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Genetics of progressive multifocal leukoencephalopathy: update on case reports with an inborn error of immunity and risk variants found in drug-linked cases

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A genetic predisposition to PML is now substantially supported by case reports of patients molecularly diagnosed with an inborn error of immunity (IEI) and progressive multifocal leukoencephalopathy (PML). Over the past 10 years, 4 IEI genes linked to PML has now grown to 26 as of 2025. Of these 26 genes believed to be causal of an IEI and PML, 24 (92%) are also linked with hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)—a severe hyper-inflammation syndrome associated with several IEI genes, most notably in 4 genes (*PRF1*, *STX11*, *STXBP2*, *UNC13D*) causing familial forms of the syndrome. Many HLH-linked genes are associated with life-threatening Epstein–Barr virus infections, which analogously suggests JC virus infection plus presence of a pathogenic variant in an HLH-linked IEI gene also increases risk of PML. PML also occurs as a serious adverse event for a subset of immunosuppressive therapies (e.g., natalizumab and rituximab) used to treat patients with immune disorders (e.g., multiple sclerosis and hematological malignancies). Recently, 4 PML risk variants were reported for use in a PML risk test to screen patients who are considering treatment with PML-linked therapies. Interestingly, of the 4 genes with a PML risk variant, 2 (*LY9* and *STXBP2*) cause or are linked to HLH. The aim of our review is two-fold: (1) raise awareness among researchers and clinicians (e.g., neurologists, oncologists, and rheumatologists) that patient genetics are a key risk factor for PML, and (2) further reinforce the rationale for screening at-risk patients for PML risk variants before prescribing a PML-linked drug.

KEYWORDS

hemophagocytic lymphohistiocytosis, inborn error of immunity, immunodeficiency, JC virus, natalizumab, progressive multifocal leukoencephalopathy, rituximab, PML

Introduction

Progressive multifocal leukoencephalopathy (PML) is a neurological disorder characterized by progressive white matter degeneration. PML occurs as a secondary and often fatal brain disease in immune-suppressed patients infected with human polyomavirus 2 (HPyV2) (1, 2), commonly known as JC virus (JCV) (3, 4). Immune-linked primary diseases associated with an increased risk of PML include HIV infection, hematological malignancies, and autoimmune disorders (3). Treatment of a patient's primary disease with an immunosuppressant therapy (or non-compliance with antiretroviral therapy in HIV-infected patients) is often a triggering factor for developing PML. We propose that a patient's underlying

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genetics are also a key risk factor for developing PML based on two lines of investigation: (1) our genome-wide study of two large cohorts of PML cases revealed four genes that increase PML risk (5, 6) and (2) our assembly of an updated review of the PML case report literature (Figure 1; Supplementary Table 1) on patients diagnosed with an inborn error of immunity (IEI) (7). We note that a majority (73%) of the cases reported in Supplementary Table 1 had a PML diagnosis of definite or probable (3, 8), but diagnostic criteria were not reported for the other PML case reports. PML is an under-appreciated risk in IEI patients and in the wide range of patients on immunosuppressant therapies. Our principal aims are to raise awareness in the clinical communities and increase the vigilance for PML onset, especially in patients with deleterious genetic variants in PML-linked IEI genes.

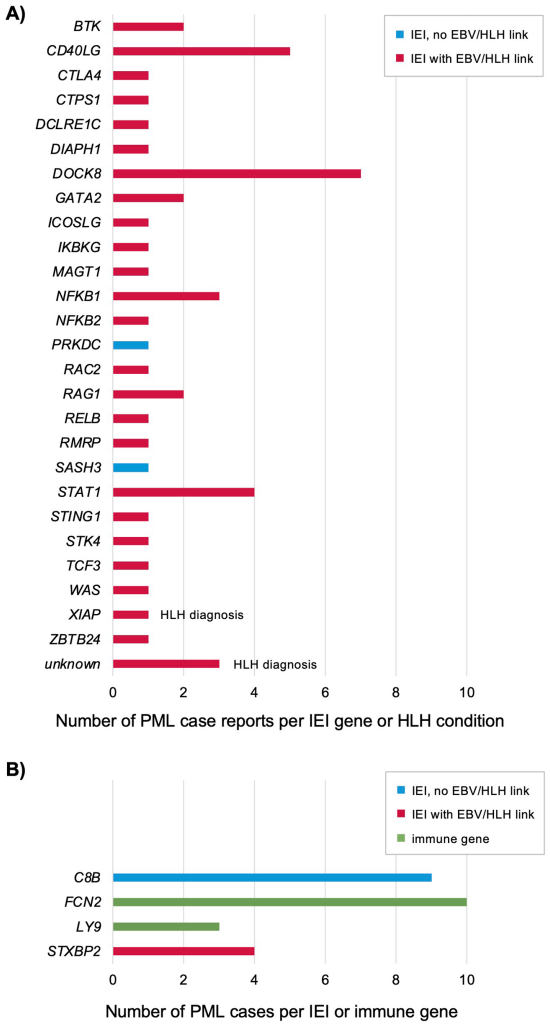

FIGURE 1
Genes reported for previously published PML cases with an IEI diagnosis, HLH diagnosis, or positive for a PML genetic risk variant (see Supplementary Table 1) (10, 20, 35–38, 96–127). **(A)** Each patient was genetically diagnosed with an IEI plus developed PML or diagnosed with HLH (indicated) and PML. All other PML cases were not reported to also have HLH, but 19 of 26 IEI genes are linked to an increased risk of EBV and/or HLH as associated features (7, 13, 16–28, 30–34, 128). **(B)** Each patient tested positive for a PML risk variant (5, 6). Two genes (*C8B* and *FCN2*) are in the complement pathway (129–133) and two genes (*LY9* and *STXBP2*) are linked to EBV/HLH (see Figure 2).

Genetic underpinnings of PML—IEI case reports and PML risk variants

Host genetics as an underlying risk factor for PML were first proposed based on a limited number of case reports in patients diagnosed with an IEI and PML (9, 10). The International Union of Immunological Societies (IUIS) Expert Committee has reported there are now 508 IEI genes (7), but none are presently reported to cause an increased risk of PML. In the last 10 years, IEI genes linked to PML based on patients diagnosed with both disorders has increased from 4 to 26 (Figure 1A; Supplementary Table 1). Including PML cases found to have a PML risk variant (Figure 1B; Supplementary Table 1) (6), the total is 28 IEI genes. Notably, a majority of these IEI genes are directly causal or implicated in an increased risk of the hyperinflammation syndrome hemophagocytic lymphohistiocytosis (HLH) (11, 12) and/or severe Epstein–Barr virus (EBV) infections (7, 13), see below for details. Of the four PML risk variant genes (Figure 1B), two are known to cause an IEI, *C8B* is 1 of 33 IEI genes causing complement deficiencies and *STXBP2* is 1 of 7 IEI genes causing familial HLH (FHL) syndromes. Two genes not yet known to cause an IEI are linked to complement and HLH, respectively—*FCN2* is 1 of 3 ficolin genes (*FCN3* is an IEI gene) and *LY9* is linked to the EBV/HLH IEI gene *SH2D1A* via interaction of their protein products—see below for details. We also note that, like IEI in general, there is extensive genetic and phenotypic heterogeneity reported for IEI plus PML genes, with many (21 of 26, 81%) linked to the broader category of common variable immunodeficiency (CVID) (14). Incomplete penetrance is common and attributed to a number of factors, such as digenic/oligogenic/polygenic inheritance (14) and allele-specific expression (termed transcriptotype) (15). Thus, it should not be surprising that many individuals with an IEI are undiagnosed and PML only emerges upon treatment with immunosuppressive drugs (see below and Supplementary Table 2).

PML and the EBV/HLH connection

Primary HLH (FHL caused by an IEI gene) and secondary HLH (often a complication of rheumatic diseases)—also known as macrophage activation syndrome (MAS) and cytokine storm syndrome (CSS)—are now considered to be a continuum of immune dysfunction (11, 12). The term HLH/MAS has been adopted by experts in the field (12) but, for simplicity, herein will be termed HLH. Since the vast majority of PML case report patients (Figure 1A) were also diagnosed with an IEI linked to EBV/HLH (24 of 26, 92%) (7, 13, 16–34), we also searched the literature and public databases for case reports of patients diagnosed with PML and HLH. We found three cases although genetic information was not reported (unknown genes in Figure 1A; Supplementary Table 1) (35–37). Along with the *XIAP* plus PML case report (38), there are four patients with a diagnosis of PML and HLH. Given the rarity of PML (39, 40) and HLH (11), this is highly unlikely to be a chance association.

PML risk genes *STXBP2* and *LY9* further underscore the connection to EBV/HLH. Familial HLH (FHL syndromes) have a high risk for serious EBV infections (13, 23, 29). Of the four FHL genes, only *STXBP2* (FHL5) is reported to have an

inheritance model of autosomal dominant (AD) or autosomal recessive (AR), while all others are AR only (7). All four PML cases with the same *STXBP2* variant were heterozygous (Supplementary Table 1) and in a comparison of natalizumab-treated multiple sclerosis (MS) patients who developed PML (n = 2/86) versus matched controls (natalizumab-treated MS patients who did not develop PML, n = 0/604) there was a 36-fold increased risk of PML (observed positive predictive value of 100%) (6). While *LY9* is not known to cause an IEI, it is 1 of 9 signaling lymphocytic activation molecule family (SLAMF) members (41, 42) involved in host defense against pathogens (43, 44). SLAMF proteins interact with the protein product of *SH2D1A* (gene alias *SAP*), an IEI gene that causes X-linked lymphoproliferative syndrome (XLP1) characterized by severe EBV infections (13, 23, 29). Another SLAMF gene, *CD48* (gene alias *SLAMF2*), is potentially the first family member linked to an IEI (not yet reported by the IUIS) and HLH based on one case report with a *de novo* variant (45). SLAMF genes are also implicated in cancers (particularly hematological malignancies) (46, 47) and autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (48). Interestingly, the SLAMF locus on chromosome 1 (1q23) harbors all nine SLAMF genes and SLE genetic linkage studies in human (between markers *SPTA1* and *FCGR3A*) (49) and mouse (50) also map to this region. Follow up studies further support the link between SLAMF genes and SLE (51–54).

To highlight the interactions between PML-linked IEI and other immune genes, we performed a protein network analysis using STRING (Figure 2) (55). The analysis included 37 genes: 26 IEI plus PML case report genes (Figure 1A), *SH2D1A*, PML risk variant genes (*STXBP2* and *LY9*, but not complement pathway genes *C8B* and *FCN2*), and other SLAMF genes. All genes had multiple connections except *ZBTB24* (Figure 2, upper right). However, 14 of 26 IEI plus PML genes (including *ZBTB24*) are linked to natural killer (NK) cell deficiency or impaired NK cell function (56, 57). PML risk genes *LY9* and *STXBP2* are also linked to NK cell function (57–59). Finally, while several complement system genes cause IEI (including PML risk gene *C8B*) (7), they are not extensively linked to HLH. However, more recent studies do show coexistence of defects in complement and HLH (60), particularly in patients diagnosed with both HLH and thrombotic microangiopathy (TMA) (61, 62).

Functional evidence for PML-linked genes and JCV

For detailed background on JCV biology, see three recent reviews (4, 63, 64). One of the earliest links between JCV and an IEI gene is a study (65) that found JCV's agnoprotein interacts with the protein product of *XRCC6* (gene alias *KU70*, a DNA repair protein) and impairs function of the protein product of IEI gene *PRKDC* (66), which causes DNA-PKcs deficiency (7). Subsequent work (67, 68) by this group identified JCV protein links to two other DNA repair genes, IEI genes *DCLRE1C* (gene alias *ARTEMIS*) and *RAD51* (a cause of Fanconi anemia) (7). PML case reports were found for patients with mutations in *DCLRE1C* and *PRKDC* (Figure 1A; Supplementary Table 1). Another group (69) reported an interaction between JCV's agnoprotein and the protein product of *AP3D1*, which is an IEI gene that causes an FHL syndrome (Hermansky-Pudlak, type 10) (7). The agnoprotein-AP3D1 interaction was validated in a proteomics study (70). Adapter protein (AP) complexes are comprised of host gene proteins, such as AP3D1, that many viruses hijack for viral propagation and evading host immune responses (71).

Further evidence supporting PML-linked genes comes from a recent study (72) using proteomic and single cell RNA sequencing methods on cerebrospinal fluid (CSF) and serum samples from PML patients. Top genes/proteins from these analyses included chemokines and their receptors (e.g., CCL4, CCL5, CCR2, CCR5, CXCR3, CXCR6) as a key feature in PML versus non-PML samples. This is not surprising given their role in NK cell biology (58, 59), but this study also highlighted a link to PML risk genes *LY9* and *STXBP2* (6). We observed the following genes in the top quartile (25%, average log2 fold change) of genes in the RNA sequencing data: CD4-PML cluster vs. other CD4 + T cells included PML risk gene *STXBP2*, 2 SLAMF genes (*SLAMF1*, *SLAMF6*), 8 PML plus IEI case report genes (*CD40LG*, *DOCK8*, *IKBKG*, *RAC2*, *RMRP*, *SASH3*, *STAT1*, *WAS*), and *ITGA4* (target of natalizumab); CD8-PML cluster vs. other CD8 + T cells included *SLAMF7*, 9 PML plus IEI case report genes (*CTPS1*, *DIAPH1*, *DOCK8*, *RAC2*, *RELB*, *RMRP*, *SASH3*, *STAT1*, *WAS*), and *ITGA4*.

Like other IEI disorders, severe infection risk is increased for some genes/viruses, although the IUIS has yet to add risk of PML due to JCV infection to a subset of their current list of 508 IEI genes (7), likely because PML from JCV infection is a rarer entity in IEI patients. We note two key parallels between EBV and JCV causing severe, life-threatening infections in IEI patients and those with milder immunodeficiency (e.g., lymphoma and SLE patients): (1) the ubiquitous presence of these viruses in worldwide populations (EBV > 90%, JCV 60–80%) (4, 13) wherein the infection is usually asymptomatic or relatively benign, and (2) both viruses are linked to HLH, which we think the current evidence suggests is due to host genetics (Figure 1; Supplementary Table 1). While co-infection with HIV and JCV leading to PML was common before the era of antiretroviral therapies (3, 4, 73), not much is known about patients co-infected with EBV and JCV. Two interesting observations that will hopefully lead to further research are EBV-JCV recombination leading to increased neurovirulence of JCV (74) and a case report of a HIV-infected patient who developed primary central nervous system lymphoma with tumors infected with both EBV and JCV (75).

Iatrogenic (drug-linked) PML as a serious adverse event (SAE) is not going away

In the first two epochs of reported PML cases, hematological malignancies and acquired immunodeficiency syndrome (AIDS) due to HIV infection were the main risk factors (3, 4). Around 2002–2005, reports of iatrogenic PML (i.e., drug-linked) were emerging (3). PML is now recognized as a significant risk factor in a wide range of patients treated with a wide range of immunosuppressive therapies for their primary disease. The highest number of drug-linked PML cases to date are from natalizumab (used to treat MS and Crohn's disease) and

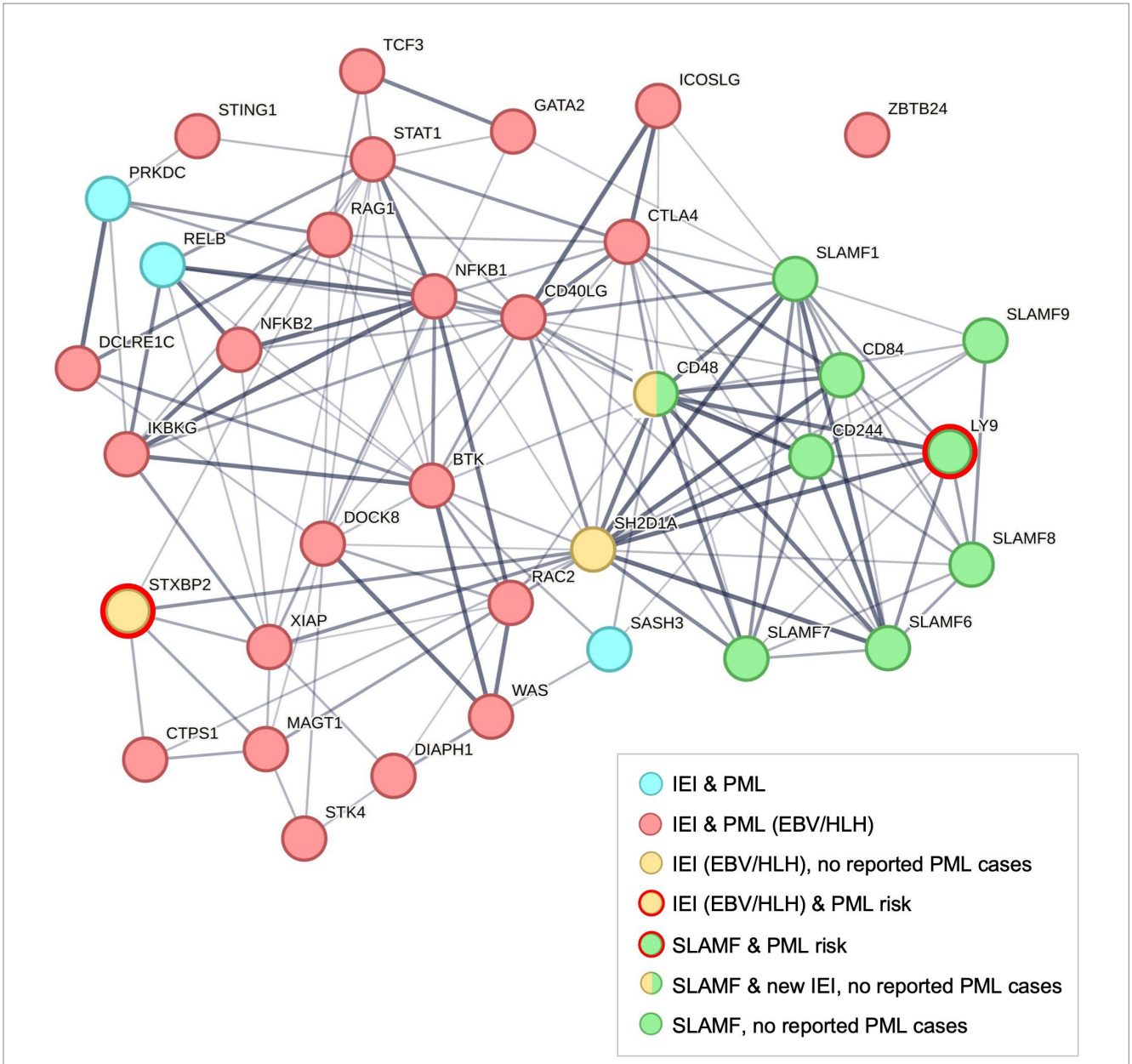

FIGURE 2
Protein network analysis of PML-linked IEI genes using STRING (55). Default STRING settings were used for 37 genes: 26 IEI + PML case report genes (see Figure 1), 9 SLAMF gene family members (41, 42), SLAMF-interacting gene *SH2D1A* (an IEI gene that causes XLP1) (7), and 2 PML risk genes (SLAMF gene *LY9* and IEI gene *STXBP2*) (5, 6). The protein–protein interaction (PPI) enrichment *p*-value is < 1.0E-16. *ZBTB24* is the only unconnected IEI & PML gene (upper right), see text. SLAMF gene *CD48* (*SLAMF2*) was recently identified as HLH-linked and a potential new IEI, the first member of this gene family found to cause an immune disorder (45, 134). Both IEI and SLAMF genes have been linked to increased risk of autoimmune diseases (48) and hematological cancers (135, 136).

rituximab, which is primarily used to treat cancers and autoimmune disorders (76–78). To assess the current landscape of drugs with the highest PML risk, we used the FDA Adverse Event Reporting System (FAERS)[1] to identify the number of PML cases reported after treatment with a given drug (Supplementary Table 2). The FAERS database is an excellent resource even though underreporting is a limitation of this database (79–81) and not all reported PML cases will have been validated as definite/probable PML (3, 8). Our FAERS analysis focused on the past 5 years (2020–2024) in order to better represent the current situation for older drugs plus highlight newer drugs with an appreciable number of PML cases. To minimize counting duplicate reports of PML cases, we filtered the data using the original manufacturer (Sender) for a given drug, although this may result in an underreporting of PML cases linked to generic drugs. Also, since natalizumab is the highest risk PML-linked drug, when filtering the data we excluded instances for a given drug if natalizumab was also listed (i.e., oftentimes multiple drugs are listed for a given PML case). Drug data in Supplementary Table 2

1 https://www.fda.gov/drugs/surveillance/fdas-adverse-event-reporting-system-faers

are grouped according to four main indications (MS, hematological malignancies, non-MS autoimmune diseases such as RA and SLE, and other). We also highlighted PML risk drugs with a boxed warning (the highest warning issued by the FDA) for PML. Finally, we listed some newer drugs that have yet to report a PML case to the FDA if it had the same mechanism of action (MOA) as drugs already linked to PML.

Even after excluding the large number of historical PML cases (i.e., before 2020), the two highest risk drugs continue to be natalizumab and rituximab. We note rituximab PML cases are listed under 3 of 4 subsections of Supplementary Table 2, reflecting its use to treat a wide range of disorders. For MS drugs, natalizumab (n = 231) and fingolimod (n = 51, 58 for all drugs targeting S1P modulators) had the highest number of PML cases but ocrelizumab (n = 28) and other CD20-targeting drugs also have an appreciable number of reported PML cases (44 total in the MS section for all CD20 drugs). Importantly, we noted FAERS now reports instances of natalizumab patients treated with extended interval dosing (EID, also termed Q6W) (82, 83), which is reported under the Reactions column as "Prescribed Underdose." About a third of natalizumab FAERS PML cases were classified as "prescribed underdose" but this did not reduce the death rate: regular dose 155 PML cases and 17% died vs. 76 underdose and 21% died.

Interestingly, we note that some MS drugs have been linked to cases of HLH (84–88), although we did not find any case reports of patients treated with these drugs who developed HLH and PML. Importantly, several IEI genes are also drug targets (Supplementary Table 2): *BTK*, *C5*, *CD19*, *CD20* (gene symbol now *MS4A1*), *CD3D*, *CD3E*, *CD3G*, *CD79B*, *JAK1*, and *JAK3* (7). The PML-linked drug belimumab targets *TNFSF13B* (gene aliases *BAFF* and *BLYS*), the ligand of IEI genes *TNFRSF13B* (gene alias *TACI*) and *TNFRSF13C* (gene alias *BAFFR*) (89). We also note there are several case reports of multiple myeloma (MM) patients diagnosed with PML (90–93). Reported drugs for a subset of these cases included bortezomib, daratumumab, ixazomib, lenalidomide, pomalidomide, and thalidomide. All of these MM drugs have been linked to $\geq$ 3 PML cases in FAERS (Supplementary Table 2). Elotuzumab, an MM drug that targets HLH-linked gene *SLAMF7*, has 5 PML cases reported in FAERS and for one case report the MM patient developed PML during treatment with lenalidomide and elotuzumab (93). There are presently limited or no warnings of PML in the prescribing information for these MM drugs (Supplementary Table 2) despite the growing number of PML cases reported to FAERS (e.g., in the last 5 years, there are 27 PML cases reported for daratumumab but still no warning of PML in its prescribing information). These observations, in concert, underscore the delicate balance of the immune system in having too much or too little of a given IEI gene product.

For clinicians and regulators, the key points to consider are: (1) drug-linked cases of PML occur for a wide range of drugs and primary diseases, (2) efforts to mitigate risk for natalizumab (e.g., EID/Q6W treatment regimen and regular JCV antibody testing) are insufficient, (3) additional early detection measures (more frequent brain MRIs, JCV testing, and other biomarkers) could be implemented for higher risk patients (not just MS patients), and (4) preventive testing for PML risk genetic variants/genes (6) may help reduce the number of drug-linked PML cases (94). Given that PML is often life-threatening, up-to-date information should be made available to clinicians, including via prescribing information (i.e., drug labels) (95), to better inform clinicians about recent advances in genetic testing for PML risk.

Constellation of PML risk factors: five recommendations for clinicians and regulators

Based on the continuing increase in PML plus IEI case reports and PML cases that carry a PML risk variant (Figure 1; Supplementary Table 1), a predominant risk factor of PML appears to be host genetics (Supplementary Figure 1). Primary diseases (each with their own predisposing genetic variants in immune-linked genes), immunosuppressant drugs, and infections (JCV is required but co-infection with HIV increases the risk and this may be true for other viruses linked to severe infections in IEI patients) also provide multiple pathways leading to the development of PML. Since there are no approved treatments for PML, prevention is the best defense. Therefore, we propose that experts in the field consider the following recommendations for increased vigilance of PML: (1) add JCV and PML to IUIS tables of IEI, (2) consider HLH/MAS (both primary and secondary) to be a concomitant risk factor of PML, (3) use the PML risk genetic test in all at risk patients (i.e., included but not limited to MS patients prior to treatment with natalizumab), (4) for at risk patients, such as carriers of the PML risk variants, implement more frequent brain MRIs plus more frequent and widespread JCV DNA and antibody testing, and (5) promote PML awareness campaigns to patients and clinicians for other diseases (and immunosuppressant drugs used to treat them) besides the MS community.

Author contributions

PE: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. ES: Data curation, Formal analysis, Writing – review & editing. SJ: Data curation, Writing – review & editing. EH: Conceptualization, Investigation, Writing – review & editing.

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Conflict of interest

EH (UK), ES (USA), PE (USA) and SJ (UK) are employees of Population Bio, Inc.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1629581/full#supplementary-material

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