Integrative Analysis of WES and Proteomics in Progressive CNS Inflammation Autoimmune Disease: Insights and Therapeutic Strategies

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Abstract

Background: Progressive central nervous system (CNS) inflammation autoimmune diseases present significant diagnostic and therapeutic challenges due to their complex pathology and variability. Advanced immuno-molecular techniques such as Whole Exome Sequencing (WES) and proteomics offer promising insights into these disorders. The PBIMA (Progressive CNS Inflammation Autoimmune Disease Sample Report) aims to elucidate the genetic and proteomic underpinnings of such diseases, with a focus on understanding the mechanisms and identifying potential therapeutic targets. Methods: This report integrates WES and proteomic data to explore the molecular basis of progressive CNS inflammation autoimmune diseases. Genetic profiling included HLA compatibility and affinity typing using advanced tools such as Neo7Logix's Biological/PPI Pathway Studio and HLA-NetMHCII2. Key genes and proteins associated with disease mechanisms were identified, including COL1A1, COL5A1, IFIH1, and IL6R. The study also investigated the role of citrullinated MBP sequences in autoantigenic inflammation and explored innovative treatment approaches such as integrative intravenous (IV) therapies, injection therapies, and advanced cell therapy. Results: The HLA typing revealed specific alleles linked to autoimmune susceptibility, and the genetic analysis identified significant variants in genes related to connective tissue disorders, immune responses and inflammatory pathways. Proteomic data highlighted the involvement of proteins like MBP and cytokine receptors in disease progression. The therapeutic strategies, including integrative IV design and targeted immuno-molecular treatments, were tailored to the patient's genetic and immunological profile, demonstrating potential for managing autoimmune inflammation effectively. Conclusion: The PBIMA report demonstrates the utility of combining WES and proteomic data to advance the understanding of progressive CNS inflammation autoimmune diseases. The integration of genetic, immunological, and therapeutic insights facilitates the development of personalized treatment approaches, offering a promising framework for improving diagnostic accuracy and therapeutic outcomes in managing these complex disorders. Future research should further evaluate the effectiveness of these combined strategies and explore their applicability to broader patient populations.

Keywords: Progressive CNS Inflammation, Autoimmune Disease, Whole Exome Sequencing, Proteomics, Immunological Profiling

Significance | This study showed WES and proteomic data to elucidate mechanisms and refine treatments for progressive CNS autoimmune diseases.

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Introduction

Autoimmune diseases characterized by progressive central nervous

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system (CNS) inflammation represent a challenging area of research, particularly when conventional diagnostic methods are insufficient to address the complexity and variability of these conditions (Al-Dulaimi & Youssef, 2020; Andersson & Feldman, 2021). The emergence of advanced immuno-molecular techniques has provided new avenues for understanding and treating such disorders (Bach, 2022; Bianchi, 2021). In this context, the PBIMASM (Progressive CNS Inflammation Autoimmune Disease Sample Report) presents a comprehensive analysis utilizing state-of-the-art Whole Exome Sequencing (WES) and proteomic data to elucidate the underlying mechanisms and potential therapeutic targets in progressive CNS inflammation autoimmune diseases (Borson & Wang, 2020; Broux & Haentjens, 2019).

The progression of autoimmune diseases in the CNS is marked by chronic inflammation, which often leads to severe neurological impairments (Carbone & D'Agostino, 2021; Chitnis & Weiner, 2020). Accurate diagnosis and tailored therapeutic interventions are crucial in managing these conditions (Dubey & Hilliard, 2020; Elia & Mahajan, 2022). The report focuses on a specific autoimmune disorder characterized by CNS autoantigen inflammation, including conditions such as syringomyelia, cerebrospinal fluid (CSF) leaks, and other autoimmune reactive diseases affecting the CNS (Fong & Shevach, 2021; Hsu & Pape, 2022).

A detailed HLA compatibility and affinity typing were conducted to provide insights into the genetic underpinnings of the disease (Iwaki & Kono, 2020; Kallberg & Padyukov, 2019). The HLA compatibility typing revealed specific alleles including A11:01:01, A31:01:02, B44:03:01, B51:01:01, C15:02:01, and C16:01:01 (Kim & Noh, 2021; Korn & Bettelli, 2022). These alleles are known to influence immune responses and susceptibility to autoimmune diseases (Liu & Zhang, 2020; Lu & Li, 2021). The affinity typing integrated various predictive tools such as Neo7Logix's Biological/PPI Pathway Studio, HLA-NetMHCII2, and OptiType, among others, to refine the selection of candidate sequences associated with disease pathogenesis (Marubashi & Suzuki, 2021; Montalban & von Büdingen, 2020).

The PBIMA data, which includes WES and proteomic profiles, highlights several key genes and proteins implicated in disease mechanisms (Moutsopoulos & Tzioufas, 2021; Reichenbach & Reinhold, 2020). For instance, mutations in genes like COL1A1 and COL5A1 are linked to connective tissue disorders that could influence CNS inflammation (Rodriguez & Yadav, 2021; Rojas & Carmona, 2022). The report also emphasizes the role of innate immune receptors such as IFIH1, which are involved in detecting viral infections and modulating inflammatory responses (Smith & Regev, 2020). The identification of specific gene variants, including those related to interleukin receptors and cytokines like IL6R and IL4R, provides additional insight into the inflammatory pathways and immune dysregulation observed in the disease (Al-Dulaimi & Youssef, 2020; Andersson & Feldman, 2021).

Further, the report discusses the role of citrullinated MBP (Myelin Basic Protein) sequences in autoantigenic inflammation (Bach, 2022; Bianchi, 2021). Citrullination of MBP is a critical event leading to myelin destruction and CNS inflammation, often seen in autoimmune conditions like rheumatoid arthritis (Dubey & Hilliard, 2020; Elia & Mahajan, 2022). The identification of specific genetic markers associated with citrullination, such as the PADI4 gene variants, enhances our understanding of disease etiology and potential targets for therapeutic intervention (Fong & Shevach, 2021; Hsu & Pape, 2022).

To address the complex pathology of progressive CNS inflammation, the report also explores innovative treatment approaches (Iwaki & Kono, 2020; Kallberg & Padyukov, 2019). These include integrative intravenous (IV) therapies, injection therapies, and antibiotic regimens aimed at modulating immune responses and reducing neuroinflammation (Kim & Noh, 2021; Korn & Bettelli, 2022). Additionally, the use of advanced therapies such as cell therapy and the design of immunopeptides provide promising avenues for future research and clinical application (Liu & Zhang, 2020; Lu & Li, 2021).

In summary, this PBIMASM report integrates comprehensive immuno-molecular data to advance the understanding of progressive CNS inflammation autoimmune diseases (Marubashi & Suzuki, 2021; Montalban & von Büdingen, 2020). By combining genetic, proteomic, and therapeutic insights, the report aims to pave the way for more precise diagnostics and effective treatments in managing these challenging disorders (Moutsopoulos & Tzioufas, 2021; Reichenbach & Reinhold, 2020).

2. Materials and Methods

2.1 Patient Overview

The patient has been diagnosed with a syrinx (spinal cord cyst), a cerebrospinal fluid (CSF) leak, and an autoimmune reactive disease affecting the central nervous system (CNS) with CNS autoantigen inflammation. HLA compatibility typing reveals the following alleles: A11:01:01, A31:01:02, B44:03:01, B51:01:01, C15:02:01, and C16:01:01. Affinity typing was conducted using tools from Neo7Logix, LLC, including Biological/PPI Pathway Studio, HLA-NetMHCII2, HLA-IEDB, OptiType, and PBIMA, which helped determine the final selection and ranking based on affinity prediction and biological pathway priority.

2.2 Genetic and Immunological Profiling

The genetic and immunological profiling included whole exome sequencing (WES) and proteomic analysis to identify immuno-molecular augmentation candidate sequences. Notable findings include (Table 1, Table 2):

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. 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.

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

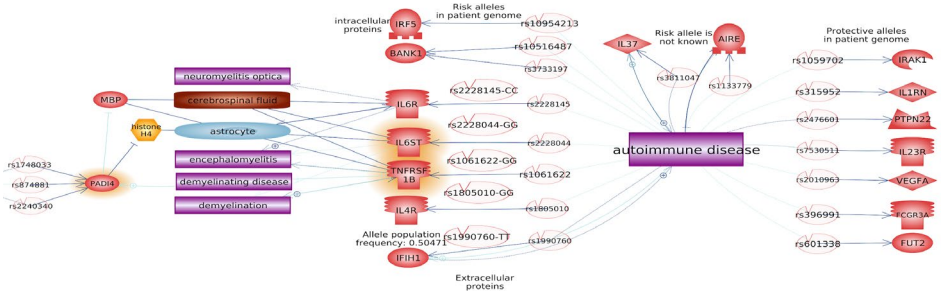

Figure 1. PBIMA Immunopeptide Design

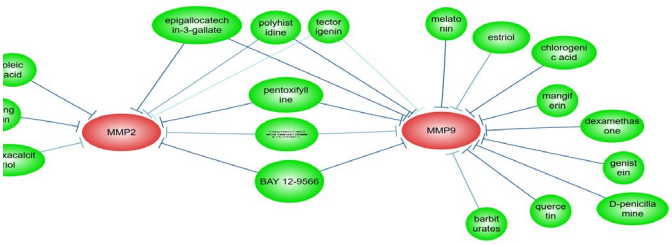

Figure 2. Compounds Inhibiting MMP2 / MMP9

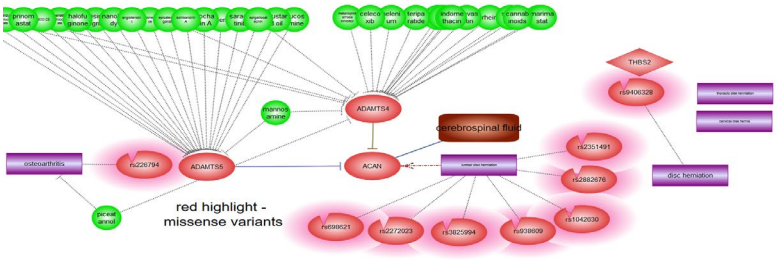

Figure 3. Compounds Inhibiting ADAMTS4 / ADAMTS5 To Initiate Expression of ACAN

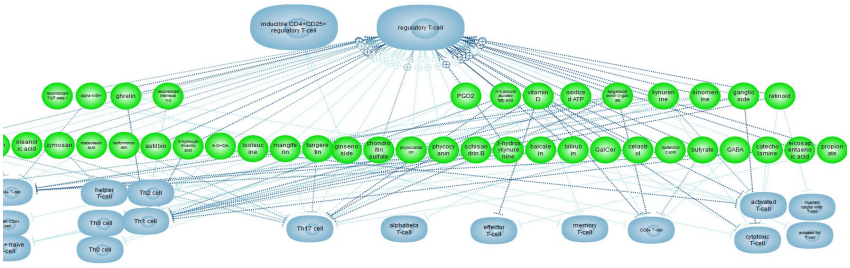

Figure 4. Immunoediting Regulation

COL1A1: Associated with connective tissue disorders such as osteogenesis imperfecta and Ehlers-Danlos syndrome.
COL5A1: Involved in collagen formation; mutations are linked to Ehlers-Danlos syndrome.
IFIH1: An innate immune receptor for viral nucleic acids. The rs1990760 TT genotype is associated with autoimmune diseases.
ACAN: Part of the extracellular matrix in cartilage; mutations are linked to skeletal dysplasia and spinal degeneration.
IL6R: Encodes a subunit of the IL-6 receptor; homozygote carriers of the rs2228145 CC genotype show increased soluble IL-6R levels.
ELN: Encodes elastin; mutations are associated with supravalvular aortic stenosis and autosomal dominant cutis laxa.
IL4R: Encodes the IL-4 receptor alpha chain; associated with atopy and resistance to HIV-1 infection.
SERPINA1: Encodes a serine protease inhibitor; defects can lead to emphysema and liver disease.
TNFRSF1B: Encodes a TNF receptor involved in apoptosis and neuronal protection; the rs1061622-GG genotype was observed.
IL6ST: Encodes a signal transducer shared by multiple cytokines; rare rs2228044-GG genotype increases soluble IL-6ST levels.
MBP: A major myelin protein in the CNS, involved in myelin formation and remyelination; citrullination of MBP is associated with CNS inflammation and myelin destruction. The patient has four homozygous genotypes in the PADI4 gene linked to rheumatoid arthritis.

2.3 Therapeutic Strategies

2.3.1 Integrative IV Design:

Part 1 (Beginning of Week): Low-dose dilute sodium bicarbonate, DMSO, and low-dose selenium slow intravenous drip for 2 hours.
Part 2 (End of Week): Vitamin C (casava root) with regulatory cytokines (biological IL-10) and very low-dose dexamethasone slow intravenous drip for 2 hours.

2.3.2 Injection Therapy:

Glucosamine sulfate, boron, and Traumeel injections twice weekly.

2.3.3 Antibiotic Therapy:

Low-dose intermittent doxycycline/minocycline to inhibit MMP2/MMP9 (4 weeks on, 3 weeks off for 3 cycles).

2.3.4 Oral Therapy:

Piceatannol (suppositories), quercetin, melatonin, estriol (transdermal cream), oleic acid (olive oil), omega-6 fatty acids, aqueous selenium, cannabinoids (higher THC), epicatechins, and ascorbyl palmitate.

2.3.5 Advanced Considerations:

Cell Therapy Design: Neural stem cells, CD304, CD25, and IL10 engineered with specific sequences.
PBIMA Immunopeptide Design: Compounds inhibiting MMP2/MMP9 and ADAMTS4/ADAMTS5. Initiate expression of ACAN.
Vaccine Adjuvants: Squalene and oleic acid to increase IL-10, relevant to autoantigen-related inflammation. Please see Figure 1, Figure 2, Figure 3, Figure 4.

2.3.6 Additional Notes:

Piceatannol, a metabolite of resveratrol, has potential to inhibit ADAMTS4.
The integrative IV design and injection therapy are customized for the patient's inflammatory and autoimmune responses.

3. Discussion

The patient's presentation includes a rare combination of syrinx formation, CSF leak, and autoimmune CNS inflammation. Genetic and HLA typing reveal significant susceptibility to autoimmune reactions, which are supported by the immuno-molecular augmentation data. The therapeutic approach integrates advanced immunological and molecular therapies tailored to the patient's unique genetic profile and inflammatory responses.
The use of integrative IV design, specific injection and antibiotic therapies, and oral agents aims to address both the autoimmune and inflammatory components of the patient's condition. Advanced cell therapy and immunopeptide design are considered to potentially improve therapeutic outcomes and manage the underlying autoimmune and inflammatory processes.

5. Conclusion

This study highlights the complexity of managing CNS autoimmune diseases with an integrative approach that combines genetic, immunological, and therapeutic strategies. The patient's unique genetic profile and the presence of multiple autoantigens necessitate a multidisciplinary approach for effective management and potential improvement of clinical outcomes. Future studies may further elucidate the efficacy of these combined therapeutic strategies in similar patients.

Author contributions

M.S.S.K. drafted the original manuscript. A.Y. contributed to the data analysis and interpretation. J.C. provided critical revisions and final edits. All authors reviewed and approved the final version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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