Homozygous Nonsense Variant In Macrophage-Expressed Gene 1 (MPEG1)/Perforin-2: A Case Study

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INTRODUCTION

Macrophage-expressed gene 1 (MPEG1) encodes for Perforin-2 (P2) which is an antibacterial protein belonging to the membrane attack complex/perforin forming (MACPF) superfamily of pore-forming proteins[1]. MACPR proteins are responsible for forming large transmembrane channels known as membrane attack complexes (MAC), acting as immune effectors against bacterial pathogens[1]. Perforin-2 (P2) is expressed in innate immune cells (macrophages, dendritic cells, natural killer cells, and neutrophils) and can be upregulated by proinflammatory signals such as type I and II interferons, lipopolysaccharides (LPS), and bacterial infections[2]. In its resting state, P2 is in the endoplasmic reticulum, Golgi, and early endosomal membranes[2]. After a bacterial infection, it is monoubiquitinated in response to inflammatory signals and redistributes to the endosomal and phagosomal bodies that contain the phagocytosed bacteria[2-3]. After re-localizing, P2 polymerizes and refolds to form large pores allowing lysozyme, reactive oxygen species, and nitric oxide to eliminate the phagocytized bacterial organisms[2-3]. In published research, five cases with heterozygous pathogenic variants in the *MPEG1* gene have been identified, all with histories that include recurrent pulmonary or soft tissue infections[4-5]. Our patient is the first documented case with a homozygous nonsense variant in the *MPEG1* gene.

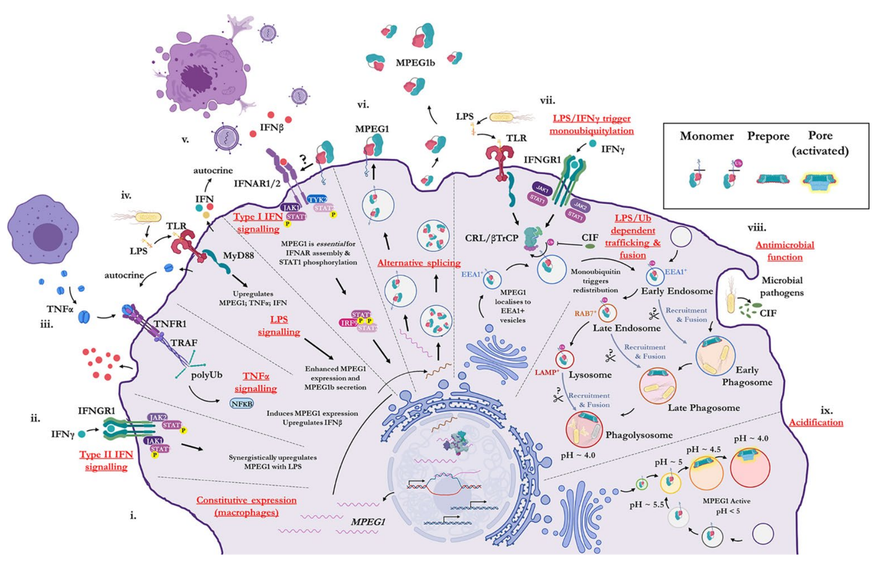

Fig. 1. *Illustration of MPEG1's role within the cell*[1]

OBJECTIVES

- To analyze the phenotypic manifestations of our patient with the *MPEG1* variant.
- Review the published literature on documented *MPEG1* cases for phenotypes and genotypes.
- Compare the published data with our patient.

METHODS & MATERIAL

- Our patient was initially evaluated at Columbia University as a part of the DISCOVER program.
- Data collected during this initial evaluation was used to characterize the clinical manifestations.
- Published literature on all the published *MPEG1* cases was reviewed and compared with the clinical features of our patient.

RESULTS: SUMMARY OF INDEX

Our Patient is a 39-year-old female of South Korean ancestry who presented with multiple issues including including bilateral sensorineural hearing loss, hyperparathyroidism, osteoporosis, a history of periodic subconjunctival hemorrhage, Crohn's disease, recurrent pancreatitis, blistering and hives on her hands, irregular menses over the last year, eczema, recent hair loss, significant dental issues and T-cell lymphocytopenia. Further dental history includes rapid and progressive enamel loss requiring approximately 3 crowns per year and has resulted in several failed root canals and lost teeth. This patient's whole exome sequencing re-analysis revealed a homozygous nonsense variant (c.445C>T (p.Arg149Ter)) in the *MPEG1* gene. She is adopted; therefore, family and pregnancy exposure histories are unknown. There is concern that she may have a variation of a common variable immunodeficiency (CVID) and intravenous immunoglobulin (IVIG) has been suggested.

RESULTS: GENOTYPIC ANALYSIS

	Index Case	Mereselis et al. 2020	McCormack et al. 2017			
Subject ID	I	II	III	IV	V	VI
MPEG1 mutation (nucleotide)	c445C>T	c.1290C>A	c.217A>G	c.946C>T	c.1192C>T	c.1213C>A
MPEG1 mutation (amino acid)	p.R149* (Arginine→ stop)	p.Y430* (Tyrosine→stop)	p.T73A (Threonine→ Alanine)	p.P316S (Proline→ Serine)	p.Q398* (Glutamine→ stop)	p.P405T (Proline→ Threonine)
MPEG1 mutation allele	Homozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous
Type of mutation	Nonsense	Nonsense	Missense	Missense	Nonsense	Missense
Mutation Origin	Unknown (adopted)	Unknown (adopted)	N/A	N/A	Father (healthy phenotype)	N/A

RESULTS:PHENOTYPIC ANALYSIS

	Index Case	Mereselis et al. 2020	McCormack et al. 2017			
Subject ID	I	II	III	IV	V	VI
Gender	F	F	F	F	F	F
Year of Birth	1979	1997	1945	1929	1956	1951
Ethnicity	South Korean (adoption)	Unknown (adoption)	Caucasian	Caucasian	Caucasian	Caucasian
History of Infections	Y; Gum infections	Y; skin and soft tissue (breast abscess and cellulitis)	Y;pulmonary MAC[a]	Y;pulmonary MAC[a]	Y;multiple pneumonias and URI's; pulmonary MAC[a]; panuveitis	Y;pulmonary MAC[a]
Most Common Infectious Organisms	N/A	*Staph aureus, Staph pseudointermedius, Enterobacter cloacae*	*Mycobacterium avium, M. intracellular, Pseudomonas*	*M. avium, M. gordonae, Pseudomonas aeruginosa*	*M. avium, M. intracellular, pseudomonas*	*M.avium, aspergillus fumigatus*
Endocrinology	Hyperparathyroidism, amenorrhea, irregular menses	N/A	Osteopenia, DMII	N/A	Osteopenia	Osteopenia
Immunology	T-cell lymphocytopenia, (concern for CVID[b])	mild NK cell lymphopenia	N/A	IgG deficiency	N/A	N/A
G.I.	Crohns (in remission), recurrent pancreatitis	Gastroparesis	N/A	N/A	N/A	N/A
MISC.	Eczema, recent hair loss, zinc deficiency, bilateral sensorineural hearing loss	Heterozygous Factor V "Leiden" variant; h/x of D.V.T. and P.E.;bilateral sensorineural hearing loss	Allergic rhinitis, h/x breast cancer s/p lumpectomy	h/x chronic lymphocytic leukemia	Lupus nephritis and cerebritis; vitiligo	COPD

DISCUSSION

- Our patient's evaluation showed symptoms consistent with an immunodeficiency; similar to that identified in the other published cases. Our subject also had additional features not clearly related to the immune system.
- The project was limited by data available only from the initial evaluation. Additionally, one of the findings of the initial evaluation was a hypermetabolic lymph node, however that could not be further studied due to the node's proximity to the carotid artery.
- Mechanistic studies are currently being performed to determine how a homozygous nonsense variant in the *MPEG1* gene differs from the published heterozygous cases.

CONCLUSION

- Based on an initial evaluation, a homozygous nonsense variant of the *MPEG1* gene is associated with an immunodeficiency.
- Due to the syndromic presentation of the subject and only having a single, initial evaluation, further testing is currently underway.

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