[2.22-13.62]	0.76
		MOG-IgG-	22	5			

*Table 2. The allelic association of DRB1\*1501, DRB1\*1503, DQA1\*0201, DQB1\*0602 and DPA1\*0301 among 11 ADEM patients and 84 healthy matched controls.*

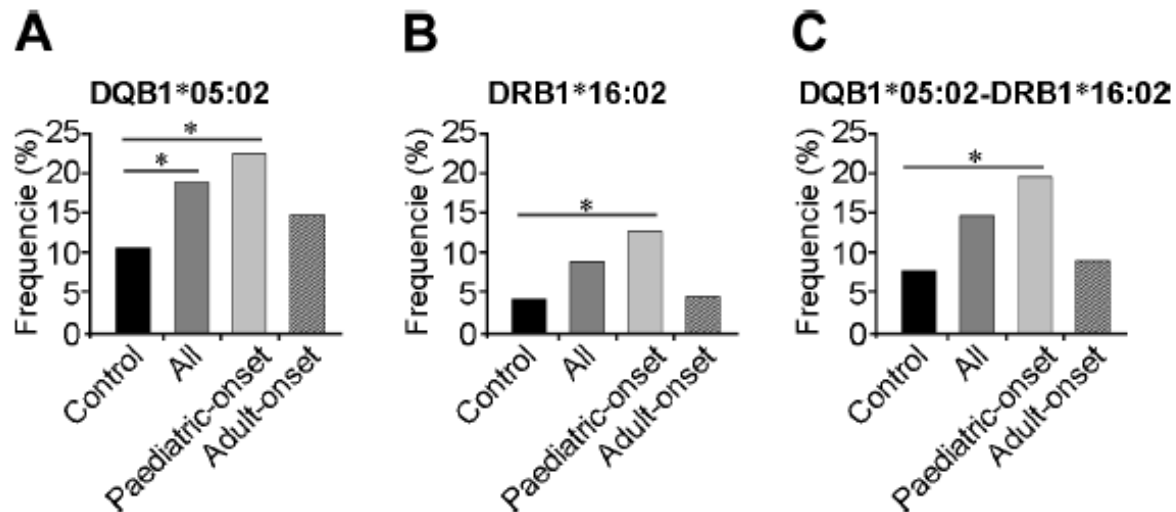
	Patients N=11 (%)	Controls N=84 (%)	p	Pc	OR
DQB1*0602	10 (90.9)	30 (35.7)	0.0004	0.0001	18.00
DQA1*0102	4 (36.3)	24 (28.5)	0.59	0.85	1.43
DRB1*1501	4 (36.3)	10 (13.0)	0.04	0.12	3.79
DRB1*1503	5 (45.4)	9 (10.7)	0.004	0.01	6.17
DPA1*0301	6 (54.5)	30 (35.7)	0.22	0.37	2.16

# ACUTE FLACCID MYELITIS

No genetic susceptibility  
noted to date



# Myelin Oligodendrocyte Glycoprotein Antibody Disease (MOGAD)



- Sun et al found that DQB1\*05:02 and DRB1\*16:02 alleles were associated with pediatric onset
- Also associated with more severe disease
- There were no risk alleles associated with adult onset in their cohort

Sun et al. J Neurol Neurosurg Psychiatry. 2020 May

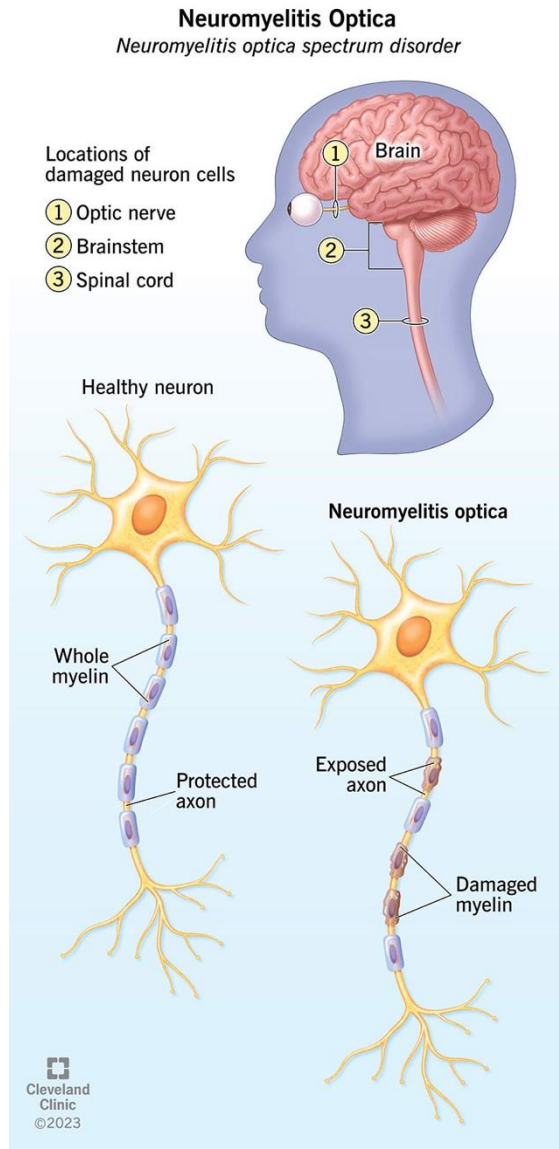




# GENETICS OF MOGAD

- IN A SEPARATE STUDY (ALSO OUT OF CHINA), SHU ET AL FOUND INCREASED PREVALENCE OF RNASET2 (RECRUITS MACROPHAGES), BANK1 (ASSOCIATED WITH SYSTEMIC SCLEROSIS) AND TNIP1 (REGULATIONS NFK-B) WHEN INVESTIGATING 28 IMMUNE RELATED GENES IN PATIENTS WITH MS, MOGAD OR NMO
- ADDITIONAL STUDIES IN THE NETHERLANDS AND UK FOUND NO HLA ASSOCIATION

# Neuromyelitis Optica Spectrum Disorder (NMOSD)



- Unlike MOGAD, there are familial and sporadic forms
- HLA-DRB1\*04:05 and \*16:02.
- HLA-DRB1\*03 associated with NMO in Afro-Caribbeans. This is the most appreciated risk focus.
- HLADRB1\*08:02 and HLA-DRB1\*16:02 have been found as risk loci, while HLA-DRB1\*09:01 has been a protective allele

# NMOSD WHOLE EXOME SEQUENCING

- Whole exome sequencing has also detected:
  - AQP4,
  - CYP27B1 (Vitamin D activator)
  - CYP7A1 (Thyroid Hormone receptor)
  - CD226 (costimulatory molecule for NK and T cells)
  - CD58 (costimulatory molecule for NK and T cells)
  - CD6 (T cell activation)
  - FCRL3(interacts with HLADRB1\*0103)
  - GPC5 (inhibits tumor growth)
  - MIF (macrophage migration inhibitory factor)
  - ATG5 (core autophagy protein)
  - PD-1.3 (programmed cell death)
  - IL2RA (expressed on activated T cells and Tregs)
  - IL7RA
  - IL17A

HLA regions	Number of samples	Population	Source of sample/ assay methods	Associations	Year	Ref
HLA-A, B, C HLA-DRB1, DQB1, DPB1 HLA-DRB1, DQB1	15 NMO patients and 606 healthy controls 42 NMO patients and 150 healthy controls	Southern Brazilian French Afro-Caribbean	Peripheral blood/ Sanger sequencing Peripheral blood/ PCR-SSO	There was significant association between HLA-DRB1*16:02, *04:05, C*15:02 alleles and NMO susceptibility. There was significant association between HLA-DRB1*03 alleles and NMO disease.	2019	(22)
HLA-DRB1, 3, 4 and 5	27 NMOSD patients and 28 healthy controls	Mulatto Brazilian (Ribeirão Preto)	Peripheral blood/ PCR-SSP	HLA-DRB1*03 and DRB1*10 alleles were overrepresented in NMOSD patients compared to controls.	2009	(24)
HLA-DRB1	35 NMO patients and 99 healthy controls	Brazilian (Mexico City)	Peripheral blood/ PCR-SSP	HLA-DRB1*03 and DRB1*10 alleles were more common in NMO cases compared to controls.	2016	(25)
HLA-DRB1, DQA1 and DQB1	65 NMO patients and 100 healthy controls	Brazilian (Rio de Janeiro)	Peripheral blood/ PCR-SSO and SSP	HLA-DRB1*01:02, 03:01, DQB1*02:01 and DQA1*01:05 alleles were more common in NMO cases compared to controls. DRB1*03:01- DQA1*05:01/3/5-DQB1*02:01, DRB1*01:02-DQA1*01:01-DQB1*05:01 and DRB1*10:01-DQA1*01:04/5-DQB1*05:01 haplotypes were associated with NMO.	2017	(26)
HLA-A, B, C, DRB1 and DQB1	71 NMO patients and 97 healthy controls	Mexican	Peripheral blood/ SBT	Risk HLA alleles for NMO: DQB1*03:01, DRB1*08:02, DRB1*16:02, DRB1*14:06, DQB1*04:02, B*35:14, B*39:06 and protective alleles include: DQB1*03:02, DQB1*02:02, DRB1*04:07, DRB1*07:01 and B*39:05	2020	(28)
HLA-A, B, DQA1, DQB1, DRB1, and DPB1	39 NMO, 6 patients at risk of NMO, and 100 healthy controls	French Caucasian	Peripheral blood/ PCR-RFLP and PCR-SSP	HLA-DQA1*102, * 501, DQB1*0201 DRB1*03 alleles were significantly associated with NMO. There was no correlation between distribution of HLA alleles and IgG antibody subgroups	2009	(29)
HLA-DRB1	22 NMO patients and 225 healthy controls	Spanish Caucasian	Peripheral blood	HLA-DRB1*10 allele was significantly associated with NMO disease.	2011	(30)
HLA-A, B, C, DRA, DRB1, DQA1, DQB1, DPA1, DPB1, E, F, G, DOA, DOB, DMA, and DMB	31 NMOSD patients and 429 healthy controls	Japanese	Peripheral blood/ NGS-based HLA genotyping	HLA-DQA1*05:03 allele had the most association with NMOSD.	2019	(31)
HLA-DRB1 and DPB1	77 NMO, 39 NMOSD patients and 367 healthy controls	Japanese	Peripheral blood/ PCR-SSO	Higher occurrence of HLA-DRB1*1602, DPB1*0501 and lower occurrence of DRB1*0901 alleles were associated with anti-AQP4 antibody positive patients.	2012	(32)
HLA-DRB1 and DPB1	165 NMOSD patients	Japanese	Peripheral blood/ SSO (Luminex)	HLA-DRB1*08:02 and DPB1*05:01 alleles were associated with disease and DRB1*09:01 was protective allele in	2021	(33)

# NMO GENETICS

More recently Saggau et al identified enrichment of T cells with HLA-DQ6.2 (DQA1\*01:02, DQB1\*06:02) reactive to AQP-4 in NMOSD patients

TABLE 3 | Continued

Genes	Number and type of samples	Population	Source of samples/ assay method	Associations	Ref
<i>CYP27B1</i> : rs12368653 rs10876994 rs118204009 rs703842 <i>CYP24A1</i> : rs2248359 11 SNPs in <i>CYP7A1</i>	110 NMO patients and 294 healthy controls	Han Chinese	Peripheral blood/ MassARRAY system and sanger sequencing	rs703842 and rs10876994 were significantly associated with NMO compared to controls.	(55)
Promoter region of <i>CYP7A1</i> <i>CD226</i> : rs763361 <i>CD58</i> : rs17426456 rs2300747 rs1335532 rs12044852 rs1016140 rs12025416	89 NMO patients and 325 controls 89 NMO patients and 129 healthy controls 98 NMO patients (AQP4-Ab <sup>+</sup> ) and 238 healthy controls	Han Chinese Southern Han Chinese Korean	Peripheral blood/ sanger sequencing Peripheral blood/ sequencing Peripheral blood/ TaqMan assay	- rs3808607 and rs1457043 were associated with NMO. -"G/G" genotype of rs3808607 had a higher protective effect on the risk of disease. -204A>C (rs3808607), -469T>C (rs3824260) and -208G>C were significantly associated with NMO. TT genotype of rs763361/Gly307Ser was associated with NMO susceptibility. - 4 SNPs (rs2300747, rs1335532, rs12044852, and rs1016140) and 2 haplotypes in the <i>CD58</i> gene were significantly associated with NMO. - rs1016140 led to T-cell hyperactivity that caused AQP4-Ab access to CNS.	(56) (57) (58) (59)
9 SNPs in <i>CD58</i> : rs1335532 rs10802189 rs56302466 rs472291 rs3789716 rs1335531 rs1335532 rs2300747 rs1016140	230 NMOSD patients and 487 healthy controls	Han Chinese	Peripheral blood/ SNPscan Kit and PCR-LDR	- rs2300747, rs1335532, rs56302466, rs1016140, and rs12044852 were associated with NMOSD. - TAGCCCAA haplotype increased and TATTACGG haplotype reduced NMOSD risk.	(60)
21 SNPs in <i>CD6</i> , <i>TNFRSF1A</i> and <i>IRF8</i> 6 SNPs in <i>FCRL3</i>	99 NMO patients and 237 healthy controls 150 NMO patients and 300 healthy controls	Korean Chinese	Peripheral blood/ TaqMan assay Peripheral blood/ MALDI-TOF-MS	rs12288280 in <i>CD6</i> gene and rs767455, rs4149577, rs1800693, and ht2, ht3 haplotypes in <i>TNFRSF1A</i> were significantly associated with NMO. G allele of -1901A>G and T allele of -658C>T polymorphism were significantly more frequent in patients	(61) (62)
7 SNPs in <i>FCRL3</i> : rs7528684 rs11264799 rs945635 rs3761959 rs2210913 rs2282284 rs2282283	132 NMO patients and 264 healthy controls	Chinese	Peripheral blood/ TaqMan assay and sequencing	Both allelic and homozygote model of s7528684, rs945635, rs3761959, and rs2282284 were significantly associated with NMO susceptibility.	(63)
9 SNPs in <i>GPC5</i> <i>MIF-173</i> rs755622	99 NMO patients and 237 healthy controls 70 NMO patients and 60 healthy controls	Korean Caucasian	Peripheral blood/ TaqMan assay Peripheral blood/ PCR-RFLP	rs1411751, rs9523762 and BL1_ht3 haplotype of <i>GPC5</i> were significantly associated with NMO. CC/GC genotypes in polymorphism were correlated with higher EDSS. These genotypes were more frequent in patients with both optic neuritis and myelitis. <i>MIF-173</i> in more associated with severity rather than susceptibility.	(64) (65)
5 SNPs in <i>ATG5</i> : rs2245214	109 NMO patients and 288 healthy controls	Southern Han Chinese	Peripheral blood/ MALDI-TOF-MS	CC genotype of rs548234 associated with NMO susceptibility while T allele of rs548234 and A allele of rs6937876 played a protective role in AQP4-	(66)

# IDIOPATHIC TRANSVERSE MYELITIS (ITM)

Felt to be sporadic  
and not familial

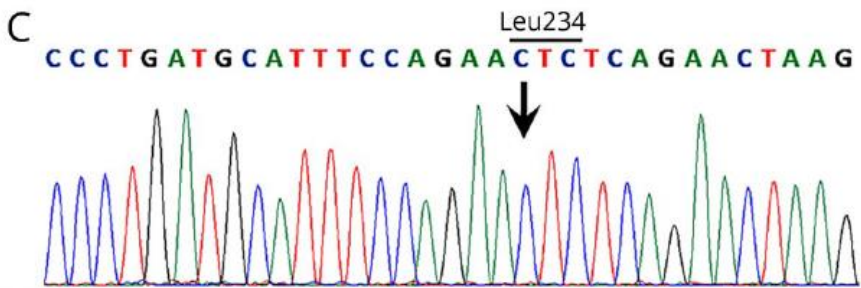
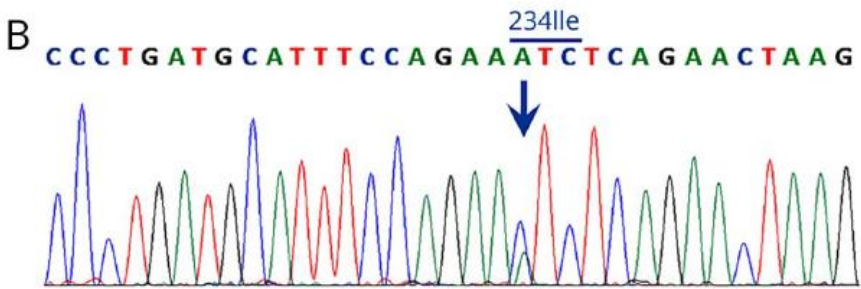
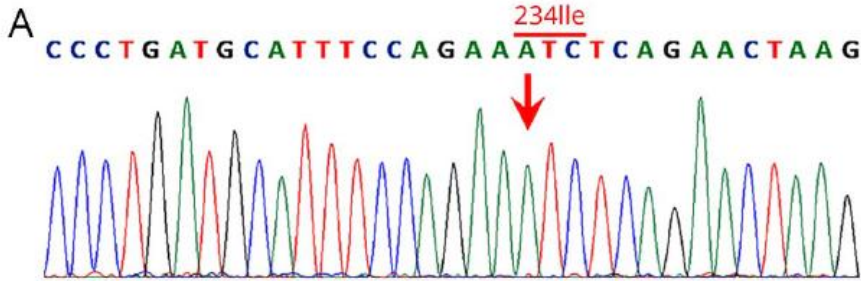


# VPS37A-L234I

# Familial monophasic acute transverse myelitis due to the pathogenic variant in VPS37A

Maureen A. Mealy, RN, Tai-Seung Nam, MD, PhD, Santiago J. Pardo, BA, Carlos A. Pardo, MD, PhD, Nara L. Sobreira, MD, PhD, Dimitrios Avramopoulos, MD, PhD, David Valle, MD, Kathleen H. Burns, MD, PhD, and Michael Levy, MD, PhD

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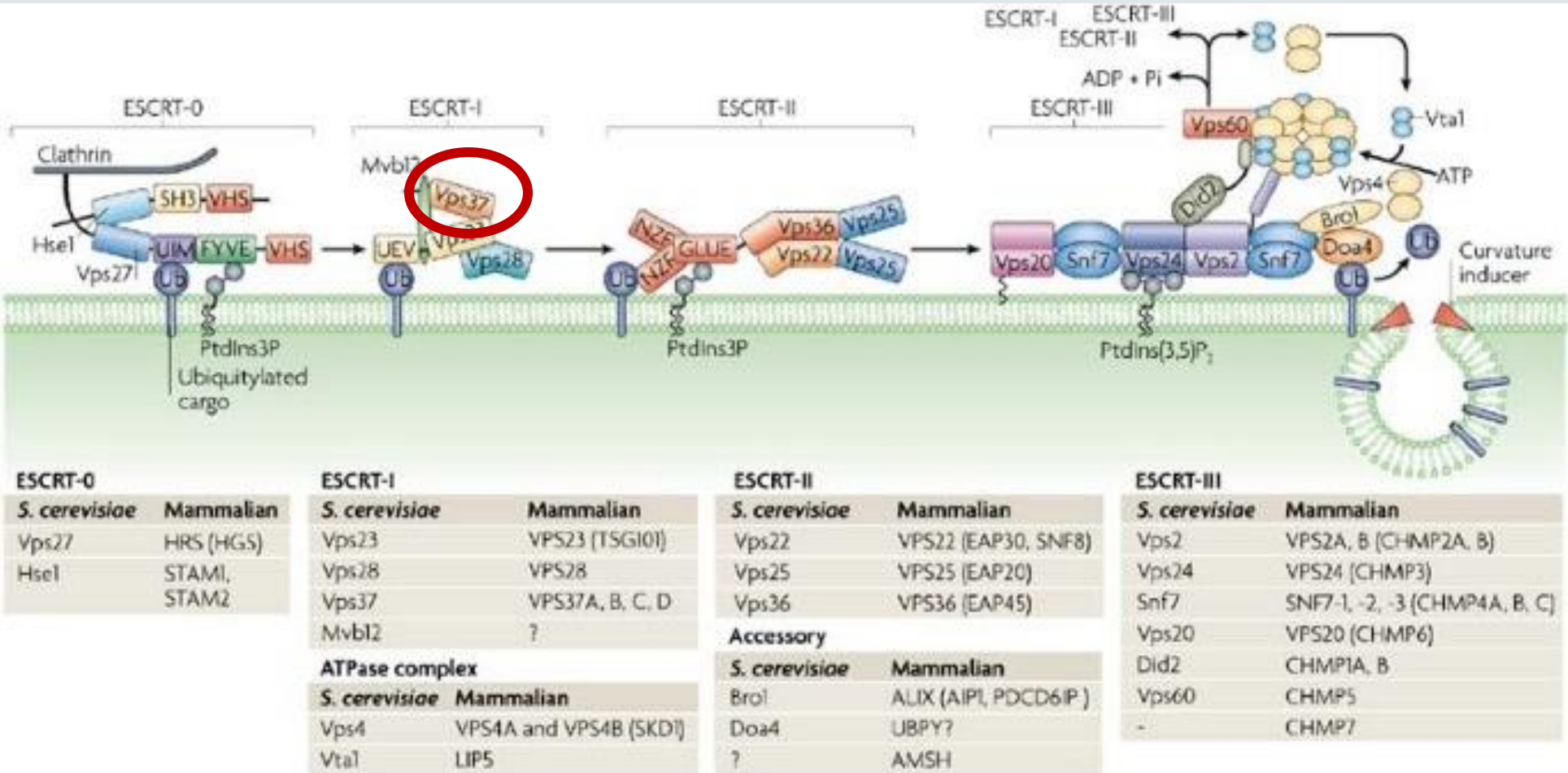


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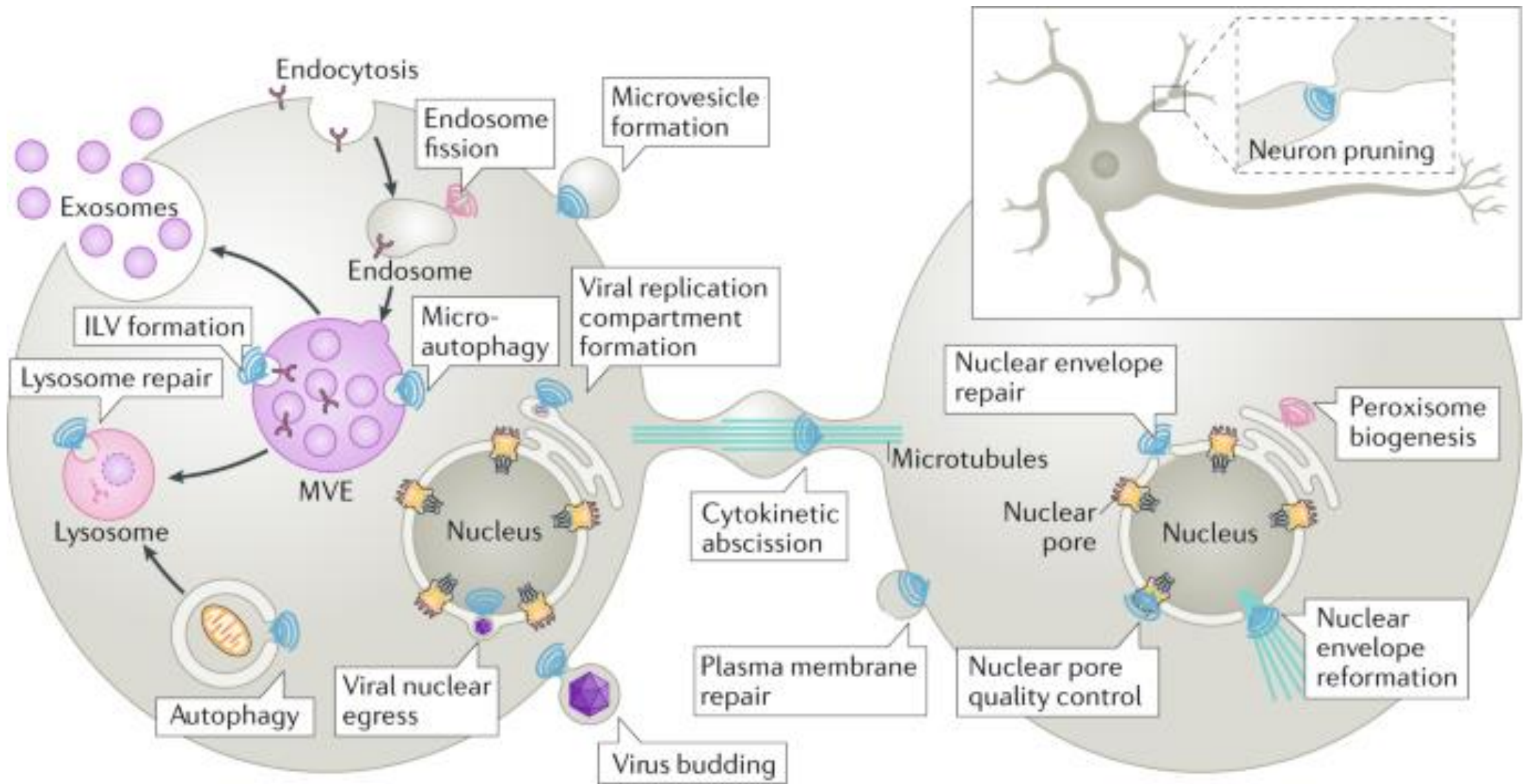
<i>Homo sapiens</i>	Pro	Asp	Ala	Phe	Pro	Glu	Leu	Ser	Glu	Leu
<i>Callithrix jacchus</i>	Pro	Asp	Ala	Phe	Pro	Glu	Leu	Ser	Glu	Leu
<i>Rattus norvegicus</i>	Pro	Asp	Ala	Phe	Pro	Glu	Leu	Ser	Glu	Leu
<i>Mus musculus</i>	Pro	Asp	Ala	Phe	Pro	Glu	Leu	Ser	Glu	Leu
<i>Gallus gallus</i>	Pro	Asp	Thr	Phe	Pro	Glu	Leu	Leu	Glu	Leu
<i>Xenopus laevis</i>	Pro	Glu	Thr	Phe	Ser	Glu	Leu	Leu	Glu	Leu
<i>Danio rerio</i>	Pro	Asp	Thr	Phe	Ser	Glu	Leu	Ser	Glu	Met

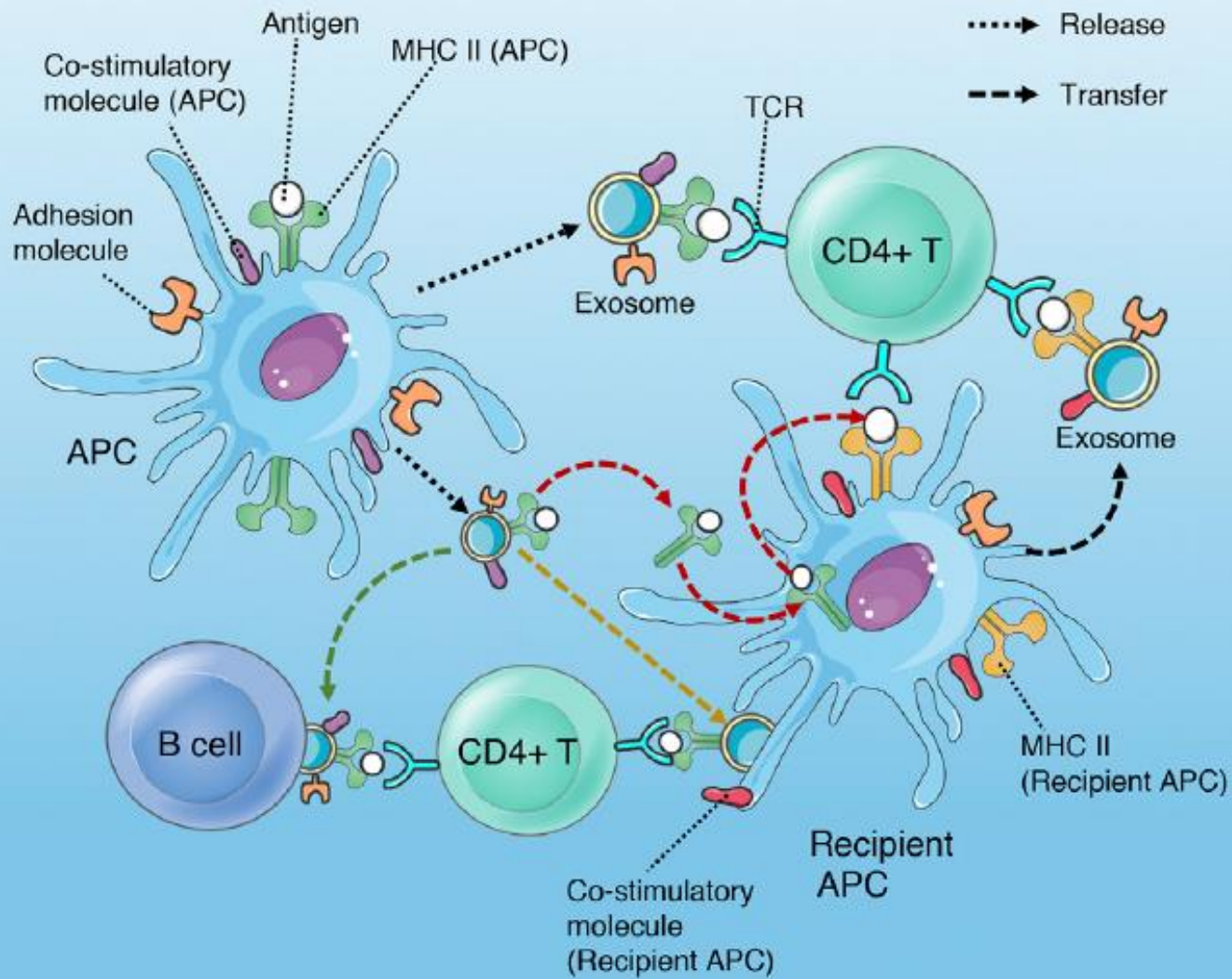
In pursuit of an etiology, genetic analysis of TM patients was undertaken and a pair of siblings with ITM were found to have a shared unique point mutation in VPS37A

# THE ENDOSOMAL SORTING COMPLEX REQUIRED FOR TRANSPORT (ESCRT)



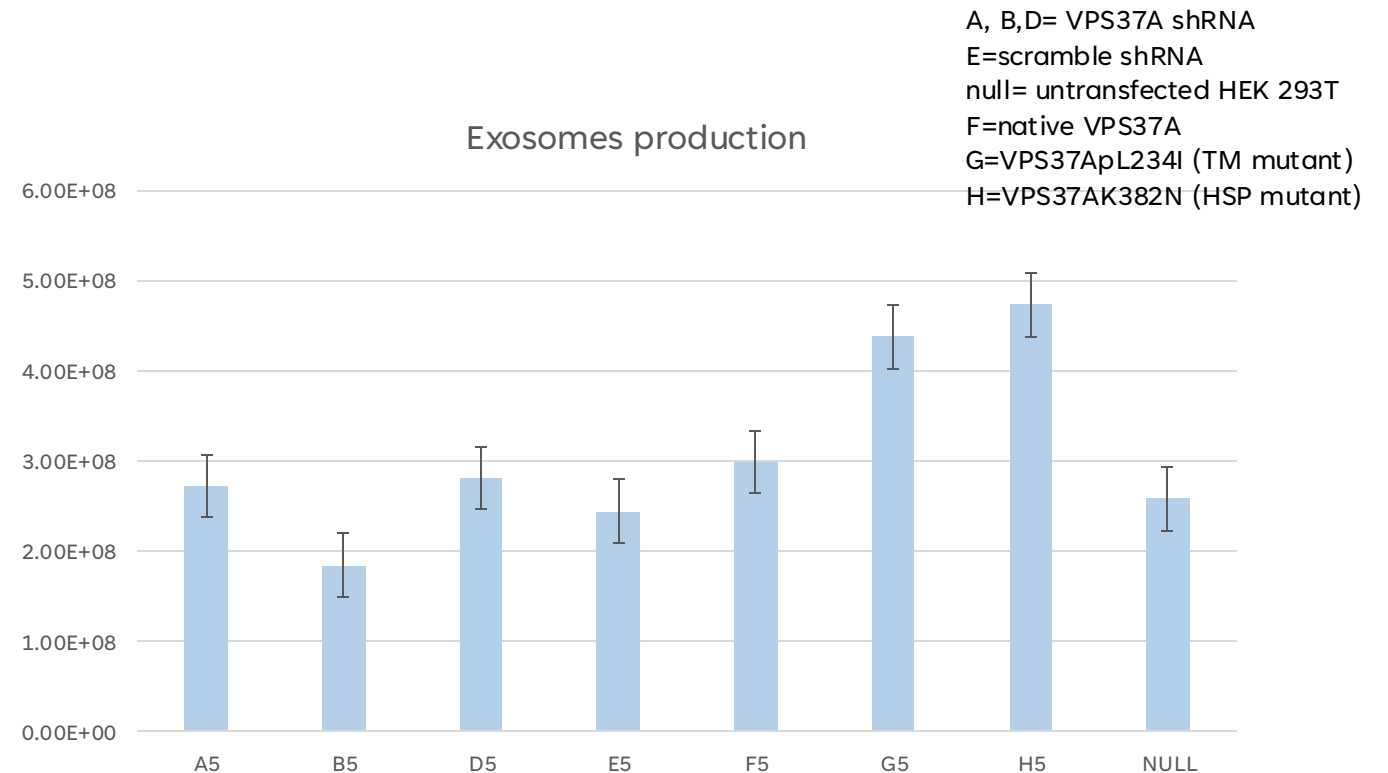






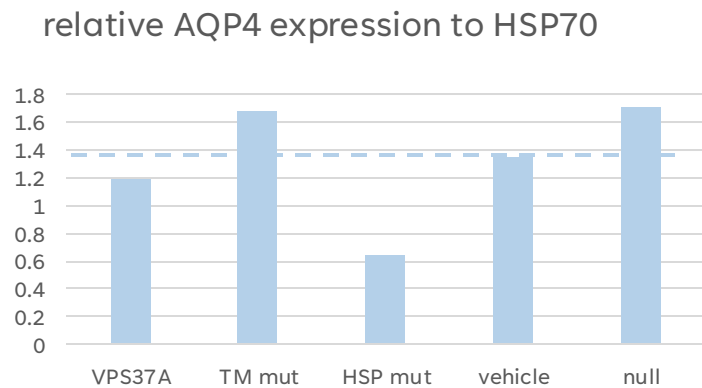
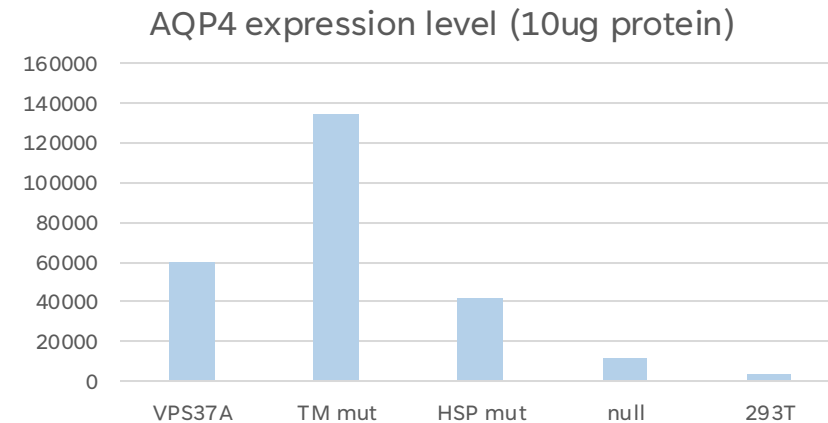
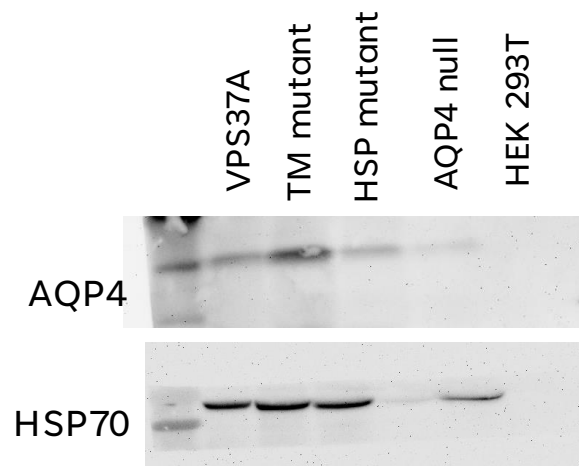
# BOTH VPS37A MUTATIONS ARE ASSOCIATED WITH INCREASED EXOSOME PRODUCTION/EXPORT

- VPS37A-L234I (TM mutant) and VPS37A-K382N (HSP mutant) were both associated with increased exosome production
- Noted variability in degree of exosome decrease with attempted KD



# CHANGES IN AQP4 CARGO IN ISOLATED EXOSOMES

1. Increased AQP4 cargo in exosomes isolated from AQP4-GFP 293T cells transfected with VPS37A TM mutant



# ADDITIONAL ESCRT MUTATIONS ASSOCIATED WITH DEMYELINATING DISORDERS

Gene	ESCRT pathway	Chromosome	rsID	Frequency in TM / general population	Effect	Number of patients with SNP	
						TM (167 cases)	NMOSD / MS / CTRL (364 / 1718 / 726 cases respectively)
IST1	III	16	rs773454925	0.60% / 0.017%	Splice donor variant	1 (c.798+1G>C)	0
CHMP1A	III	16	rs374723745	0.60% / 0.0013%	Stop gain	1 (c.698C>G; p.Ser233*)	0

# ADDITIONAL ESCRT MUTATIONS ASSOCIATED WITH DEMYELINATING DISORDERS

Gene	ESCRT pathway	Chromosome	rsID	Frequency in TM / general population	Effect	Number of patients with SNP				
						TM (167 cases)	NMOSD (364 cases)	MS (1718 cases)	CTRL (726 cases)	Demyelinating disease (Total / Frequency)
STAM2	0	2	rs747171028	0.60% / 0.026%	Mis-sense	1 (c.259C>T, p.Arg87Cys)	1 (C>A; Arg>Ser)	2 (C>A; Arg>Ser)	0	4 / 0.13%
CHMP4C	III	8	rs114287276	0.60% / 0.026%	Mis-sense	1 (c.455G>A, p.Arg152Gln)	2 (G>A; Arg>Gln)	1 (G>A; Arg>Gln)	0	4 / 0.13%
TSG101	I	11	rs34385327	0.60% / 0.56%	Mis-sense	1 (c.501G>A, p.Met167Ile)	5 (G>A; Met>Ile)	2 (G>A; Met>Ile)	0	8 / 0.27%
VPS4A	ATPase complex	16	rs184892976	0.60% / 0.039%	Mis-sense	1 (c.1171G>A, p.Asp391Asn)	4 (G>A; Asp>Asn)	4 (G>A; Asp>Asn)	0	9 / 0.30%
IST1	III	16	rs139513735	0.60% / 0.059%	Mis-sense	1 (c.505G>A, p.Ala169Thr; c.22G>A, p.Ala8Thr; c.466G>A, p.Ala156Thr)	1 (G>A; Ala>Thr)	1 (G>A; Ala>Thr)	0	3 / 0.10%

**WHAT CAN WE DO?**

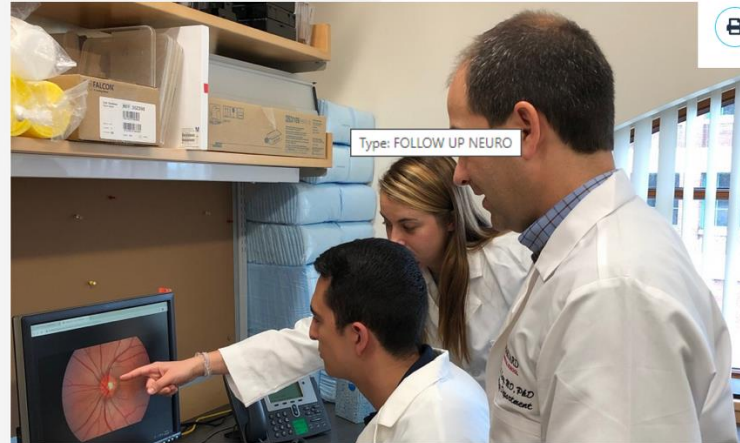
# Ongoing Research

## Neuroimmunology Clinic and Research Laboratory

Welcome to the Neuroimmunology Clinic & Research Lab at Massachusetts General Hospital. We provide leading-edge patient care, clinical research, education and awareness about rare autoimmune disorders of the central nervous system.

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## Residuals of TM in MOGAD


**ALSO AVAILABLE THROUGH THE MGH NEUROIMMUNOLOGY CLINIC PAGE**

**[HTTPS://WWW.MASSGENERAL.ORG/NEUROLOGY/TREATMENTS-AND-SERVICES/NEUROIMMUNOLOGY-CLINIC](https://www.massgeneral.org/neurology/treatments-and-services/neuroimmunology-clinic)**



A decorative graphic on the left side of the slide showing a molecular structure with various colored spheres (red, blue, green, purple) connected by thin lines, set against a light gray background.

# Conclusions

- It is very rare to find a gene directly responsible for a single disease.
  - Usually genetics can potentially create a background where you are at increased risk for developing a disease
  - Often there may be multiple genes and other factors at play
  - However, genetics can help guide us in potential therapeutic targets for disease
- 
- A decorative horizontal bar at the bottom of the slide with a gradient from light blue on the left to light green on the right.

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# Thank you

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# GENOME WIDE ASSOCIATION STUDIES (GWAS)

Review Article

## Genome-wide association studies in neurology

Meng-Shan Tan<sup>1</sup>, Teng Jiang<sup>2</sup>, Lan Tan<sup>1,2,3</sup>, Jin-Tai Yu<sup>1,2,3</sup>

These initial studies allowed for the discovery of a role of inflammation in neurodegenerative disorders like Parkinson's disease, Alzheimer's disease and ALS

It also shed light on particular genetic risk factors in MS