PBIMA℠ Immuno-Molecular Augmentation Progressive CNS Inflammation Autoimmune Disease Final Sample Report

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Abstract

In this report, we described PBIMA (WES and Proteomic) data for Progressive CNS Inflammation Autoimmune Disease.

Key words: WES, Proteomics, PBIMA, CNS Inflammation Autoimmune Disease

Diagnosis: Syrinx, CSF Leak, Autoimmune Reactive Disease CNS / CNS Autoantigen Inflammation

HLA Compatibility Typing:
A*11:01:01
A*31:01:02
B*44:03:01
B*51:01:01
C*15:02:01
C*16:01:01

HLA Affinity Typing: Neo7Logix, LLC (Biological /PPI Pathway Studio, HLA-NetMHCII2, HLA-IEDB, OptiType and PBIMA Citrullinated Fragment Sequence Location Selection) Selection is bas-ed upon affinity prediction, biological pathway priority, PPI association. Prediction tools named above are integrated in final selection process where indicated. Ranking with proprietary Neo7Logix prediction and selection.

PBIMA (WES and Proteomic) Immuno-Molecular Augmentation Candidate Sequence Data:

Legend:
COL1A1: This gene encodes the pro-alpha1 chains of type I collagen whose triple helix comprises two alpha1 chains and one alpha2 chain. Type I is a fibril-forming collagen found in most connective tissues and is abundant in bone, cornea, dermis and tendon. Mutations in this gene are associated with osteogenesis imperfecta types I-IV, Ehlers-Danlos syndrome type VIIA, Ehlers-Danlos syndrome Classical type, Caffey Disease and idiopathic osteoporosis.

COL5A1: This gene encodes an alpha chain for one of the low abundance fibrillar collagens. Fibrillar collagen molecules are trimers that can be composed of one or more types of alpha chains. Type V collagen is found in tissues containing type I collagen and appears to regulate the assembly of heterotypic fibers composed of both type I and type V collagen. This gene product is closely related to type XI collagen and it is possible that the collagen chains of types V and XI constitute a single collagen type with tissue-specific chain combinations. The encoded procollagen protein occurs commonly as the heterotrimer pro-alpha1(V)-pro-alpha1(V)-pro-alpha2(V).

Significance | Cancer Immunotherapy data

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Mutations in this gene are associated with Ehlers-Danlos syndrome, types I and II. Alternative splicing of this gene results in multiple transcript variants.

IFIH1: Innate immune receptor which acts as a cytoplasmic sensor of viral nucleic acids and plays a major role in sensing viral infection and in the activation of a cascade of antiviral responses including the induction of type I interferons and proinflammatory cytokines. Its ligands include mRNA lacking 2'-O-methylation at their 5' cap and long-dsRNA (>1 kb in length). Upon ligand binding it associates with mitochondria antiviral signaling protein (MAVS/IPS1) which activates the IKK-related kinases: TBK1 and IKBKE which phosphorylate interferon regulatory factors: IRF3 and IRF7 which in turn activate transcription of antiviral immunological genes, including interferons (IFNs); IFN-alpha and IFN-beta. Responsible for detecting the Picornaviridae family members such as encephalomyocarditis virus (EMCV) and mengo encephalomyocarditis virus (ENMG). Can also detect other viruses such as dengue virus (DENV), west Nile virus (WNV), and reovirus. Also involved in antiviral signaling in response to viruses containing a dsDNA genome, such as vaccinia virus. Plays an important role in amplifying innate immune signaling through recognition of RNA metabolites that are produced during virus infection by ribonuclease L (RNase L). May play an important role in enhancing natural killer cell function and may be involved in growth inhibition and apoptosis in several tumor cell lines. This gene may act as an Inflammatory antagonist in autoantigenic presentation and immune regulatory mechanisms.

A common polymorphism in IFIH1 (rs1990760, A946T) confers increased risk for autoimmune disease, including type 1-diabetes PMID 28475461. Juie has rs1990760 TT genotype

ACAN: This gene is a member of the aggrecan/versican proteoglycan family. The encoded protein is an integral part of the extracellular matrix in cartilagenous tissue and it withstands compression in cartilage. Mutations in this gene may be involved in skeletal dysplasia and spinal degeneration. Multiple alternatively spliced transcript variants that encode different protein isoforms have been observed in this gene. This proteoglycan is a major component of extracellular matrix of cartilagenous tissues. A major function of this protein is to resist compression in cartilage. It binds avidly to hyaluronic acid via an N-terminal globular region. ACAN (CSF Leak Specific) expressed as a self-antigen one way to increase ACAN production is by inhibition of ADAMTS4 / 5 metalloproteases that specifically degrade ACAN.

IL6R: This gene encodes a subunit of the interleukin 6 (IL6) receptor complex. Interleukin 6 is a potent pleiotropic cytokine that regulates cell growth and differentiation and plays an important role in the immune response. The IL6 receptor is a protein complex consisting of this protein and interleukin 6 signal transducer (IL6ST/GP130/IL6-beta), a receptor subunit also shared by many other cytokines.

Dysregulated production of IL6 and this receptor are implicated in the pathogenesis of many diseases, such as multiple myeloma, autoimmune diseases and prostate cancer. Alternatively spliced transcript variants encoding distinct isoforms have been reported. A pseudogene of this gene is found on chromosome 9.

Homozygote carriers of 358Ala (rs2228145[C]) had a 2-fold increase in soluble IL-6R levels compared with 358Asp homozygotes. (PMID 23582566). Julie has rs2228145 CC genotype.

ELN: This gene encodes a protein that is one of the two components of elastic fibers. Elastic fibers comprise part of the extracellular matrix and confer elasticity to organs and tissues including the heart, skin, lungs, ligaments, and blood vessels. The encoded protein is rich in hydrophobic amino acids such as glycine and proline, which form mobile hydrophobic regions bounded by crosslinks between lysine residues. Degradation products of the encoded protein, known as elastin-derived peptides or elastokines, bind the elastin receptor complex and other receptors and stimulate migration and proliferation of monocytes and skin fibroblasts. Elastokines can also contribute to cancer progression. Deletions and mutations in this gene are associated with supravalvular aortic stenosis (SVAS) and autosomal dominant cutis laxa.

IL4R: This gene encodes the alpha chain of the interleukin-4 receptor, a type I transmembrane protein that can bind interleukin 4 and interleukin 13 to regulate IgE production. The encoded protein also can bind interleukin 4 to promote differentiation of Th2 cells. A soluble form of the encoded protein can be produced by proteolysis of the membrane-bound protein, and this soluble form can inhibit IL4-mediated cell proliferation and IL5 upregulation by T-cells. Allelic variations in this gene have been associated with atopy, a condition that can manifest itself as allergic rhinitis, sinusitis, asthma, or eczema. Polymorphisms in this gene are also associated with resistance to human immunodeficiency virus type-1 infection. Alternate splicing results in multiple transcript variants.

Associations of interleukin-4 receptor gene polymorphisms (Q551R, I50V) with rheumatoid arthritis: Evidence from a meta-analysis (PMID 23972290). Julie has IL4R Val50 (rs1805010 GG) genotype

SERPINA1: The protein encoded by this gene is secreted and is a serine protease inhibitor whose targets include elastase, plasmin, thrombin, trypsin, chymotrypsin, and plasminogen activator. Defects in this gene can cause emphysema or liver disease. Several transcript variants encoding the same protein have been found for this gene. Short peptide from AAT: reversible chymotrypsin inhibitor. It also inhibits elastase, but not trypsin. Its major physiological function is the protection of the lower respiratory tract against proteolytic destruction by human leukocyte elastase (HLE). Implications on destructive actions of HLE in CNS related inflammation.

TNFRSF1B: The protein encoded by this gene is a member of the TNF-receptor superfamily. This protein and TNF-receptor 1 form a heterocomplex that mediates the recruitment of two anti-apoptotic

proteins, c-IAP1 and c-IAP2, which possess E3 ubiquitin ligase activity. The function of IAPs in TNF-receptor signalling is unknown, however, c-IAP1 is thought to potentiate TNF-induced apoptosis by ubiquitination and degradation of TNF-receptor-associated factor 2, which mediates anti-apoptotic signals. Knockout studies in mice also suggest a role of this protein in protecting neurons from apoptosis by stimulating antioxidative pathways.

In healthy controls, we observed lower levels of the sTNF-RII in carriers of the TT genotype compared to TG/GG genotype (p = 0.04). In RA there was the same behaviour between TT and TG/GG carriers, even though the difference was not statistically significant (PMID 15603867). Julie has rs1061622-GG genotype.

IL6ST: The protein encoded by this gene is a signal transducer shared by many cytokines, including interleukin 6 (IL6), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), and oncostatin M (OSM). This protein functions as a part of the cytokine receptor complex. The activation of this protein is dependent upon the binding of cytokines to their receptors. vIL6, a protein related to IL6 and encoded by the Kaposi sarcoma-associated herpesvirus, can bypass the interleukin 6 receptor (IL6R) and directly activate this protein. That causes phosphorylation of IL6ST tyrosine residues which in turn activates STAT3. Mediates signals which regulate immune response, hematopoiesis, pain control and bone metabolism. Essential for survival of motor and sensory neurons and for differentiation of astrocytes. Required for expression of TRPA1 in nociceptive neurons (By similarity). Required for the maintenance of PTH1R expression in the osteoblast lineage and for the stimulation of PTH-induced osteoblast differentiation. Required for normal trabecular bone mass and cortical bone composition.

In the OSLO population, 124 (22.7%) subjects were hetero- or homozygote for the rare C allele. Individuals carrying the polymorphism had significantly higher levels of sgp130. In a multivariate linear regression model this association remained significant (adjusted p=0.001). In the VIENNA population, 48 (16.1%) subjects were hetero- or homozygote for the rare C allele. Consistent with the former study, sgp130 levels were significantly higher in carriers of the polymorphism compared to wildtype carriers (adjusted p=0.038). In the VIENNA population, sgp130 levels were significantly higher in diabetic patients. In the OSLO population, sgp130 was higher in patients with increased body mass index and in smokers (p<0.05). In conclusion, this is the first study to report a significant association between the gp130 polymorphism G148C (rs3729960) and serum levels of sgp130 (PMID 24629561). Julie has rare rs2228044-GG genotype according to dbSNP. Assuming that article reports variants from the opposite DNA strand Julie carries allele that increases soluble IL6ST levels.

MBP: The classic group of MBP isoforms (isoform 4-isoform 14) are with PLP the most abundant protein components of the myelin membrane in the CNS. They have a role in both its formation and stabilization. The smaller isoforms might have an important role in remyelination of denuded axons in multiple sclerosis. The non-classic group of MBP isoforms (isoform 1-isoform 3/Golli-MBPs) may preferentially have a role in the early developing brain long before myelination, maybe as components of transcriptional complexes, and may also be involved in signaling pathways in T-cells and neural cells. Differential splicing events combined with optional post-translational modifications give a wide spectrum of isomers, with each of them potentially having a specialized function. Induces T-cell proliferation.

MBP-Citrullinated: MBP-Citrullinated sequences reflect the replacement of arginine with citrulline. Citrulline is not included in the 20 standard amino acids encoded by DNA in the genetic code. Instead, it is the result of a post-translational modifications. MBP citrullination downstream effect is CNS inflammation and myelin destruction by autoantibodies against myelin protein. Julie has four homozygous genotypes in the PADI4 gene (rs1748033, rs874881, rs2240340, rs11203366). First three genetic variants have been linked to rheumatoid arthritis. PADI4 gene product is involved in rheumatoid arthritis because it can aberrantly citrullinate MBP causing its instability and misexpression on plasma membrane. MBP citrullination generates neo-epitopes (PMID 27097548) in rheumatoid arthritis.

Gene Definitions provided by GeneCards
https://www.genecards.org

Table 1. MHC Class I Sequences

	Protein Symbol	Peptide	RefSeq ID - position
1	COL1A1	GVMGFPGPK	NP_000079-578
2	COL5A1	SVHKKNVTL	NP_000084-171
3	IFIH1	RADESTYVL	NP_071451-824
4	ACAN	RAISTRYTL	NP_001356197-158
5	IL6R	SANATSLPV	NP_000556-348
6	ELN	KAAKYGAAV	NP_000492-591
7	IL4R	SEWSPSTKW	NP_000409-213
8	SERPINA1	FAFSLYRQL	NP_000286-57
9	TNFRSF1B	VAIPGNASM	NP_001057-188
10	IL6ST	KTNHFTIPK	NP_002175-68
11	MBP-109-117	RSQPGLCNM	NP_001020252-75

Table 2. Citrullinated MHC Class II Sequences

	Protein	Sequence
1	MBP-R25	YLATASTMDHA(cit)HGFLPRHRDTG
2	MBP-R49	LDSIGRFFGGD(cit)GAPKRGSGKVP
3	MBP-R122	DENPVVHFFKNIVTP(cit)TPPPSQGKGRG
4	MBP-R130	PRTPPPSQGKG(cit)GLSLSRFSWGA
5	MBP-R122/R130	P(cit)TPPPSQGKG(cit)G

Sequences Note:

14: MBP-R122 9mer fragment of citrullinated sequence portion affinity prediction completed by IEDB and PBIMA Citrullinated Fragment Sequence Location Selection. All sequences are predicted and ranked by Neo7Logix Platform as noted above.

Vaccine Adjuvants: Squalene / Oleic Acid naturally increase IL10. These adjuvants are indicated in autoantigen related inflammation.

Additional Notes:

Piceatannol
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5444415/), can inhibit ADAMTS4. Piceatannol is a metabolite of resveratrol found in red wine, grapes, passion fruit, white tea, and Japanese knotweed. https://www.amazon.com/Zetpil-Piceatannol-Pterostilbene-Cardiovascular-Suppositories/dp/B00UZD7T9C

Integrative IV Design: Two Part IV design should include (12 week Design and Evaluate):

Part 1 (Beginning of week): Low dose dilute Sodium bicarbonate / DMSO / Low Dose Selenium slow intravenous drip (2 hours)

Part 2 (End of the week): Vitamin C (Casava Root) with Regulatory Cytokines (Biological IL-10) with very low dose Dexamethasone slow intravenous drip (2 hours)

Injection Therapy: Glucosamine Sulfate / Boron / Traumeel Injection 2X weekly

Antibiotic Therapy: Low Dose Intermittent Doxycycline / Minocycline to inhibit MMP2 / 9 neurodegenerative related inflammation (4 weeks on 3 weeks off for 3 cycles)
https://www.dovepress.com/metalloproteinases-and-neurodegenerative-diseases-pathophysiological-a-peer-reviewed-fulltext-article-MNM

https://link.springer.com/article/10.1007/s13311-011-0038-0https://link.springer.com/article/10.1007/s13311-011-0038-0

Other Considerations:

Oral Therapy: Piceatannol (suppositories), Quercetin, Melatonin, Estriol (transdermal cream), Oleic Acid (Olive Oil), Omega 6 Fatty Acids, Aqueous Selenium, Cannabinoids (higher THC), Epicatechins, Ascorbyl Palmitate (*These agents influence Inhibition of MMP2 / 9 and ADAMTS4 / 5 which influence inflammatory cytokines and facilitate neuronal tissue destruction*)

Advanced Considerations:

Cell Therapy Design: Neural Stem Cells / CD304 / CD25 / IL10 engineered with sequences.
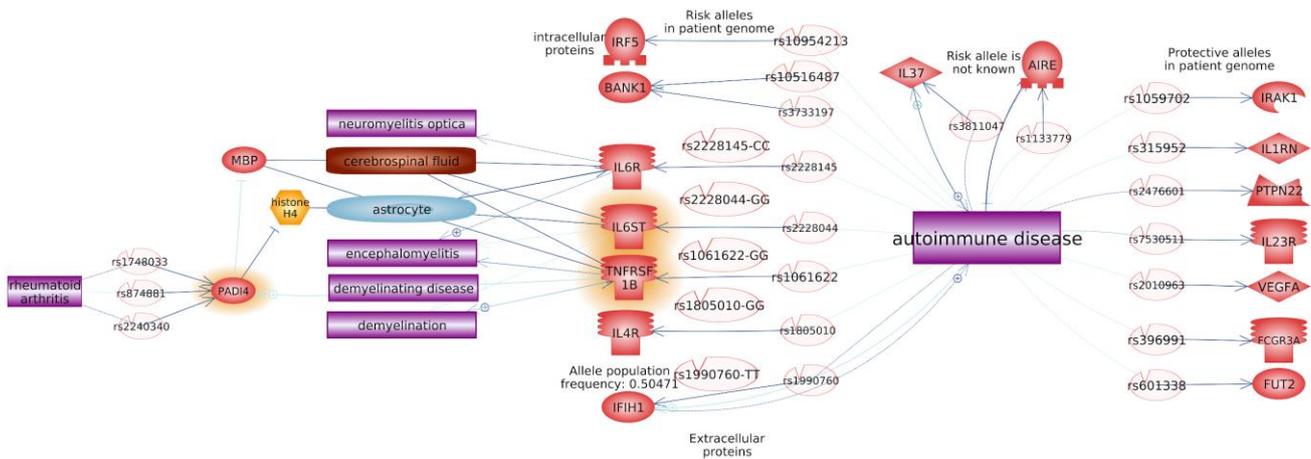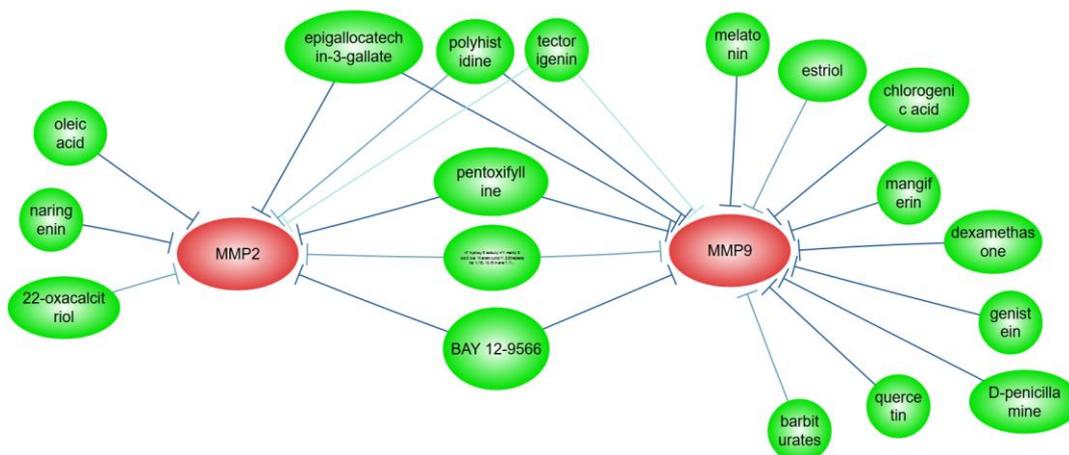https://www.sciencedirect.com/science/article/pii/S0925443915003336

Figure 1. PBIMA Immunopeptide Design

Figure 2. Compounds Inhibiting MMP2 / MMP9

Figure 3. Compounds Inhibiting ADAMTS4 / ADAMTS5 To Initiate Expression of ACAN

Figure 4. Immunoediting Regulation

Author Contribution

Acknowledgment

Competing financial interests
The author(s) declare no competing financial interests.

References