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Review

Association of Primary Minor Immunodeficiencies and Autoimmune Syndromes in Humans: Current Status, Existing Problems and Prospects for Further Research

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Abstract: Autoimmune manifestations of primary minor immunodeficiencies (PMDs)—highly prevalent conditions that may represent a population-level model of autoimmunity—have not been systematically analyzed. The study aims to evaluate the current evidence for associations between PMDs and autoimmune syndromes. A systematic search of PubMed (MEDLINE) for 1980–2025 was conducted using keywords related to PMDs and autoimmune syndromes. The search was performed in two stages: an initial broad screening and a subsequent refined search with specific disease-related terms. High-quality peer-reviewed studies most relevant to the study objectives were selected. Available evidence indicates that PMDs commonly manifest through autoimmune syndromes according to a principle of universality, with important geographic, ethnic, age-related, sex-related, and ontogenetic variation. The strength of PMD–autoimmunity associations varies widely, reflecting major heterogeneity in both disease mechanisms and study quality. Key factors influencing clinical and epidemiological findings include terminological inconsistencies, multiple autoimmune pathways, heterogeneity of PMD origin and evolution, overlap with other immunodeficiencies and comorbidities, variability of clinical phenotypes, difficulties distinguishing PMDs from secondary immunosuppression, and the absence of standardized diagnostic criteria for many PMDs. Elementary models of autoimmune induction in immunocompromised individuals are proposed, together with a framework for personalized assessment of autoimmune disease in the context of PMDs, and implications for rational immunotherapy are discussed. PMDs are associated with diverse autoimmune syndromes and likely represent a major etiological factor of human autoimmunity at the population level. However, this data should be validated in further studies.

Keywords: Primary Immunodeficiency; Immune Dysregulation; Autoimmune Disease Susceptibility

1. Introduction

The last decade has been marked by a rapid increase in the frequency of autoimmune diseases in the human population [1–3]. There is a growing awareness that autoimmune lesions are associated with an increasing burden on human health and society, which intensifies scientific research in this area [4,5]. Despite impressive progress in describing the effector mechanisms of autoimmunity [6], insufficient attention has been paid to the origin of this immune-mediated phenomenon [7]. In particular, the etiology of autoimmune syndromes [8,9], the initial stages of their pathogenesis [10], the role and place of the initial stimuli that trigger autoimmunity [11], as well as the conditions that contribute to the breakdown of immune tolerance to the body's own antigens under the influence of triggers have been studied insufficiently [12].

The results of recent scientific research in the field of clinical immunology, immunogenetics, microbiology and molecular biology have shed light on the fundamental factors and conditions for the development and mechanisms of initiation of autoimmune reactions in humans [13]. This data, however, has not yet received proper generalization and systematization and is insufficiently implemented in clinical practice [14]. The role of immunodeficiencies, especially inborn errors of immunity [15], in the induction of immune-dependent syndromes in general and autoimmune reactions in particular has been shown [16]. The understanding of the spectrum of known primary immunodeficiencies (PID), their epidemiology, and genetic and clinical heterogeneity has expanded [17]. Diagnostic criteria have been clarified, including the association with autoimmune phenomena [18]. Children with autoimmunity, allergy and lymphoproliferative syndromes may suffer from an inborn error of immunity in at least in 26% of cases [19]. The data have been accumulated on the response to immunotherapeutic interventions in various diseases of the immune system [20]. The unprecedented heterogeneity of PID has been shown, among which such forms of the disease have been identified (for example, mannose-binding lectin deficiency [21] or selective IgA molecule deficiency [22]), which are sufficient in frequency in the population and degree of clinical manifestation to be a relevant model of the etiological factor in the development of heterogeneous human autoimmune syndromes on a population scale and, accordingly, for routine clinical practice of doctors of various specialties.

These significant scientific achievements lead to the understanding of the fact that it is precisely those clinically manifest PIDs that are widespread in the human population that may be an insufficient link in the complex structure of modern ideas about the origin of autoimmunity in humans. So, immunotherapy is a potential way to carry out an integrated treatment of a complex of syndromes associated with autoimmunity [16,23].

Despite the unprecedented accumulation of scientific evidence, new ideas have not yet been properly reflected in the current standards of diagnosis and treatment in rheumatology. One of the reasons for this discrepancy may be the lack of scientifically substantiated models that would combine into a single whole the important components of the mechanism of development of autoimmune syndromes in immunocompromised individuals. This model must take into account the state of immunity, the action of microbial triggers and the induction of autoreactive immunocompetent cells and autoantibodies as an effector link in a complex pathological process [24]. The creation of such relevant models will not only clarify the understanding of autoimmunity as a complex integral immune-dependent phenomenon. But it will also improve modern algorithms for the diagnosis and treatment of various autoimmune syndromes. It helps to make personalized multidisciplinary approaches aimed not only at relieving the clinical consequences of the disease. The purpose will be to eradicate the causes of the development of autoimmunity in each specific case.

2. The Aim of the Study

Based on the analysis of data from scientific publications, to assess the current evidence base of the association of primary minor immunodeficiencies and autoimmune syndromes in humans in order to create, based on the synthesis of such data, an integrative model of the development of autoimmunity as a universal pathological clinical phenomenon in immunocompromised individuals with the identification of ways to improve diagnostics, therapy, and prophylaxis.

3. Research Objectives

1. to study the evidence base accumulated so far on the association of primary minor immunodeficiencies and autoimmune syndromes in humans;
2. to carry out a critical analysis of the conditions and factors that could have influenced both the current depth of study of the problem and the results of the conducted clinical studies;
3. to outline ways to solve existing problems and outline promising directions for further research;
4. to present a generalized scientific concept dedicated to the role of primary minor immunodeficiencies in autoimmune syndromes in humans for basic science and routine clinical practice.

4. Materials and Methods

4.1. Baseline Data

Before proceeding to the description of the search process, it should be noted that the methodological developments used in this work have been highlighted in previous publications. They include the formulation of the

definition of PMD and 13 attributive criteria for establishing the minor nature of immunodeficiency, as well as a table of differential diagnosis of classical and minor immunodeficiencies, which was developed based on the analysis of 65 years of data accumulation in publications from the scientific database PubMed (MEDLINE).

Unlike the classical model of PID—typically described as an uncommon and clinically severe condition with substantial lethality—PMDs are relatively frequent in the general population and present with broad phenotypic diversity and unpredictable patterns of progression.

In this article, the terms "PMD", "minor PID", and "mild immunodeficiency" are used synonymously to refer to the same phenomenon. This should be emphasized to avoid confusion.

Thus, the following criteria for identifying primary immunodeficiency as a minor disease of the immune system were applied (these criteria were derived from a previous systematic review devoted to the phenomenology of PMD as such):

1. Occurrence rates within the general population that are considerably higher than expected for traditionally recognized primary immunodeficiency disorders.
2. Functional impairment limited to a single element of the immune system rather than combined or systemic defects.
3. Clinical manifestation that is not age-restricted and may arise at any period of life.
4. Persistence of a clinically inapparent state throughout development in a substantial subset of affected individuals (approximately one-fifth or more).
5. An unstable disease pattern marked by alternating quiescent intervals and sudden symptomatic episodes differing in intensity and duration.
6. Pronounced variability of clinical expression, observable both among genetically related individuals and within the same patient over time.
7. Symptom severity typically low enough to resemble immune-associated conditions seen in individuals without confirmed immunodeficiency.
8. Published observations describing cases in which symptoms regress without targeted therapeutic intervention.
9. Clinical reports indicating either uncertain disease trajectories or comparatively favourable long-term outcomes.
10. Documented instances of atypical or unforeseen disease-related complications.
11. Rare descriptions of abrupt and unexplained fatal events in affected persons.
12. Evidence suggesting that certain immune abnormalities may confer evolutionary or biological advantages under specific conditions.
13. Historical tendencies toward underestimation or dismissal of these immune abnormalities due to their apparently mild clinical significance.

Immunodeficiency was considered minor in published papers if at least 9 of the 13 proposed criteria were met (all allocated 36 PMD's nosological units correspond to at least 9 of 13 criteria when extrapolating back 13 criteria for publications on the topic of PMD in PubMed (MEDLINE) from 1960 to 2025).

Based on these criteria, an original clinical and laboratory classification of PMD was developed and validated during a preliminary systematic search, which outlined the list and structure of nosological forms that can be called PMDs and have been adequately described in the scientific literature to date. All analyses carried out further in this systematic review are based on previous developments, adequately published in peer-reviewed medical scientific periodicals.

This systematic review does not develop diagnostic criteria, a list, or a classification of PMDs, but only uses an already developed and well-founded nomenclature that has previously been reviewed and published. This systematic review is dedicated to finding evidence of the association of PMDs with autoimmune syndromes, to demonstrate at what stage of development of this problem we are currently considering and how the accumulated data can be applied in clinical medicine. In addition, this systematic review will critically revise the developed nomenclature on the specific example of studying the association with the autoimmunity phenomenon, to show what difficulties and pitfalls prevent a deep and comprehensive study of the problem in order to optimize further research in this

area.

4.2. Analytical Parameters

Study type: systematic literature review.

Data source: PubMed (MEDLINE).

Time frame: 1980–2025.

Search strategy: Two-stage keyword-based screening (broad → specific).

Disease domains: PMDs and autoimmune syndromes in humans.

Inclusion criteria: meta-analysis, systematic reviews, population studies, randomized controlled trials, well prepared retrospective researches and suitable clinical cases, 20 well characterized nosological forms of PMDs from the list of key words at the second stage of selection (from transitory hypogammaglobulinemia of infancy to cyclic neutropenia), 36 well known nosological forms of autoimmune syndromes from the list of key words at the second stage of selection (from rheumatic fever to celiac disease), 1980-2025 years of publication, adults and children, men and women.

Exclusion criteria: case reports, editorials, non-English, non-retrievable, methodological problems in scientific research, non-included PMD in the list of PMDs nosological forms, non-included nosology in the list of autoimmune syndromes, years of publication below 1980, non-available full text or well-prepared abstract.

Evidence weighting: Preference for meta-analyses, population studies, and controlled clinical trials

Outcome measures: Frequency, spectrum, and strength.

4.3. Methodology of Selection (Study Selection Process)

During the presented study, a systematic review of the results of scientific publications on the outlined topic from the abstract electronic scientometric bibliographic database of publications from peer-reviewed medical periodicals PubMed (MEDLINE) was carried out for the period from 1980 to 2025 by keywords through a sequential two-stage search.

At the initial stage of the scientific search, such general keywords as “primary immunodeficiency”, “inborn errors in immunity”, “primary minor immunodeficiency”, “primary mild immunodeficiency”, “immunosuppression”, “immunodepression” were used, which were combined in an arbitrary order with such general keywords as “autoimmunity”, “autoagression”, “autoreactivity”, “autoimmune syndrome”, “autoimmune disease”, “rheumatic syndrome”.

As a result of the preliminary scientific search, 1,177 scientific publications were found, 74 of which were included in the literature list of this review based on full compliance with the aim and objectives of this study.

In further in-depth scientific research, the following clarifying keywords from the field of primary minor immunodeficiencies were used: “transitory hypogammaglobulinemia of infancy”, “unclassified hypogammaglobulinemia”, “selective IgM deficiency”, “selective IgA deficiency”, “selective IgG subclasses deficiency”, “selective IgE deficiency”, “selective IgD deficiency”, “selective myeloperoxidase deficiency”, “selective eosinophilic peroxidase deficiency”, “selective mannose binding lectin deficiency”, “deficiency of serine proteases, associated with mannose binding lectin”, “NK-cell deficiency”, “NKT-cell deficiency”, “CD16 molecule deficiency”, “CD8 molecule deficiency”, “CD64 molecule deficiency”, “idiopathic CD4 + T-cell lymphopenia”, “chronic idiopathic neutropenia”, “chronic benign neutropenia”, “cyclic neutropenia”, which were combined in any order with such clarifying keywords from the field of autoimmune syndromes as “rheumatic fever” (RF), “systemic sclerosis” (SS), “scleroderma” (ScD), “antiphospholipid syndrome” (APL), “rheumatoid arthritis” (RA), “juvenile idiopathic arthritis” (JIA), “systemic lupus erythematous” (SLE), “lupus nephritis” (LN), “primary Sjögren’s syndrome” (pSS), “dermatomyositis” (DM), “seronegative arthritis” (SA), “systemic vasculitis” (SV), “autoimmune thyroiditis” (AT), “Grave’s disease” (GD), “type 1 diabetes mellitus” (DM1T), “Addison disease” (AD), “pernicious anemia” (PA), “autoimmune cytopenias” (AC), “autoimmune hemolytic anemia” (AHA), “idiopathic thrombocytopenic purpura” (ITP), “aplastic anemia” (AA), “vitiligo (VG)”, “autoimmune encephalitis” (AE), “pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections” (PANDAS), “autoimmune polyneuropathy” (AP), “Crohn’s disease” (CD), “non-specific ulcerative colitis (NUC)”, “ankylosing spondylarthritis” (AS), “autoimmune hepatitis” (AH), “autoimmune uveitis” (AU), “myasthenia gravis” (MG), “multiple sclerosis” (MS), “Guillain-Barré syndrome” (GBS), “Behcet syndrome” (BS), “Henoch-Schonlein purpura” (HSP), “pemphigus vulgaris” (PV), “celiac disease” (CeD). As a result of the in-depth search, an

additional 1138 scientific articles were found, of which 227 were included in the final list of literature based on full compliance with the aim and objectives of the study.

In total, 301 scientific publications were included in the final list of literature after two consecutive stages of selection.

Boolean operator structure

Boolean operators were structured to maximize sensitivity while maintaining specificity in identifying relevant publications. The search strategy combined controlled vocabulary and free-text terms using predefined logical operators.

PMDs were linked using the OR operator to capture terminological variability (e.g., "minor immunodeficiency" OR "partial immunodeficiency" OR "mild immunodeficiency variants"). Autoimmune syndromes were similarly grouped using OR (e.g., "autoimmune disease" OR "autoimmunity" OR "immune-mediated disorder").

These two concept blocks were then combined using the AND operator to ensure the retrieval of studies addressing both PMDs and autoimmune manifestations simultaneously. Where appropriate, exclusion criteria were applied using the NOT operator to remove studies focusing exclusively on secondary immunodeficiency, immunosuppressive therapy, malignancy-associated immune dysfunction, or animal models.

Nested Boolean logic and parentheses were used to preserve correct operator precedence, and truncation symbols were applied selectively to capture word variants. This structured Boolean approach ensured comprehensive coverage of relevant literature while minimizing the retrieval of irrelevant records (**Table 1**).

Table 1. PRISMA 2020—Compliant Search Strategy.

Search Component	Terms and Boolean Structure	Purpose
Concept 1: Primary minor immunodeficiencies (PMDs)	("primary immunodeficiency" OR "primary minor immunodeficiency" OR "inborn errors in immunity" OR "primary mild immunodeficiency" OR "immunosuppression" OR "immunodepression")	Capture heterogeneous terminology for PMDs
Concept 2: Autoimmune syndromes	("autoimmune disease" OR "autoimmunity" OR "autoimmune syndrome" OR "rheumatic syndrome")	Capture a broad spectrum of autoimmune manifestations
Concept combination	(Concept 1) AND (Concept 2)	Identify studies addressing both PMDs and autoimmunity
Exclusion block	NOT ("secondary immunodeficiency" OR "immunosuppressive therapy" OR "HIV" OR "malignancy-associated immunodeficiency" OR "animal model")	Exclude secondary and non-human studies
Filters applied	Humans; English language; publication years 1980–2025	Ensure relevance and feasibility
Database	PubMed (MEDLINE)	Primary literature source
Search type	Two-stage: broad screening followed by refined disease-specific searches	Increase sensitivity and specificity

Full PubMed query

Stage 1. Broad sensitivity search

(("primary immunodeficiency" OR "primary minor immunodeficiency" OR "inborn errors in immunity" OR " primary mild primary immunodeficiency" OR " immunosuppression")
AND
("autoimmune disease" OR "autoimmunity" OR "autoimmune syndrome" OR " rheumatic syndrome"))
NOT
("secondary immunodeficiency" OR HIV OR malignancy OR "immunosuppressive therapy")
AND Humans[Mesh]
AND English[lang]

Stage 2. Refined precision search

(("selective IgA deficiency"[Title/Abstract] OR SIgAD[Title/Abstract]

OR "IgG subclass deficiency"[Title/Abstract]
OR "specific antibody deficiency"[Title/Abstract]
OR "selective IgM deficiency"[Title/Abstract] OR SIgMD[Title/Abstract]
OR "partial complement deficiency"[Title/Abstract]
OR "MBL deficiency"[Title/Abstract]
OR "mannose-binding lectin deficiency"[Title/Abstract]
OR "Selective IgE deficiency"[Title/Abstract] OR SIgED[Title/Abstract]
OR "Selective IgD deficiency"[Title/Abstract] OR SIgDD[Title/Abstract] … and other keywords)
AND
("autoimmune cytopenia"[Title/Abstract]
OR "autoimmune thyroiditis"[Title/Abstract]
OR "inflammatory bowel disease"[Title/Abstract]
OR "autoimmune arthritis"[Title/Abstract]
OR "systemic lupus erythematosus"[Title/Abstract]
OR "rheumatoid arthritis"[Title/Abstract] … and other keywords))
NOT
("secondary immunodeficiency"[Title/Abstract]
OR HIV[Title/Abstract]
OR AIDS[Title/Abstract]
OR malignancy[Title/Abstract]
OR chemotherapy[Title/Abstract]
OR "immunosuppressive therapy"[Title/Abstract]
OR "organ transplantation"[Title/Abstract]
OR mouse[Title/Abstract]
OR murine[Title/Abstract]
OR animal[Title/Abstract])
AND Humans[Mesh]
AND English[lang]

4.4. Risk of Bias

Wide diversity of PMDs and autoimmune syndromes in humans, different amount of known PMDs and autoimmune syndromes in different decades, differences in criteria for autoimmune syndromes and PMDs diagnosis verification in different years, non-standardized methodological approaches for 45 years of scientific studying, extremely uneven distribution of articles in the decade according to some nosological forms, different depth of study of the problem in various PMDs and autoimmune syndromes, which made it difficult to generalize.

Risk of bias was addressed through multiple complementary methodological safeguards. First, selection bias was reduced by applying predefined eligibility criteria and a two-stage screening process that included both title/abstract and full-text assessment, minimizing preferential inclusion of studies with positive findings.

Second, information and misclassification bias were limited by prioritizing studies with clearly defined diagnostic criteria for primary minor immunodeficiencies and autoimmune syndromes, and by excluding studies in which immune abnormalities could be explained by secondary immunosuppression, age-related immune dysfunction, or transient immune changes.

Third, reporting and publication bias were mitigated by evaluating the consistency of findings across multiple independent studies and study designs rather than relying on isolated reports. Associations supported only by single or low-quality studies were treated as hypothesis-generating.

Fourth, confounding bias was addressed through qualitative stratification by immune pathway, PMD type, age group, and autoimmune phenotype, allowing separation of biologically distinct mechanisms.

Finally, interpretive bias was minimized by using an evidence-weighted synthesis approach in which conclusions were driven primarily by higher-quality, reproducible data and by explicitly acknowledging residual uncertainty in the limitations section.

4.5. Data Extraction

In compiling the reference list, priority was assigned to studies providing the highest levels of scientific evidence. These included systematic reviews and meta-analyses, large population-based investigations, randomized controlled trials, well-designed retrospective case–control studies, and extensive analytical reviews grounded in clinical research data. Reports describing isolated clinical cases were excluded unless they offered notable historical relevance or unique contextual significance, as such evidence is generally considered limited in reliability.

Several categories of publications were omitted from consideration, including correspondence to editors, commentaries and rebuttals, conference abstracts, opinion-driven papers, proceedings of scientific meetings, textbook chapters, and monographic sections. Non-English publications, papers lacking accessible full texts or informative abstracts, and studies relying on obsolete diagnostic approaches were also excluded. Particular caution was exercised regarding works employing outdated laboratory techniques—such as rosette-based assays previously used for diagnosing cellular immunodeficiencies—because these methods may compromise diagnostic validity and the reliability of derived conclusions.

Greater emphasis was placed on research published within the past decade in order to incorporate contemporary advances and the most current perspectives in immunodiagnostics. Nevertheless, because comprehensive systematic evaluations of the relationship between primary minor immunodeficiencies and autoimmune syndromes remain scarce, efforts were made to integrate evidence accumulated across the entire searchable timeframe. Restricting the analysis to a narrow publication window would have produced a fragmented and potentially misleading representation of the field, particularly given the markedly uneven historical distribution of studies across specific immune disorders.

The methodological rigor and scientific credibility of each publication served as decisive criteria for inclusion. Key considerations included robustness of study design, appropriateness of statistical methodology, reliability and clinical relevance of laboratory diagnostic techniques, clarity and quality of illustrative materials reflecting primary data, and the overall validity and evidentiary strength of the authors' interpretations.

4.6. Study Quality Assessment

The quality of evidence included in this systematic review was assessed using an evidence-weighted, design-sensitive approach tailored to the heterogeneity of studies on PMDs. Each publication was evaluated for clarity and validity of PMD and autoimmune syndrome definitions, adequacy of exclusion of secondary immunodeficiency and age-related immune dysfunction, appropriateness of study design and population selection, and internal consistency between immunological findings and clinical outcomes.

Higher methodological weight was assigned to meta-analyses, population-based cohort studies, and controlled clinical trials with clearly defined diagnostic criteria and exclusion strategies. Observational studies with limited control of confounders were included with moderate weight, while case reports and small uncontrolled series were restricted to qualitative, hypothesis-generating interpretation only.

Given the absence of uniform diagnostic standards for many PMDs and the exploratory nature of this research field, a formal numerical scoring system was not applied. Instead, studies were categorized as providing high, moderate, or low confidence evidence. Evidence-weighted synthesis ensured that principal conclusions were driven primarily by higher-quality and more reproducible data.

4.7. Potential Confounders

Factors that distort true PMD–autoimmunity associations were heterogeneous diagnostic criteria for PMDs, overlap between primary and secondary immunodeficiency, trigger-dependent expression of autoimmunity, genetic modifiers influencing autoimmune phenotype, comorbid infections and immune-modulating therapies.

Several methodological strategies were applied to minimize the impact of potential confounders in this systematic review. First, strict eligibility criteria were used to preferentially include studies with clearly defined diagnostic criteria for PMDs and autoimmune syndromes, reducing misclassification bias. Studies in which immune abnormalities could be attributed to secondary immunodeficiency, immunosuppressive therapy, malignancy, chronic infection, or malnutrition were excluded or analyzed separately. Second, age-related immune dysfunction was addressed by prioritizing studies that applied age-adjusted immunological reference ranges and explicitly distin-

guished PMDs from immune immaturity or immunosenescence. Third, subclinical or transient immune abnormalities were minimized by excluding studies based solely on isolated laboratory findings without clinical relevance or longitudinal confirmation. Fourth, heterogeneity arising from comorbid conditions and mixed immune phenotypes was addressed through stratified qualitative synthesis according to immune pathway, PMD category, and autoimmune phenotype. Finally, conclusions were based primarily on consistent findings replicated across independent studies and supported by mechanistic plausibility, limiting the influence of residual confounding factors.

4.8. Selection Bias

Factors affecting who enters clinical studies were recruitment from tertiary referral centres, overrepresentation of severe autoimmune cases, exclusion of asymptomatic or mildly affected PMD carriers, underdiagnosis of subclinical immunodeficiency, and loss of patients with transient or fluctuating PMD phenotypes.

Selection bias was minimized through several predefined methodological measures. First, a comprehensive search strategy covering a wide time span (1980–2025) and using both broad and specific keywords was employed to reduce the likelihood of preferential inclusion of studies reporting positive or severe outcomes.

Second, a two-stage screening process was applied, consisting of independent title/abstract screening followed by full-text eligibility assessment, ensuring that study inclusion was based on predefined criteria rather than outcome direction.

Third, to avoid overrepresentation of severe or atypical cases, population-based studies and large cohort analyses were prioritized over tertiary referral center reports and highly selected clinical series. Small case reports and narrowly defined cohorts were excluded or restricted to qualitative interpretation.

Fourth, studies focusing exclusively on advanced autoimmune disease or treatment-refractory cases were interpreted cautiously, and their findings were not allowed to disproportionately influence overall conclusions.

Finally, conclusions were based on consistency across diverse populations, study designs, and immune phenotypes, reducing dependence on any single selectively recruited cohort.

4.9. Inherent Constraints

Biological and methodological limitations were the extreme phenotypic variability of PMDs, the evolutionary instability of immunodeficiency over time, mixed and overlapping pathogenic mechanisms, the limited availability of population-based immune screening, and difficulty separating causation from association.

Inherent biological and methodological constraints of studying PMDs and autoimmunity were acknowledged and mitigated through study design and analytical strategy. First, extreme phenotypic heterogeneity and temporal variability of PMDs were addressed by synthesizing evidence across multiple immune pathways and clinical phenotypes rather than relying on single-disease models.

Second, overlapping pathogenic mechanisms were managed through mechanistic stratification of PMDs (innate vs. adaptive; cellular vs. humoral), allowing differentiation of shared versus distinct autoimmune pathways. This reduced oversimplification arising from biological complexity.

Third, limitations related to non-uniform diagnostic standards were mitigated by prioritizing studies with clearly defined criteria and by evaluating consistency of associations across studies using different diagnostic thresholds.

Fourth, the inability to infer causality from observational data was addressed by applying temporal, mechanistic, and reproducibility criteria when interpreting associations, thereby reducing overinterpretation of correlational findings.

Finally, conclusions were framed conservatively, emphasizing population-level patterns and reproducible trends rather than absolute estimates, and residual constraints were explicitly acknowledged in the limitations section.

4.10. Exclusion of Overlap with Subclinical Immunodeficiencies, Age-Related Immune Dysfunction, and Secondary Immunosuppression

To minimize misclassification, studies were critically assessed for potential overlap between PMDs, subclinical immune variations, age-related immune dysfunction, and secondary immunosuppression.

Subclinical immunodeficiencies were excluded by prioritizing studies in which PMDs were defined using established laboratory thresholds or clearly stated diagnostic criteria rather than incidental or borderline immune

abnormalities detected in asymptomatic populations. Reports describing isolated laboratory deviations without clinical relevance or longitudinal confirmation were excluded.

Age-related immune dysfunction (immunosenescence or immune immaturity) was addressed by excluding studies in which immune abnormalities could be reasonably attributed to physiological extremes of age. Pediatric studies required persistence of immunological abnormalities beyond age-adjusted reference ranges, while adult studies were evaluated for explicit differentiation between PMDs and age-associated declines in immune parameters.

Secondary immunosuppression was excluded by preferential inclusion of studies that ruled out immunosuppressive medications, malignancy, chronic infections, malnutrition, or systemic inflammatory diseases as primary causes of immune dysfunction. Studies in which immune abnormalities developed exclusively after initiation of immunosuppressive therapy or as a direct consequence of autoimmune disease activity were excluded.

When complete exclusion was not possible due to limitations in reporting, such studies were retained only for qualitative synthesis and interpreted with caution. This approach reduced contamination of the PMD cohort and strengthened inference regarding primary immunodeficiency-associated autoimmunity.

4.11. Software Versions

Graphical abstract created using BioRender (web-based platform, BioRender.com; accessed 2025). Final layout and vector export prepared in Adobe Illustrator CC 2024. Figures were created with BioRender (BioRender.com) and finalized in Adobe Illustrator CC 2024 (**Table 2**).

Table 2. PRISMA 2020—Aligned Methods Summary.

No.	Section/Topic	Description
1	Title	Systematic review of associations between primary minor immunodeficiencies and autoimmune syndromes
3	Rationale	PMDs are common, clinically significant, and insufficiently studied as population-level contributors to autoimmunity
4	Objectives	To assess evidence for PMD–autoimmunity associations and develop an integrative pathogenic model
5	Eligibility criteria	Peer-reviewed human studies reporting defined PMDs and clinically confirmed autoimmune syndromes; exclusion of secondary immunodeficiency–only studies
6	Information sources	PubMed (MEDLINE)
7	Search strategy	Two-stage search: broad immunodeficiency/autoimmunity terms followed by PMD- and disease-specific keywords
8	Selection process	Title and abstract screening followed by full-text eligibility assessment
9	Data collection process	Structured qualitative extraction of study design, PMD type, autoimmune outcomes, and methodological characteristics
10	Data items	PMD category, affected immune pathway, autoimmune syndrome type, study design, evidence level
11	Study risk of bias assessment	Qualitative assessment of diagnostic validity, selection bias, confounding, and reporting transparency
12	Effect measures	Not applicable (qualitative and evidence-weighted synthesis)
13a	Synthesis methods	Narrative synthesis with hierarchical evidence weighting
13b	Handling heterogeneity	Stratification by immune pathway, PMD type, and autoimmune phenotype
13c	Missing data	No imputation; studies with incomplete data were included only in the qualitative synthesis
13d	Multiple comparisons	No formal correction; robustness ensured via consistency, evidence hierarchy, and mechanistic plausibility
14	Reporting bias assessment	Indirect assessment through comparison of higher- and lower-quality studies
15	Certainty assessment	Evidence categorized as high, moderate, or low confidence
16	Study selection	Two-stage screening resulted in the final inclusion of 301 publications
17	Study characteristics	Broad range of PMDs, autoimmune syndromes, study designs, and populations
18	Risk of bias in studies	Diagnostic heterogeneity and selection bias were identified as major limitations

Table 2. *Cont.*

No.	Section/Topic	Description
19–22	Results synthesis	Qualitative summary of PMD–autoimmunity associations without pooled quantitative estimates
23	Discussion	Interpretation of findings, limitations, and clinical implications
24	Registration	Not registered (exploratory systematic review)

Identification of PMDs and their association with autoimmune syndromes in this systematic review was achieved through a rigorous, multi-step process (**Figure 1**). The initial stage involved broad keyword searches in the PubMed (MEDLINE) database, followed by a more targeted selection using specific nosological forms and syndromes. Each included publication was carefully evaluated for relevance and quality, with priority given to robust study designs and up-to-date diagnostic methodologies. Through this approach, the review aimed to ensure that only well-characterised PMDs and autoimmune syndromes, supported by substantial evidence, were considered, thereby enhancing the reliability of the findings.

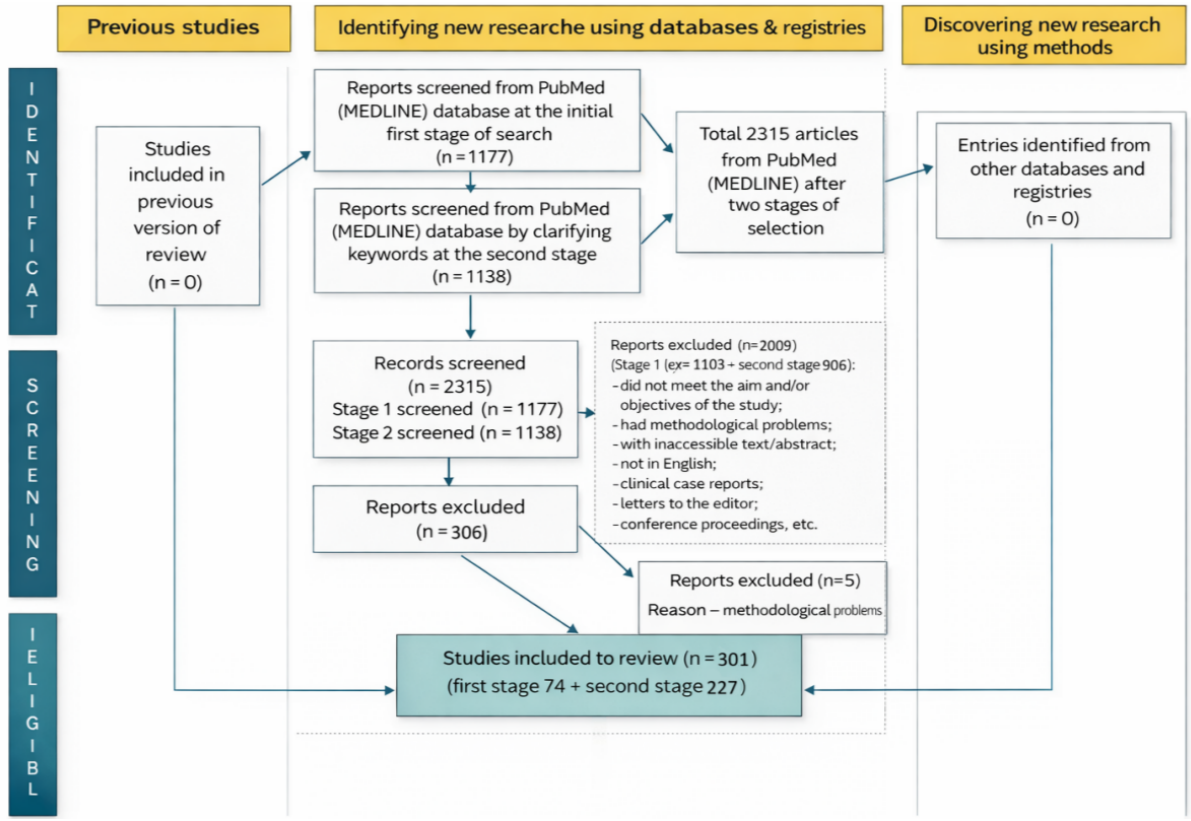

Figure 1. Scheme of the research structure (PRISMA flow diagram 2020).

5. Methodological Framework and Evidence Synthesis Strategy

5.1. Justification for Key Methodological Choices

1. Use of a long time frame (1980–2025)

Autoimmune manifestations of primary minor immunodeficiencies (PMDs) have been described unevenly over decades, with many entities reported only sporadically or in small cohorts. Restricting the search to recent years would have systematically excluded foundational observations and rare but informative associations, leading to biased underestimation of PMD–autoimmunity links.

2. Two-stage search strategy

A broad first-stage search was necessary to capture heterogeneous terminology used for PMDs and autoimmune syndromes. The second, refined stage allowed targeted identification of specific PMD–autoimmunity pairs, minimizing false negatives while reducing irrelevant retrieval.

3. Preference for high-quality study designs

Meta-analyses, population-based studies, and controlled clinical trials were prioritized because they reduce random error, selection bias, and publication bias compared with isolated case reports. Case reports were excluded unless historically or mechanistically informative.

4. Inclusion of multiple PMD categories

PMDs encompass diverse defects of innate and adaptive immunity. Limiting analysis to antibody deficiencies or classical PIDs would have produced a reductionist model and failed to capture the universality of autoimmunity across immune pathways.

5. Focus on clinically significant PMDs

PMDs were selected because of their high population prevalence and measurable clinical impact, making them more suitable for modelling autoimmunity at a population level than rare, severe primary immunodeficiencies.

6. Emphasis on heterogeneity and bias assessment

Explicit identification of diagnostic variability, phenotype instability, and overlap with secondary immunodeficiency was essential to prevent misclassification and over- or underestimation of true PMD–autoimmunity associations.

5.2. Prespecified Analyses

Before data extraction, the following analyses were defined:

- PMD–autoimmunity mapping

Identification of associations between individual primary minor immunodeficiencies and specific autoimmune syndromes across published studies.

- Strength of evidence assessment

Classification of PMD–autoimmunity associations according to study design, sample size, and level of evidence (meta-analyses, population studies, controlled trials, observational studies).

- Mechanistic stratification

Grouping of PMDs by affected immune pathways (innate vs. adaptive; cellular vs. humoral) to assess whether autoimmune risk differed by immunological domain.

- Phenotypic heterogeneity analysis

Evaluation of variability in autoimmune expression across the same PMD, including mono-autoimmune versus poly-autoimmune phenotypes.

- Bias and confounder evaluation

Systematic identification of diagnostic, selection, and biological factors that could distort observed PMD–autoimmunity associations.

- Integrative model synthesis

Development of a unified conceptual model linking PMDs, immune dysregulation, and autoimmune disease development.

5.3. Assumptions Testing

Key working assumptions were evaluated through predefined cross-checks within the literature corpus:

1. Universality of PMD–autoimmunity association

This assumption was tested by examining whether autoimmune syndromes were reported across multiple, mechanistically distinct PMDs (humoral, cellular, innate, and adaptive). Consistent reporting across unrelated PMDs supported a non–disease-specific, universal relationship.

2. Population relevance of PMDs

Prevalence data from epidemiological and screening studies were compared with autoimmune disease frequencies to assess whether common PMDs could plausibly contribute to autoimmunity at the population level.

3. Independence from secondary immunodeficiency

Studies distinguishing congenital or genetically determined PMDs from treatment- or disease-induced immunosuppression were analysed separately to confirm that autoimmunity occurred in primary immune defects.

4. Causative rather than coincidental association

Temporal sequencing (PMD preceding autoimmunity), familial clustering, and mechanistic plausibility (defects in tolerance, clearance, or immune regulation) were used to test whether observed associations exceeded chance co-occurrence.

5. Robustness to diagnostic heterogeneity

Findings were compared across studies using different diagnostic thresholds and laboratory definitions to determine whether associations persisted despite methodological variability.

5.4. Missing Data Handling

Because this study was based on published literature, missing data primarily reflected incomplete reporting within individual studies rather than loss of raw patient data. To minimize bias from incomplete information, the following approach was applied:

Study-level inclusion

Studies were included if they provided sufficient data to confirm both the presence of a primary minor immunodeficiency and an autoimmune syndrome, even if some secondary variables (e.g., demographic details or laboratory thresholds) were missing.

Outcome prioritization

When multiple outcome measures were reported, the most clinically relevant and clearly defined autoimmune outcomes were used. Studies lacking definable autoimmune endpoints were excluded.

No statistical imputation

No imputation or reconstruction of missing numerical data was performed, because raw datasets were not available and imputation across heterogeneous study designs would introduce artificial precision.

Qualitative synthesis for incomplete data

Associations reported without full quantitative detail were included only in qualitative synthesis, not in any comparative or evidence-weighting assessments.

Sensitivity to reporting bias

The impact of missing information was evaluated by comparing results from well-documented studies with those from incompletely reported studies to ensure that key conclusions were not driven by poorly reported data.

5.5. Corrections for Multiple Comparisons

Because this work was a qualitative and evidence-weighted systematic review rather than a single pooled quantitative meta-analysis, formal statistical correction for multiple comparisons (e.g., Bonferroni or false discovery rate adjustment) was not applied. Instead, control for multiplicity was addressed through methodological safeguards:

Evidence hierarchy

Associations were weighted according to level of evidence (meta-analyses, population studies, controlled trials, observational studies), reducing the impact of spurious findings from small or uncontrolled reports.

Consistency requirement

PMD–autoimmunity associations were considered robust only when supported by multiple independent studies or by large population-based analyses.

Mechanistic plausibility filter

Reported associations were evaluated in the context of known immunological mechanisms (tolerance failure, impaired clearance, immune dysregulation), limiting false-positive interpretations.

Separation of exploratory and confirmatory findings

Rare or single-study associations were treated as hypothesis-generating rather than confirmatory evidence.

This approach minimized inflation of false-positive conclusions while preserving sensitivity to detect biologically meaningful PMD–autoimmunity relationships.

6. Results and Discussion

6.1. Critical Analysis of the Conditions and Factors That Could Have Influenced Both the Current Depth of Study of the Problem

6.1.1. General Results

It has been found that diseases of the immune system often manifest as autoimmune syndromes along with other clinical symptoms due to the weakening of the function of maintaining immune tolerance to the antigens of the body [25]. Autoimmunity is a class or representative feature of immunodeficiencies. It is naturally observed in both primary and secondary immunodeficiencies, in cases of damage to both innate and adaptive immunity, with the involvement of both cellular and humoral components of the immune system [26]. An autoimmune syndrome can be the first clinical manifestation of previously asymptomatic PID [27]. There are even such forms of PID, such as primary polyendocrinopathy syndromes, which manifest exclusively in the form of autoimmunity without other clinical manifestations [28].

The study identified the current evidence base of the association of primary minor immunodeficiencies and autoimmune syndromes in humans, which is demonstrated in the relevant section of this publication. When studying the material, the main potential factors were identified that could influence the state of the current evidence base and could be an obstacle to the rational conduct of further research. Such factors include terminological aspects, a wide variety of mechanisms of autoimmunity development, extreme heterogeneity of immunodeficiencies in origin, form and evolutionary scenario, the possibility of arbitrary combination with other immunodeficiencies and diseases, the phenomena of variability of the clinical course and heterogeneity of the clinical picture, the difficulty of distinguishing the phenotypes of PID and associated secondary immunosuppression, unspecified diagnostic criteria for a number of immunodeficiencies, difficulties in distinguishing the phenotypes of immunodeficiencies and associated autoimmune syndromes. All these factors are described in detail below. The aim is to understand both the reasons for the current gaps in the evidence base and ways to overcome potential systematic errors. It is important, accordingly, to improve the quality of scientific research when conducting further controlled studies in the outlined direction.

6.1.2. Terminological Aspects

Currently, common variable immunodeficiency (CVID) and selective IgA deficiency are the most studied PIDs from the point of view of induction of autoimmune syndromes in humans [29]. In these PIDs, the development of almost all known clinical nosologies of autoimmune nature has been described and a specific spectrum of autoimmunity in the clinical picture has been established. However, certain autoimmune reactions have been described in almost all known PIDs. Therefore, the association of PID and autoimmune syndromes now seems obvious. However, the low frequency in the population of most PIDs does not allow us to consider these rare clinical phenomena sufficiently representative on a population scale. Rare PIDs can not play the role of a universal source of develop-

ment of the phenomenon of autoimmunity, which is quite common among people.

Currently, more than 450 forms of PID are known in humans [30], most of which occur only in a meager 1–1.5% of the modern human population [31]. These are the so-called classical PIDs. For example, they are "classical" PIDs according to Goudouris [4], or "classic" PIDs according to Sacco et al. [30]. They were the first to be described in the history of the study of human immune system diseases. An example of such an immunodeficiency is the so-called "classic ataxia-telangiectasia" according to Lnu et al. [32]. Classical PIDs are sometimes also called major immunodeficiencies. This term was proposed by Gross et al. in 1992 [33] and supported by Azizoglu et al. in 2024 [34]. These diseases usually involve many immune factors simultaneously and result in clinical manifestations of marginal severity with a dramatic course of the disease and a mostly unfavourable prognosis.

In contrast to classical (major) PID, there are so-called minor PID. Such a term was proposed by Litzman et al. in 1995 [35], and supported by Vivarelli et al. in 2021 [36]. These immunodeficiencies involve mostly only one immune factor. Such diseases are milder in clinical manifestations without the obligatory pattern of early onset, marginal severity of clinical manifestations, dramatically unfavourable course of the disease, and high mortality. Alternatively, primary minor immunodeficiencies (PMIDs) are sometimes called mild immunodeficiencies. Such a term was proposed by Van Kessel et al. in 1999 [37] and supported by Janssen et al. in 2018 [38]. Their clinical symptoms in many (but not all) cases can be milder than those of classical diseases of the immune system. Sometimes PMDs are also referred to as incomplete PID. Such a term was proposed by Smits et al. [39]. Really, in some of them only fragments of the broader immunological phenotypes of well-known classical PIDs are formed. For example, selective IgA deficiency can be considered as part of the CVID phenotype [40]. There are even proposals to designate PMDs as "immunodeficiency-like states" [41]. In fact, they are similar, but do not fully correspond to the clinical and laboratory features of classical PID.

Minor (mild, incomplete) diseases of the immune system, numbering only about 30-40 nosologies, collectively cover more than 20% of the modern inhabitants of the planet. So, PMDs are fairly representative models of the etiological factor of autoimmune syndromes in humans on a population scale. The accumulation of additional evidence in the field of PMDs strengthened the idea that autoimmunity as a phenomenon is a consequence of immunodeficiency at the population level. There are not only individual rare cases in some families with rare diseases of the immune system [42]. The classification of PMDs according to the affected immune factor, branch and type of immunity described so far in humans is given in **Table 3**.

Table 3. Classification of known PMDs in humans.

No.	Classification
I	Disorders of the cellular branch of innate immunity: A. Quantitative: a. neutrophil disorders: - familial benign neutropenia (FBN) [43]; - chronic idiopathic neutropenia (CIN) [44]; - cyclic neutropenia (CyN) [45]. b. eosinophil disorders: - chronic idiopathic eosinopenia (CIE) [46]. c. lymphocyte disorders: - natural killer cell deficiency (NKD) [47]; - natural killer T-cell deficiency (NKTD) [48]; - CD16 molecule deficiency (CD16D) [24]. d. monocyte disorders: - selective monocytopenia (SM) [49]. B. Qualitative: - neutrophil myeloperoxidase deficiency (MPOD) [50]; - eosinophilic peroxidase deficiency (EPOD) [51]; - primary perforin deficiency (PPD)* [52]; - CD64 molecule deficiency (CD64D) [53].
II	Disturbances of the humoral branch of innate immunity: - deficiency of complement system proteins, primarily the terminal components of the cascade that form the membrane attack complex, C6D [54], C7D [55], C8D [56], C9D [57]; - deficiency of mannose-binding protein (lectin) deficiency (MBLD) [21]; - deficiency of serine protease type 2 associated with mannose binding protein (lectin) (mannose binding protein (lectin) associated serine protease 2 deficiency (MASP1D) [58]; MASP2D [59].

Table 3. *Cont.*

No.	Classification
III	Deficiency of the humoral branch of adaptive immunity: - transitory hypogammaglobulinemia of infancy (THI) [60]; - unclassified hypogammaglobulinemia (UH) [61]; - selective (isolated) IgM deficiency (SIgMD) [62,63]; - selective (isolated) IgG deficiency (SIgGD) [64]; - selective (isolated) IgG subclass deficiencies (SIgGSD) [65]: (SIgG1D [37], SIgG2D [66], SIgG3D [67], SIgG4D [68]); - selective (isolated) IgA deficiency (SIgAD) [69]; - selective (isolated) IgA subclass deficiencies (SIgASD): SIgA1D, SIgA2D [70]; - selective (isolated) secretory IgA deficiency (SsIgAD) [71]; - selective (isolated) IgE deficiency (SIgED) [72,73]; - selective (isolated) IgD deficiency (SIgDD) [74,75]; - specific antibody deficiency with normal IgG [76], including antipolysaccharide antibodies (SAD, SPAD) [77] or monogenic inborn errors of immunity with impaired IgG response to polysaccharide antigens but normal IgG levels and normal IgG response to protein antigens [78]; - impaired glycosylation of IgA1, or galactosa-deficient IgA1 [78]; - other dysimmunoglobulinemias (combined deficiencies of immunoglobulins of different classes and/or subclasses), such as combined deficiency of IgA1, IgG2, IgG4 and IgE [79] or IgG1, IgG3, IgE [80] or IgM, IgA, IgE, SPAD [81].
IV	Deficiency of the cellular branch of adaptive immunity: - idiopathic CD4 + T-cell lymphocytopenia (ICD4 + TL) [82,83], or non-SCID T-cell lymphopenia at newborn screening [84]; - iCD8 molecule deficiency (CD8D) [85].
V	Combined immunodeficiencies, such as a combination of NK cell deficiency and chronic neutropenia in GINS1 deficiency [86] or a combination of MBLD and IgA1 with impaired glycosylation [87].

Note: * excluding hemophagocytic lymphohistiocytosis.

Although in most cases the distinction is clear, the line between major PID and PMD can sometimes be blurred in atypical forms of classical PID. It was shown, for example, by a novel mutation in the BTK (Bruton tyrosine kinase) gene. In such cases, the laboratory phenotype of X-linked agammaglobulinemia is reduced to a selective deficiency of the IgM molecule, mimicking this form of PMD [88].

6.1.3. Diversity of Mechanisms of Autoimmunity

Currently, the following mechanisms of induction of autoimmunity in PMD have been identified: altered responses of germinative centers of lymphatic follicles of immune organs [89], disruption of the pathways of central [90] and peripheral negative selection of lymphocytes [1], uncontrolled proliferation of lymphocytes, ineffective function of the cytoskeleton of immunocompetent cells [28], defects in innate immunity accompanying persistent hyperinflammation [91] and defective clearance of the organism from infectious agents that can act as triggers of autoimmunity [28]. Microbial triggers can induce autoimmunity through the mechanism of molecular mimicry, bystander activation and through the mediation of superantigens [1]. In immunodeficiencies, the formation of the normal intestinal microbiome may be disrupted [92]. It can lead to a state of secondary immune dysregulation with a predisposition to autoimmunity [93].

The pathways of autoimmunity differ in disorders of innate and adaptive immunity. Sogkas G et al. identify the following main mechanisms for the induction of autoimmune reactions in inborn errors of immunity: increased proinflammatory cell death, activation of myeloid cells, involvement of the cGAS-STING (cyclic GMP-AMP synthase -stimulator of interferon genes) pathway, hyperactivation of innate immunity receptors, dysregulation of signals from proinflammatory cytokines, defects in the maturation and/or functioning of Tregs, defects in apoptosis of activated lymphocytes [94]. In contrast, the predominant pathways of autoimmunity differ in cellular and humoral immunodeficiencies. In humoral immunodeficiencies, as in complement and immunoglobulin system defects, the primary focus is on weakening the clearance of microorganisms [95], apoptotic material and cellular detritus [96], disruption of the functioning of the antiidiotypic immunoglobulin network [97] and the pathways of solubilization and resolubilization of circulating immune complexes [98]. But in cellular immunodeficiencies, the prerogative belongs to the damage of the fundamental reciprocal relationships between regulatory subpopulations of lymphocytes Th1, Th2, Th17, Treg [1] and, accordingly, the formation of an aberrant balance of key cytokines IFNγ/IL-4/IL-17/IL-10 [99], anomaly activation of proinflammatory pathways, for example, IL-6 R/JAK/STAT3 [100], and the associated disruption of the processes of polarization of macrophages M0/M1/M2 [101] (**Table 4**). Heterogeneity of patho-

genetic mechanisms of autoimmunity in PMD is noted even within the framework of one nosological unit. Thus, such diversity was well characterized by Bagheri Y et al. on the example of SIgAD [102].

Table 4. The mechanism of development of autoimmunity at different PMDs.

No.	Immune Defect	Tolerance Breakdown	Autoimmune Pathway	Clinical Forms
1	Cellular innate immunity (phagocytosis, NK cells, NKT-cells)	Increased proinflammatory cell death, activation of myeloid cells, involvement of the cGAS-STING pathway, hyperactivation of innate immunity receptors, dysregulation of signals from proinflammatory cytokines [94]	Delay hypersensitivity (IV-type reactions according to Gell-Coombs classification)	RA, CD, AS
2	Humoral innate immunity (complement system)	Impaired blood clearance of microbial antigens, delayed removal of autoantigens and detritus in necrotic and apoptotic foci, delayed clearance of circulating immune complexes by macrophages in the spleen and liver [96]	Cytotoxic (II-type reactions according to Gell-Coombs classification) and immune complex disorders (III-type reactions according to Gell-Coombs classification)	SLE, SV, APL, LN, glomerulonephritis
3	Cellular adaptive immunity (T-helpers, cytotoxic T-cells)	Aberrant reciprocal relationships between regulatory subpopulations of lymphocytes Th1, Th2, Th17, Treg [1], pathological balance of key cytokines IFNγ/IL-4/IL-17/IL-10 [99], anomaly activation of IL-6 R/JAK/STAT3 pathway [100], disruption of polarization of macrophages M0/M1/M2 [101]	Cytotoxic (II-type reactions according to Gell-Coombs classification) and delayed hypersensitivity (IV-type reactions according to Gell-Coombs classification)	RA, CD, AS, DM1T, AA, NUC, AC
4	Humoral adaptive immunity (immunoglobulins)	Overload of mucous membranes with microbial antigens, disruption of the functioning of the antiidiotypic immunoglobulin network [97] and the pathways of solubilization and resolubilization of circulating immune complexes [98]	Cytotoxic (II-type reactions according to Gell-Coombs classification) and immune complex disorders (III-type reactions according to Gell-Coombs classification)	SLE, SS, DM, pSS, SA, NUC, AC, CeD

The unprecedented diversity of mechanisms of autoimmunity development even with the same immunodeficiency creates some difficulties. They exist both in the fundamental understanding of the problem of autoimmune manifestations of PMDs in theoretical medicine, and in the assessment of the pathogenesis of autoimmune syndromes in clinical studies and the personalized search for the mechanism of autoimmunity development in an immunocompromised patient in medical practice.

6.1.4. Heterogeneity by Origin

The above-mentioned PMDs are primary, since they are all genetically determined phenomena. At the same time, PMDs can be of three types depending on their ability to be inherited and the chronology of occurrence. First, PMDs can be hereditary phenomena [103]. The causal genetic abnormality of PMD is inherited from the parents with the appearance of an associated immunological phenotype from the moment of birth and can be further transmitted to the offspring (the pathological gene is contained in the germ cells of the fertile proband). Secondly, PMDs can be inborn [104,105], or congenital [106,107]. The causal genetic abnormality of PMD is not transmitted by the germ cells of the parents. It originated during embryogenesis under the influence of certain factors, and forms an immunological phenotype from the moment of birth. It is not transmitted to subsequent generations. Errors are not contained in the germ cells, but they cause a violation of the endurance and/or fertility of the carrier. The examples are various chromosomopathies, which are the cause of SIgMD in humans in at least 16.2% of cases [108]. Thirdly, PMDs can be acquired diseases [109]. They are the result of the delayed formation of the immunological phenotype until the period of postnatal ontogenesis without the obligatory ability to be inherited by subsequent generations. Acquired forms of PMD may result from genetically determined epigenetic dysregulation of genome expression with postnatal onset of the phenomenon of epigenetic reprogramming [110]. For example, it is possible in SIgAD [111]. The PMDs may be transferred during allogeneic bone marrow transplantation from a donor to a recipient during postnatal ontogeny. Such cases have been described, in particular, in SIgG2SD [112], SIgAD [109,113] and CyN [114]. The

fact that PMDs may in some cases be acquired creates some confusion with secondary immunodeficiencies. They are considered exclusively acquired conditions. It requires some changes in the nomenclature to clarify terminological confusion.

In accordance with the division of PMD into hereditary, congenital and acquired, Freiberger et al., using the example of SIgAD, propose to distinguish between sporadic and familial forms of PMD in humans [115]. Highly consanguineous populations are affected by PMDs [116]. Such a simple classification may be more convenient for clinical practice.

The complexity of the situation lies in the fact that currently known forms of PMDs can be interpreted as hereditary, congenital and acquired. It is possible in the case of genetically determined immunoregulatory disorders associated with methylation [111]. The existing nomenclature, which distinguishes only primary and secondary immunodeficiencies, cannot adequately represent the complex pattern of immunocompromised states in humans, so it requires significant refinement in accordance with modern scientific achievements.

6.1.5. Heterogeneity in Form

PMDs can be quantitative [43] and qualitative [50], transient [60] and permanent [22], cyclic [45] and irregular [82] in manifestations associated with damage to the innate [21] and adaptive immunity [82], humoral [22] and cellular [82] branches, the local mucosal compartment of the immune system [71] and systemic immunity [82].

In terms of quantitative immune factor deficiencies, PMDs are described as total [117] (absolute [118,119] and complete [24,50,120]), and partial [33,119,121] (subtotal [117], moderate [122] and subnormal [67,123]). In terms of qualitative immune factor deficiencies, PMDs are described as complete [50], profound [124], and moderate [125]. All of them may be clinically significant. While total forms of some PMDs may be rare [63], partial immunodeficiencies are a fairly common phenomenon in the general population. They are typical among patients with immune-dependent syndromes [33,126] (**Figures 2** and **3**).

Thus, the manifestation of mild hypogammaglobulinemia with subnormal values of serum concentrations of immunoglobulins of different classes was shown by Janssen LMA et al. Such patients have recurrent respiratory infections, bronchiectasis, persistent pain phenomena, cognitive impairment, a feeling of pronounced weakness and social interaction disorders [38]. Subnormal SIgG1SD leads to the development of autoimmune syndromes (50.0%), hypothyroidism (24.1%), atopy (29.8%), and other forms of allergy (31.5% of cases) [127]. Subnormal SIgG3SD also leads to the development of autoimmune syndromes (33.1%), hypothyroidism (14.9%), atopy (29.8%), and other forms of allergy (41.3% of cases) [67]. Subnormal deficiencies of C6 and C7 may be clinically manifested [128].

Figure 2 illustrates the hierarchical structure of PMDs according to the depth of deficiency of the affected immune factor and its functional activity. PMDs are subdivided into quantitative (classical PMD, cPMD) and qualitative or functional (functional PMD, fPMD), each of which may present as complete, total, partial, subtotal, or subnormal forms. In contrast to classical primary immunodeficiencies, where immune defects are usually profound and stable, PMDs form a continuous spectrum of immunological impairment, ranging from minimal subclinical abnormalities to near-complete loss of a specific immune component. Importantly, even subnormal and moderate deficiencies can be clinically significant, particularly in predisposing to autoimmune and immune dysregulatory syndromes. A key feature highlighted in this figure is the distinction between quantitative and qualitative defects. In functional PMDs, the concentration of an immune factor may remain within the normal range, whereas its biological activity is critically impaired, leading to defective immune regulation and loss of tolerance. Therefore, reliance on absolute laboratory values alone may underestimate the true degree of immune dysfunction in such patients. Overall, **Figure 2** emphasizes that PMDs are not binary conditions but represent a continuum of immune insufficiency with direct implications for susceptibility to infection, allergy, and autoimmunity, underscoring the need for integrated quantitative and functional immunological assessment in both research and clinical practice.

Figure 3 demonstrates the conceptual relationship between quantitative and qualitative PMDs according to the depth of deficiency of the affected immune factor. The diagram illustrates how both numerical reductions (quantitative PMD) and functional impairments (qualitative PMD) can lead to comparable levels of immune insufficiency, even when absolute laboratory values appear normal. The figure emphasizes that immune competence is determined not only by the concentration of immune components but also by their biological activity. Thus, a patient with normal levels of an immunological parameter but severely reduced functional capacity may be immunologically equivalent to another patient with a marked quantitative deficiency. This overlap explains why individuals

with functional PMD can develop recurrent infections, immune dysregulation, and autoimmune syndromes despite apparently "normal" laboratory profiles. By aligning quantitative and qualitative deficiencies along the same continuum of immune factor availability and activity, **Figure 3** highlights the need for an integrated diagnostic approach. Functional assays should complement conventional quantitative measurements in order to accurately characterize immune status and identify clinically significant immunodeficiency. Overall, **Figure 3** supports the concept that PMD represents a multidimensional spectrum of immune dysfunction, in which both the amount and the performance of immune factors determine the risk of immune-mediated pathology, including autoimmunity.

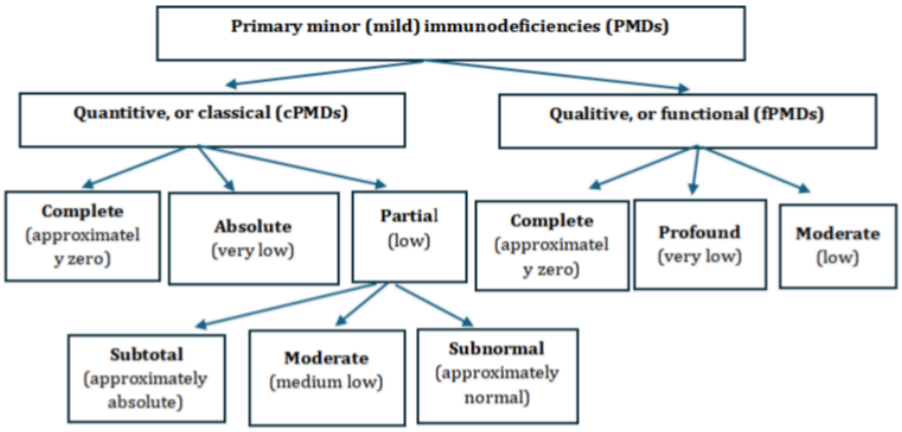

Figure 2. Structure of PMD by depth of deficiency of the affected immune factor [24,35,37,47,50,67,119,122,124,125].

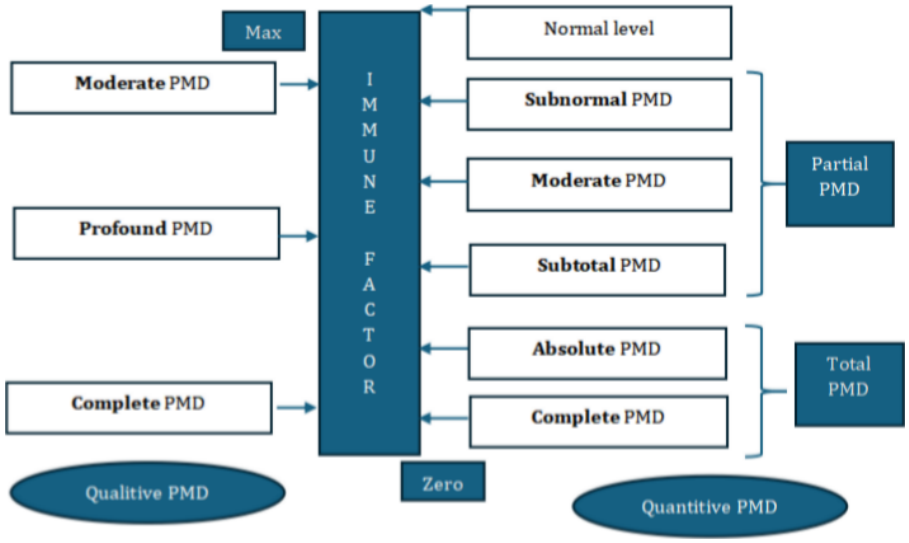

Figure 3. Correlation of different forms of quantitative and qualitative PMD by the depth of deficiency of the affected immune factor.

Research investigating associations between PMDs and autoimmunity should encompass the full spectrum of the multimodal diversity of known immunodeficiency forms. It is necessary to avoid reductionist approaches to assessment. Such mistakes may produce biased results by modifying and/or downplaying the associations between PMDs and autoimmune syndromes in humans.

6.1.6. Heterogeneity of Evolutionary Scenarios of the Laboratory Phenotype

Sgrulletti M et al. point to fundamentally different evolutionary scenarios of the development of PMDs during human ontogenesis. It may have an impact on the risk and manner of autoimmune manifestation in different

nosologies and in different patients [129]. Thus, spontaneous progression of SIgAD to the CVID phenotype at a certain point in ontogenesis with the formation of the phenomenon of hypogammaglobulinemia is possible [40]. Conversely, an unexpected reduction of the immunological phenotype of CVID with profound hypogammaglobulinemia persisting for many years to limited manifestations of SIgAD is also known [130].

However, not only inter-nosological, but also intra-nosological individual evolutionary scenarios of PMD events are possible. As Lim CK et al. showed, by the puberty period, the total form of SIgAD transforms into the partial form of SIgAD in at least 60% of cases [131]. It is explained by the phenomenon of age-related maturation of the human immune system.

Such metamorphoses may be associated with the fact that one and the same mutation can lead to different immunological phenotypes depending on additional conditions. Thus, mutations in the TACI gene (transmembrane activator and CAML interactor), or TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B) can lead to the formation of a hypogammaglobulinemia phenotype in some patients with the immunological picture of CVID, and selective deficiencies of classes and subclasses of immunoglobulins in others, even within the same family [132].

In accordance with the phenomenon of evolutionary instability of the laboratory phenotype in PMDs, Joller PW et al. in 1981 proposed to distinguish between transitory and persistent forms of SIgAD in humans [133].

Similarly, Johnson ML et al., studying age-dependent changes in the immunological phenotypes of CVID and SIgAD, distinguished progressive and reversible forms of the diseases. It could differ even among members of the same family with the same PMD [133].

Considering the known fluctuations in the levels of the affected immune factor, Kazi A et al., using the example of SIgED, proposed a classification of PMD according to the evolutionary scenario of events. Firstly, they distinguished a stable, or "chronic" SigED form. The depth of the immune factor deficiency is relatively the same in different periods of ontogenesis. The secondary, "oscillating" form of SIgED was described. The depth changes significantly throughout life in different directions. Thirdly, "newly diagnosed" SIgED forms are possible. An unknown further development scenario is present in such cases. Fourthly, "normalized" SIgED forms are observed. A gradual approach of the affected immune indicator to the normal level during a certain period of ontogenesis was evaluated [134].

The maximum manifestation of the normalization form of the evolutionary scenario of PMD development is the so-called reversal [131], or reversible [135] humoral deficiencies in children. The compensation of the immunological phenotype up to 12 years of age is observed in such cases. The proportion of reversible forms of humoral PMDs can reach 50% of cases in some nosologies [131] (**Figure 4**).

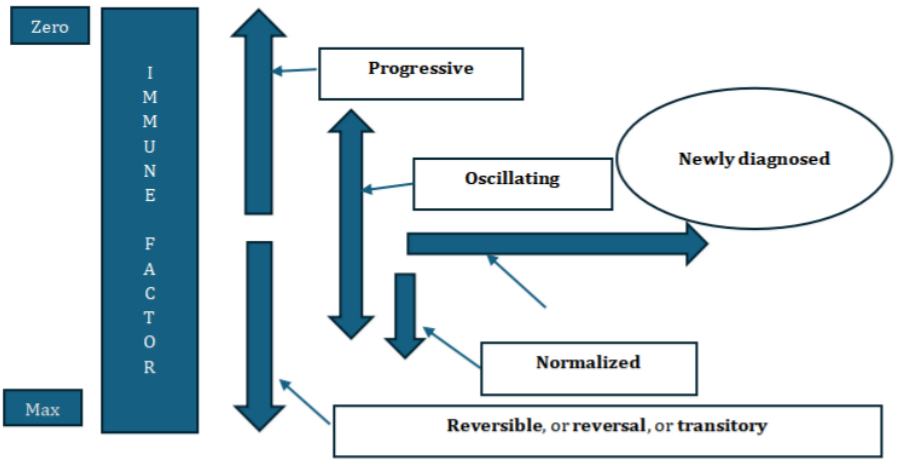

Figure 4. Diversity of evolutionary scenarios of PMD development by the number of affected immune factors [131, 133–135].

Figure 4 illustrates the diversity of evolutionary trajectories of PMDs during human ontogenesis, based on longitudinal changes in the level or activity of the affected immune factor. The figure highlights that PMDs are dynamic rather than static conditions, and that their immunological phenotypes may change substantially over time. Several principal evolutionary patterns are depicted. In the progressive form, the depth of immunodeficiency increases

over time, potentially leading to worsening immune dysregulation and a rising risk of autoimmune and infectious complications. In the oscillating form, immune factor levels fluctuate, creating alternating periods of apparent immunological stability and vulnerability. The normalized form reflects gradual recovery or partial compensation of immune function, whereas the reversible (transitory) form describes temporary immunodeficiency, particularly in childhood, with subsequent normalization during immune system maturation. Finally, the newly diagnosed form represents cases in which the long-term trajectory has not yet been established. This dynamic view is essential for understanding the relationship between PMD and autoimmunity. Autoimmune manifestations may arise not only in progressive or severe immunodeficiency, but also during transient or apparently favourable normalization phases, when immune regulation remains unstable despite improving laboratory values. Consequently, a single time-point measurement may fail to capture the true immunological risk profile of a patient. Overall, **Figure 4** underscores that PMDs are evolving biological phenomena, and that their temporal behaviour must be considered in both clinical management and research on immune-mediated diseases, particularly autoimmunity.

We must take into account the full spectrum of evolutionary scenarios for the development of PMDs when conducting clinical studies. It may allow more accurate reproduction of patterns of association with autoimmune syndromes. The development of autoimmunity can be observed even in seemingly prognostically favourable normalization scenarios of events. But such PMD forms are often mistakenly excluded from scientific studies as clinically insignificant phenomena.

6.1.7. The Problem of Combined Forms of PMDs

PMD is most often an isolated, or selective phenomenon [40]. Only one immune factor is affected in such cases. The term “isolated” PMD was proposed by Barton et al. in 2014 [136]. We think that the term “isolated” is much better than “selective”. It can avoid misdiagnosis with immunodeficiencies with selective predisposition for one microbe. However, there are also reports of combined [33] or complex [118] forms of PMDs. Several different diseases of the immune system are noted in one patient in such cases. It’s together cause immunodeficiency is an integral phenomenon. The term “complex” PMDs was proposed by Hogendorf et al. [118]. We think that the term “complex” PMD is much better than “combine”. It points not only to coexisting, but also to possible interactions between different PMDs in one person.

Currently, 4 forms of immune system diseases combinations involving PMDs are known. Firstly, combinations with other genetic diseases associated with immunosuppression were possible. The example is a combination of SIgG4SD and Down syndrome [68]. Secondly, the combination of PMD with classical PID is known. For example, CVID and SMBLD may coexist in some patients [27]. Thirdly, PMD may combine with another PMD. The combination of C6D and C7D is described [128]. And, fourthly, PMD may coexist with secondary immunodeficiencies. For example, in patients with AIDS, SMBLD may be present [137]. The character of a combination affects the risk, nature and severity of associated autoimmune reactions and sensitivity to treatment.

If we talk about the combination of different PMDs in one patient, then we should distinguish between the combination of different PMDs with damage to one branch of the immune system and different branches of the immune system. For example, phagocytosis is affected in the combination of MPOD and CyN [138]. It is a monomodal combination, or monomodal complex form of PMD. The complement system and the humoral component of adaptive immunity are affected in the combination of SMBLD and SIgGSD [139]. It is a bimodal combination, or a bimodal complex form of PMD. It is possible to combine not only two, but many PMDs in one patient in an arbitrary manner. There are polymodal combinations, or polymodal complex forms of PMD. For example, Bijker EM et al. reported the simultaneous presence of SIgMD, NKD and SPAD in one patient with invasive pneumococcal infection [140].

A distinction should be made between cases of a single immunodeficiency with the phenotype of several PMDs and combinations of several independent genetically heterogeneous PMDs. In the first case, the pseudocombinations are present. For example, the combination of SIgAD and SIgED in the case of a single etiological mutation in the DCLRE1C (DNA Cross-Link Repair 1C) gene presence is a typical pseudocombination [141]. In the second case, the true combinations are present. The example of true combinations is the case of coexisting C6D and C7D in one patient caused by two independent mutations in the C6 and C7 genes [128].

When talking about the combination of PMD and secondary immunodeficiency, one should distinguish between a combination of unrelated diseases and a combination of related PMD and secondary immunodeficiency, which is essentially a consequence of PMD. The case of an unrelated combination is coexisting AIDS and SMBLD in

the same patient [137]. Thus, it has been shown that SIgG2SD can lead to the production of autoantibodies to IgA molecules. It can be due to the formation of secondary IgA deficiency, which expands the immunological phenotype of primary SIgG2SD [142]. This is an example of a related combination.

In monomodal combined PMD, the so-called "matryoshka" effect may be observed. In such cases each subsequent smaller immunodeficiency, when deepening the diagnostic search, appears as if incorporated into another, larger one. It is possible, for example, in the case of SIgGD with low total IgG concentration in the blood [64]. During further studying the subclass composition of the IgG pool, SIgG2SD can be additionally detected [66], and further, within the deficient IgG2 pool, SPAD [77]. And all these three humoral PMDs may be independent diseases. There are so-called "hidden" combinations.

Clinical trials should consider the possibility of various combined forms of PMDs. The detection of them may facilitate the wider involvement of specialized genetic studies in the diagnostic search process. It may more accurately reproduce the complex patterns of association of different PMDs and various autoimmune syndromes in humans.

6.1.8. The Problem of Diagnostic Criteria for PMDs

As Batista CHR et al. showed on the example of SIgMD, in the diagnosis of PMDs in humans different diagnostic criteria can still be applied to the same PMD in different patients, which can create confusion in the diagnostic process [108]. At the same time, Janssen LMA et al. on the example of the so-called "truly" SIgMD demonstrated how the use of too strict (and in essence reductionist) laboratory diagnostic criteria distorts the real frequency of PMDs in the population [63]. It transfers a large number of so-called unclassified forms of SIgMD in humans (unclassified primary antibody deficiency (unPAD)) into a diagnostically uncertain "gray" zone, which, however, can also have significant clinical significance [143].

Two approaches are usually used in the diagnosis of PMDs: absolute and relative. The absolute approach declares a fixed rigid limit below which the immunodeficiency zone is located. For example, we can make a diagnosis of SIgED at a serum IgE concentration below 2.0–2.5 kU/L [144]. With apparent simplicity, such an approach may hide several pitfalls. One of them is associated with differences in measurement results when using different laboratory techniques, even within the same diagnostic method. Thus, when using classical ELISA, the criterion for diagnosing SIgED is a serum IgE concentration below 10 IU/mL. It was shown by Schoettler et al. [145]. However, modern ELISA reagents with more accurate calculation of the result allow using a diagnostic limit for SIgED at the level of 2.0 kU/L [72]. Therefore, when diagnosing PMDs, it is important to consider the fact in what way a given laboratory performs measurements. This complicates the formation of unified standards in the field of PMDs.

The relative approach indicates that for the diagnosis of PMDs a decrease in the level of an immunological indicator by at least 2 standard deviations (SD) from a well-characterized age-, ethnic- and/or geographic norm is necessary [33,118]. Batista CHR et al. compared the informativeness of the absolute (less than 0.2 g/L in children and 0.3 g/L in adults) and relative approaches (a decrease of 2 SD from the regional norm) in SIgMD. It was shown that the same frequency of allergic rhinitis, bronchial asthma and respiratory infections in both groups is present [108]. The problem with the approach is that for many immune indicators there are still no relevant data on regional, ethnic and/or age-related norms. And the normal ranges from different laboratories are often based on insufficiently verified information. They can even contradict each other, which creates diagnostic confusion.

When diagnosing immunoglobulin subclass deficiencies, the more significant diagnostic data may not be absolute data, but the ratio of concentrations of different subclasses to each other. For example, absolute subclass proportions, 60–70% IgG1, 20–30% IgG2, 5–8% IgG3 and 1–3% IgG4, or a stable interclass ratio of the type "IgG1 greater than IgG2 greater than IgG3 greater than IgG4" according to Papadea and Check are useful [146]. It is possible to use the proportions of individual IgG subclasses relative to the pool of total IgG in the blood (IgG1:IgG2:IgG3:IgG4 = 22:8:2:1) [147]. Special indices of the correlations of different subclasses of immunoglobulins with each other can also be informative. For example, in SIgG2SD, the feasibility of using the IgG1/IgG2 index for verification of the clinical diagnosis of this PMD has been shown [148]. However, these features are often ignored in clinical studies and are still used to a limited extent in clinical practice.

It is also necessary to consider the presence of not only quantitative, but also qualitative forms of PMDs. In the latter case, despite the normal amount of the immune factor, its functional activity is critically reduced. Thus, there can be both quantitative (classical) and qualitative (functional) NKD [47]. Although many scientific studies about the association with autoimmunity have taken into account exclusively the quantitative form of these PMDs. It may

be a reductionist non-relevant approach.

The diagnostic criteria for PMD may vary depending on the functional state of the organism. It is not always considered in scientific research. Thus, the lower limit of the normal serum concentration of MBL in pregnant women is twice as high as in the general population [149]. Regarding immune factors that perform the function of acute phase proteins, the criterion for associated PMDs may vary depending on both the state of the autoimmune syndrome (exacerbation or remission) and the function of the target organ affected by autoimmunity (for example, hypo- or hyperthyroidism in AT). It was shown in the example of SMBLD [150].

The diagnostic criteria for PMDs proposed for clinical practice should not be rigid, but rather adaptive and flexible. It has to consider both the known features, spectrum of diversity and evolutionary scenarios of the development of PMDs themselves, and the functional state of the host organism and the specifics of the associated autoimmune syndrome.

6.1.9. The Problem of Variability of Clinical Course

PMDs are characterized by unprecedented heterogeneity and variability of clinical phenotype. It complicates their diagnosis in clinical practice and the selection of patients for participation in studies. These two phenomena lead to a certain discrepancy between the laboratory and clinical phenotypes of PMDs. It was well characterized in SIgAD by Aghamohammadi A et al. on the example of the depth of immunodeficiency and the associated severity of clinical manifestations of autoimmunity [151]. It was shown by Gulez N et al. in SIgAD on the example of the number of autoantibodies in the blood serum and the severity of symptoms of autoimmunity [152].

Variability consists of the possibility of asymptomatic periods in the course and arbitrary change or layering of heterogeneous syndromes in the same PMD in different patients. The asymptomatic state can be associated with the implementation of compensatory mechanisms within the immune system. Jönsson G et al. showed that the G2M(n) allotype, which is associated with high synthesis of antipolysaccharide IgG2, can compensate to some extent for the infectious manifestations of MBLD [153]. However, indirect (aberrant) compensations can be unstable and incomplete, which causes the transient asymptomatic period of PMDs. Barka et al. showed a pathological multireactive pattern of autoantibody production in patients with asymptomatic SIgAD. It indicated the readiness to induce autoimmune disease under the influence of a trigger even during the “favourable” phase of the disease [154]. Catanzaro JR et al. revealed the formation of intestinal dysbiosis with secondary immune dysregulation in SIgAD. It was identified despite the compensatory hyperproduction of secretory IgM, which eliminated the infectious syndrome [155]. Back in 1996, it was demonstrated that initially asymptomatic SIgAD in healthy blood donors during follow-up manifests itself as infectious, autoimmune and/or oncological syndromes within the next 10 years in at least 80% of cases [156]. It indicates the illusory nature of the notion of lifelong asymptotic status as a representative feature of PMDs in humans.

PMDs during the asymptomatic period are often excluded from clinical studies and dispensary observations in medical practice. So, this incomplete penetrance in inborn errors of immunity was presented as a “skeleton in the closet” by Bogunovic [157]. It may hide a systematic error. The asymptomatic course of PMDs during this period of ontogenesis does not exclude the possibility of the development of associated autoimmunity in the next decade of the patient’s life.

6.1.10. The Problem of Heterogeneity of Clinical Phenotype

Heterogeneity is associated with fundamentally different clinical manifestations of the same PMD in different patients, despite the degree of kinship between them [158]. The phenomenon of heterogeneity can be intra- and intersyndromal. In the intrasyndromal phenomenon, the heterogeneity of the clinical picture of PMD is manifested within one associated clinical syndrome. If we talk more specifically about autoimmunity, then one family member with the same PMD may suffer from SLE, the second—from RA, and the third—from SS [115]. In the intersyndromal phenomenon of heterogeneity, in one family member with a certain PMD, an infectious syndrome may prevail, in the second—allergic, and in the third—autoimmune. It creates the illusion of the presence of different, unrelated diseases in one family [145,159]. But really it is one disease with different clinical manifestations.

Yazdani R et al., considering the phenomenon of heterogeneity of the clinical picture, used as an example SIgAD. They proposed a classification of PMDs according to the current clinical phenotype, distinguishing asymptomatic, minor infections, allergic, autoimmune, and severe phenotypes of immune system diseases [160].

The case reports suggest the principle of universality - the possibility of any autoimmune reaction devel-

oping in any PMD. But data from controlled clinical trials suggest a possible closer association between certain PMDs and some autoimmune reactions, such as SMBLD and SLE [161]. The principle of universality leads to two clinical phenomena that are still poorly understood by clinicians. The first one—the development of different forms of autoimmunity in members of the same family with the same PMD, as occurs, for example, in families with SIgAD [158]. And the second one—development of the same autoimmune syndrome with similar clinical manifestations in different, unrelated patients with fundamentally different PMDs. Thus, the SLE phenotype can develop both in SIgAD (humoral immunodeficiency) [22], in MBLS (complement system deficiency) [162] or in ICD4 + TL (cellular immunodeficiency) [82].

One of the reasons for the heterogeneity of autoimmune syndromes in PMDs is the phenomenon of pathogenetic heterogeneity of PMDs themselves. It was demonstrated by Bagheri Y et al. using the example of SIgAD. As it turned out, impaired maturation of B-lymphocytes into plasma cells committed to IgA synthesis in SIgAD can be caused by various factors. Among them, the influence of HLA molecules, abnormal composition of T- and B-lymphocyte subpopulations, impaired expression of cytokine, chemokine and their receptor genes, abnormalities in apoptosis regulation and changes in the intestinal microbiome [102].

The veil of mystery surrounding the problem of choosing the form of autoimmunity in PMD in a particular patient has now been lifted [163]. It has been determined that the so-called channelling of the autoimmune syndrome into a certain form in PMDs. It may be influenced by some additional mutations that critically disrupt immune regulation in PMDs, but do not determine the laboratory phenotype of PMD itself. Thus, Ferreira et al. in a controlled clinical study demonstrated that the presence of an additional mutation interferon-induced helicase 1 (IFIH1) rs1990760G>A contributes to the more frequent formation of SLE and DM1T phenotypes in patients with SIgAD [164]. A similar pattern of influence in SIgAD was identified in the polymorphism c-type lectin domain family 16, member A (CLEC16A) rs6498142C>G and 29 other loci [164]. Another factor that may direct autoimmunity in a certain way in PMDs is HLA molecules [165,166], in particular, the 8.1 haplotype in SIgAD [167] (**Figure 5**).

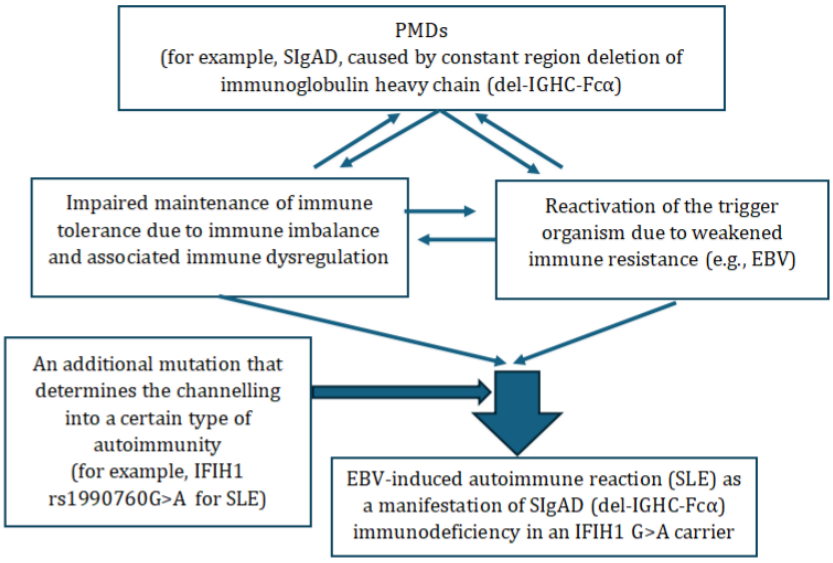

Figure 5. Elementary schematic diagram of the mechanism of induction of autoimmunity in immunocompromised individuals with PMD.

Although there is no close correlation between immunological and clinical phenotypes in PMDs [151], there are some data indicating increasingly severe consequences for the development of autoimmunity as the immune deficiency deepens. Thus, it has been shown that pSS and AT are formed more often in CVID (hypogammaglobulinemia) than in SIgGSD [136]. Barton JC et al. in a comparative clinical study involving 35 patients with CVID and more than 300 people with SIgGSD demonstrated a relationship between the depth of humoral immunodeficiency and the severity of associated infectious and autoimmune syndromes [136].

Figure 5 presents a simplified mechanistic model of autoimmune disease induction in immunocompromised

individuals with PMDs. The scheme integrates genetic susceptibility, impaired immune defence, microbial triggering, and immune dysregulation into a unified pathogenic cascade. The model shows that PMD, caused for example by a structural defect in immunoglobulin genes (such as deletion of the IgA constant region), leads to weakened immune resistance against latent or persistent microorganisms, such as Epstein–Barr virus (EBV). Reactivation or persistent replication of such triggers promotes chronic immune stimulation and the generation of cross-reactive immune responses. In this immunologically unstable environment, molecular mimicry, bystander activation, and defective clearance of antigenic material facilitate the breakdown of immune tolerance. An important element of the model is the role of additional genetic modifiers that do not determine the immunodeficiency phenotype itself but direct ("channel") the autoimmune response into a specific clinical form. For example, polymorphisms in genes such as IFIH1 (rs1990760 G>A) predispose SIgAD carriers to the development of SLE rather than other autoimmune diseases. Thus, PMD creates a permissive background for autoimmunity, whereas modifier genes and environmental triggers determine the specific autoimmune phenotype. Overall, **Figure 5** conceptualizes autoimmunity in PMD as the result of a multistep interaction between primary immune insufficiency, microbial triggers, immune dysregulation, and genetic channelling factors, providing a framework for understanding the remarkable heterogeneity of autoimmune manifestations in immunodeficient individuals.

Usually, the formation of one autoimmune syndrome in a patient with PMD is reported. But cases of two or even multiple autoimmune syndromes with one immune dysfunction are also possible. Shimamura Y et al. described the development of two autoimmune syndromes in a person with SIgMD: SLE and APS [168]. In contrast, Hua L. et al. reported a case of SIgAD in a 48-year-old patient with three autoimmune syndromes: AHA, SLE and AT [69]. Baleva MP. et al. in the partial form of SIgAD described the development of even four syndromes: AD, AH, AT and CeD [169].

The form of PMD may affect not only the actual development of a particular autoimmune syndrome, but also the structure of its clinical manifestations. PMDs transform the clinical picture of the associated autoimmune syndrome in different ways, enhancing some manifestations and, conversely, weakening others. Thus, Tanha N et al. found that SMBLD increases the risk of developing severe LN in the structure of the clinical picture of SLE [170]. Hogendorf A. et al. stratified DM1T by associated PMDs. They demonstrated that not only the severity and clinical course of autoimmune endocrinopathy depended on immunodeficiency, but also the pattern of comorbidity [118]. However, SMBLD can attenuate the inflammatory and immunological phenotypes of the associated pSS, as Ramos-Casals M. et al. described [171].

PMDs can also complicate the laboratory diagnosis of some associated immune-dependent syndromes. They can affect the informativeness of key verification paraclinical tests that are widely used in clinical practice. It is noted, for example, in SIgAD and CeD. There are pseudo-negative results of the determination of specific IgA to tissue transglutaminase in serum [172]. Kojo S et al. recommend dividing SLE, SS and pSS into α-GalCer-positive and α-GalCer-negative variants. So, NKTD affects the severity, prognosis and sensitivity to treatment of these autoimmune syndromes [173]. Indeed, associated PMDs can affect both sensitivity and tolerance to several recommended treatment approaches for autoimmune syndromes. Thus, Rahiminejad MS et al. demonstrated a contraindication to splenectomy in ITP associated with SPAD. In such cases, a higher risk of developing septicaemia as a result of curative surgery is present [77].

The results of clinical studies indicate that the risk of developing autoimmune syndromes is higher than in the general population, not only in patients with PMDs themselves, but even in their closest relatives. They were considered healthy until the manifestation of autoimmunity, without developing characteristic immunological phenotypes of PMDs [125,174].

Thus, the unprecedented heterogeneity of PMDs in clinical manifestations should be taken into account when conducting scientific studies. Possible impact of PMDs on the form, severity, course, prognosis and treatment of the associated autoimmune syndrome is also important. It would allow a more complete and deeper characterization of the relationship between PMDs and the phenomenon of autoimmunity in the human population.

6.1.11. Correlation of PMD and Secondary Immunosuppression Phenotypes

Autoimmune diseases that have developed in a patient with PMDs can induce secondary immunodeficiency by consuming immune factors and deepening the state of immune dysregulation. It complicates the structure of the existing immunodeficiency in such cases. Ballow M et al. speak of "crossovers" between primary and secondary immunodeficiencies in the case of autoimmune syndromes and malignant neoplasms [175]. States of immunocom-

promise are formed, which are more than a simple summation of symptoms of primary and secondary immunodeficiency. This phenomenon requires special terminology for its description, which, however, has not yet been developed. We propose to designate such states as "tertiary" immunodeficiency, emphasizing their complex, integral nature.

It has been shown that secondary immunodeficiency can mask PMDs. For example, it is described in secondary hypogammaglobulinemia caused by rituximab (a monoclonal antibody to the CD20 molecule of B-lymphocytes). This secondary immunodeficiency can mask pre-existing SIgAD or CVID associated with the autoimmune syndrome or neoplasia for which rituximab was prescribed [175,176]. Hypogammaglobulinemia caused by SLE can mask pre-existing humoral PMDs (SIgAD and/or SIgG2SD) that previously led to the development of the autoimmune disease itself [177]. Pre-existing PMDs can significantly determine the subsequent formation of secondary immunodeficiencies. For example, secondary hypogammaglobulinemia from the use of rituximab can be determined not only by the pharmacological action of the immunobiological drug, but also by the pre-existing humoral PMDs underlying the present autoimmunity [178,179].

It is difficult to assess the ratio of contributions of primary and secondary immunodeficiencies to the immunological profile of a patient with an autoimmune syndrome. It is important to evaluate the results of the multifaceted interaction between them. Therefore, Ottaviano G et al. speak of a kind of mysterious border ("enigmatic border") between primary and secondary hypogammaglobulinemia when using rituximab in SLE and oncological lesions [180]. Sogkas G et al. demonstrated that hypogammaglobulinemia in rheumatic diseases, initially diagnosed in the clinic as secondary (i.e., caused by the autoimmune process itself), in at least 46.9% of cases is actually associated with congenital mutations that disrupt the process of antibody genesis (i.e., primary in nature) [94].

The difficulty of distinguishing the phenotypes of PMDs and associated secondary immunosuppression in autoimmunity may lead to an underestimation of the role of PMDs in the development of autoimmune syndromes. It can result in a large overestimation of the significance of secondary immunodeficiency in such cases.

6.1.12. Correlation of PMD and Autoimmune Syndrome Phenotypes

Sometimes PMDs can mimic some autoimmune diseases. For example, CVID with associated T-cell lymphoma caused confusion with JIA in the report of Jesus et al. [181]. In another case, CyN completely imitated the manifestations of CD according to the data of the publication of Guarino et al. [182]. The phenotype of some autoimmune syndromes can change to the PMD's phenotype during ontogenesis. For example, the typical syndrome complex of SLE can gradually transform into the clinical and immunological phenotype of CVID with a picture of hypogammaglobulinemia and systemic inflammation [183]. This transformation is called the term "transition" according to Goldstein and Karsh [183]. But Baum et al. proposed another term, "conversion," for such cases [184].

Scientific studies often ignored the phenomena of mimicry and transition (conversation). It may be a systematic error in the field of association of PMDs and autoimmune syndromes.

6.2. Current Evidence Base for the Association of PMDs and Autoimmune Syndromes in Humans

The current evidence base for the association of PMDs and known autoimmune syndromes in humans is quite heterogeneous and differs significantly across PMDs. It can range widely from the results of multiple well-designed meta-analyses and systematic reviews in MBLD (evidence level A) and a single meta-analysis in SIgAD (A). In SIgED and CIE, a number of large population-based studies are available (B). The results of multi- and single-centre prospective controlled clinical trials and retrospective observational reviews in ICD4 + TL, NKD, NKTD, UH, THI, SIgGD, SIgMD, SIgGSD and SPAD are presented (B, C). The data from small controlled and uncontrolled clinical trials and multiple case reports in MPOD, CD8D, and CD16D are available (C). Casuistic well-prepared clinical reports of individual patients in FBN, CIN, CyN, MASP2D, CD64D and deficiencies of the terminal components of the complement system C6-C9 are present (D). There are currently no reports of autoimmunity in EPOD, SM, PPD and SIgDD (0).

Certain geographic, regional, racial, ethnic, age, gender and ontogenetic features of the association with certain PMDs and/or autoimmune syndromes are noted. However, it should be tested in additional clinical studies for relevance.

The results of the study of the current evidence base of the Association of PMDs and Autoimmune Syndromes in Humans are systematized in **Table 5**. There are additional indications of the nature of PMDs, frequency in the

modern human population, diagnostic criteria in clinical practice and levels of evidence of the detected relationship (according to the Centre for Evidence-Based Medicine). It can improve the understanding of the detected associations and their potential clinical significance on a population scale.

Table 5. Current evidence for the association of PMDs and known autoimmune syndromes in humans.

PMD	Affected Branch of the Immune System	Frequency/ Prevalence in the Population	Diagnostic Criteria	Evidence Base	Level of Evidence (Centre for Evidence-Based Medicine)
MBLD	Complement system	5–10% of the modern population	Partial form < 1,000 ng/mL, total form < 500 ng/mL, complete form < 50 ng/mL	Meta-analysis Xu et al. (2021), 14 studies from 36 databases, polymorphisms in exon 1 of MBL2—RA risk in Brazilian and Indian populations, MBL2 promoter—in East Asian populations [21]. Meta-analysis Mahto et al. (2020), 23 studies, 3074 patients with SLE and 3,985 controls: MBL-2 variants (A > O and A > B)—SLE risk, promoter polymorphism (Y-221X)—protection from SLE [162]. Meta-analysis Zhang et al. (2015), 18 studies, 4,810 patients and 4,585 controls: polymorphism of codon 54 of MBL2—RA risk, especially seropositive and erosive forms, more often in East Asian populations [185]. Meta-analysis by Yuan et al. (2021) (20 studies, 7,194 patients, 7,401 healthy individuals): MBL2 A/B and A/O polymorphisms—risk of SLE [161]. Meta-analysis by Song et al. (2014), 12 studies, 1623 patients, 1671 controls, functional MBL alleles D, L and X—risk of RA, MBL B allele—protection from pSS [186]. El Alami et al. (2026), case-control study, 435 adults, association with DM2T in the Moroccan population [187]. Kaur et al. (2024), case-control study, MBL2 variants act as plausible markers for RA [188]. Jahan et al. (2024), adults with GBS (n = 300) and healthy controls (n = 300) in Bangladesh, association with GBS and severity of GBS [189]. Controlled clinical trials are associated with DM [190], AS [191], NUC and CD [192], and PANDAS as a form of AE [6]. Clinical case reports indicate the possibility of association with almost all known forms of autoimmunity.	2A (high strength)
THI	Humoral branch of adaptive immunity	1:164 confirmed THI and 1:103 possible THI	Serum immunoglobulin concentration of all classes < 7 g/L, or < 2 SD from the lower limit of normal	Moschese et al. (2008), prospective clinical study, 77 children—autoimmune diseases in 4% of cases, with preservation of immunological phenotype during the first 24 months and risk of autoimmune reactions among 28% of individuals without full compensation of immunological phenotype after 24 months [60].	2C (low strength)
UH	Humoral branch of adaptive immunity	4/5–1/5 of patients with a primary diagnosis of THI	Serum immunoglobulin concentration of all classes < 7 g/L, or < 2 SD from the lower limit of normal	Kubicka-Trzaska (2000), retrospective observational study, 50 adults (29 women (58%) and 21 men (42%)), UH in 11 individuals with AU (22% of cases) [193]. Cuadrado et al. (2019), cross-sectional study, 83 adults with LN. UH in 8.4% of cases [194].	2C (low strength)
SIgAD	Humoral branch of adaptive immunity	1:170–1:400	Partial form < 0.6 g/L, total form < 0.07 g/L, or < 2 SD below the lower limit of normal	Vosughimotlagh et al. (2023), meta-analysis, systematic review, 40 studies, adults and children, various autoimmune syndromes in 22% of cases, most often in CeD, CD, NUC, RA [22]. Ludvigson et al. (2014), population-based cohort study, 2100 patients with SIgAD, 18 653 controls, risk of DM1T (5.9% vs. 0.57%), CD (2.4% vs. 0.42%), NUC (1.7% vs. 0.46%), RA (2.2% vs. 0.5%), JIA (0.76% vs. 0.09%), SLE (0.57% vs. 0.06%), AT (2.46% vs. 0.59%) [195]. Odineal et al. (2020), extensive literature review, adults and children, strong association of SIgAD and SLE, AT, DM1T, CD, NUC, RA, JIA, AS, VG; weaker association—ScD, CeD, AH, ITP, AHA [196]. Wang et al. (2011), large-scale screening results, close association with GD, SLE, DM1T, CeD, MG, RA [197]. Güngören et al. (2025), retrospective analysis, n = 45, autoimmune syndromes in 13.3% cases, predominantly—AT, vitiligo, ITP [198]. Clinical case reports indicate an association with almost all known forms of autoimmunity.	3A (high strength)
SIgMD	Humoral branch of adaptive immunity	1:385	Partial form < 0.8 g/L, total form < 0.4 g/L, or < 2 SD below the lower limit of normal	Ni et al. (2020), cross-sectional epidemiological study, 139,668 adults, various autoimmune syndromes in 60.32% of cases [199]. Caka et al. (2021), retrospective analysis, 55 children, 18% autoimmune and immunoinflammatory syndromes (BS, AC, CD, AP, DM1T) [200]. Lucuab-Fegurgur and Gupta et al. (2019), retrospective analysis, 62 adults, various autoimmune syndromes in 43% of cases [201]. Goldstein et al. (2006), retrospective analysis, 36 adults, antinuclear antibodies (ANA) in 13% of cases [202]. Yel et al. (2009), retrospective analysis, 15 adults, various autoimmune syndromes in 20% of cases [203]. Cuadrado et al. (2019), cross-sectional study, 83 adults with LN. SIgMD in 16.9% of cases [194]. Perazzio et al. (2016), a prospective controlled study, 300 adults with SLE, 301 controls. SIgMD and/or SIgGSD in 28.7% of cases vs. 3.3% of controls; $p < 0.001$ [41].	2B (moderate strength)
SIgGSD	Humoral branch of adaptive immunity	Frequency: 1:26–1:400	<60% IgG1, <20% IgG2, <5% IgG3, <1% IgG4, or "IgG1 greater than IgG2 greater than IgG3 greater than IgG4", or proportions of individual subclasses relative to the total IgG pool (IgG1:IgG2:IgG3:IgG4 = 22:8:2:1)	Barton JC et al. (2014), observational clinical study, 398 adults with SIgGSD, various autoimmune syndromes, especially pSS and AT [136]. Barton et al. (2022), observational clinical study, 132 women with SIgGSD (48 subnormal IgG1, 49 combined subnormal IgG1/IgG3, 35 subnormal IgG3)—SLE, RA, pSS [204]. Hogendorf et al. (2021), observational retrospective study, 395 children with DM1T, humoral deficiencies, mostly SIgGD, SIgAD, in 22.8% of cases [118]. Oxelius et al. (1986), observational study, 313 children with SIgGSD, DM1T and SHP with SIgG3D [205].	2B (moderate strength)
SIgGD	Humoral branch of adaptive immunity	Unspecified	Serum IgG concentration <6 g/L [58], or <2 SD below the lower limit of normal	Shin et al. (2020), comparative study. CVID—105, SIgG2SD—108, SIgGD—129, SPAD—44 adults. Higher frequency of autoimmune reactions against connective tissue in PMD and neoplasia in CVID with the same frequency of infections [206].	2B (moderate strength)

Table 5. *Cont.*

PMD	Affected Branch of the Immune System	Frequency/ Prevalence in the Population	Diagnostic Criteria	Evidence Base	Level of Evidence (Centre for Evidence-Based Medicine)
SPAD	Humoral branch of adaptive immunity	Unspecified	Specific IgM <37; IgG <26; IgA <13 U/mL (to bacterial polysaccharides), or attenuated response to polyvalent polysaccharide pneumococcal vaccine (<0.035 μg/mL)	Filion et al. (2019), comparative study of CVID (mean serum IgG concentration = 2.5 g/L) (n = 124) and SIgGD (5.5 g/L) (n = 128) in adults. Higher frequency of various autoimmune syndromes in CVID (40%) compared with SIgGD (15%), especially AC (33% vs. 5% of cases) ($p < 0.0001$) [64]. Gerek et al. (2025), comparative study. Higher frequency of various autoimmune syndromes in CVID (n = 111) (33,3%) compared with SIgGD (n = 19) (10,5%) [207]. Dogru et al. (2025), comparative study. Higher frequency of AC in CVID (n = 270) compared with SIgGSD (n = 96), but in SIgGSD, higher JIA [208]. Lacombe et al. (1997), retrospective analysis, 119 adults with SIgGD in a screening of 3,005 persons, risk of various autoimmune syndromes [209]. Khokar and Gupta (2019), retrospective analysis, 78 adults, increased frequency of various autoimmune syndromes in SIgGSD [210]. Rahiminejad et al. (2013), case-control study, 36 children, SIgGSD in 11%, SPAD in 39% of cases in ITP [77]. Khil'chenko et al. (2020), observational study, 100—PV, 100—pemphigus foliaceus, 99—bullous pemphigoid, 55 adults—linear IgA bullous dermatosis, association with SIgG2SD [211]. Bertoli et al. (2014), observational study, 28 adults with autoimmune cochleovestibular neuritis in 275 controls, association with subnormal SIgG1SD and SIgG3SD [123]. Barton et al. (2016), observational study, 54 adults, subnormal SIgG1SD—various autoimmune syndromes in 50.0% of cases, especially AT [127]. Barton et al. (2020), observational study, 18 adults, subnormal SIgG2SD—various autoimmune syndromes in 44.4% of cases [66]. Barton et al. (2016), observational study, 121 adults, subnormal SIgG3SD—various autoimmune syndromes in 33.1% of cases, especially AT [67]. Eriksson et al. (1995), prospective controlled study, SIgG2SD in 30 of 34 adults with pSS. The IgG1/IgG2 index is higher than in the control group (n = 40) ($p < 0.0001$) [148].	2B (moderate strength)
SIgED	Humoral branch of adaptive immunity	1:30 (3%)	Partial deficiency <10 IU/mL. Total deficiency < 10 IU/mL (classical ELISA), and < 2.0–2.5 kU/L (high-precision ELISA)	Magen et al. (2014), epidemiological study, 18,487 people, various autoimmune syndromes in children and adults [72]. Al et al. (2021), population-based study, 34,809 patients (21,875 children, 12,934 adults), various autoimmune diseases in 15.4% of cases [212]. Nemet et al. (2025), population-based study (n = 123,393), higher number of autoimmune syndromes in SIgED (HR = 1.266; 95% CI: 1.099–1.458) compared to normal IgE levels [213]. Smith et al. (1997), controlled clinical study, 420 adults, Allergy-Immunology Clinic, various autoimmune syndromes in SIgED in 46%, in the control group—in 15% of cases ($p < 0.0001$) [126]. Zhang et al. (2024), cross-sectional study, Tertiary hospital, 223 adults, various autoimmune syndromes in 10.31% of cases [214]. Ünsal et al. (2025), retrospective study, Immunodeficiency referral center, 677 adults, various autoimmune syndromes in 18.3% of cases [215]. Gerek et al. (2025), retrospective cohort study (n = 3,692), autoimmune syndromes were higher in the SIgED versus controls (25.2% vs. 15.6%; $p < 0.001$), especially – AT, vitiligo, BD [216]. Picado et al. (2023), retrospective analysis, 52 adults, various autoimmune syndromes in 34.6% of cases [144].	1B (moderate strength)
ICD4 + TL	Cellular branch of adaptive immunity	Frequency : 1:400 in Europe	< 500 cells per 1 μl—partial deficiency, < 300 cells per 1 μl—complete deficiency	Cudrici et al. (2021), prospective single-center study, 67 adults, autoimmune syndromes in 54% of cases, one in 34% of cases, two or more in 20% of cases. Another 19% of patients have autoantibodies with an incomplete clinical phenotype [217]. Perez-Diez et al. (2020), prospective single-center study, 72 adults, polymodal autoantibody profile as a representative feature [218]. Régent et al. (2014), retrospective analysis, 40 adults, various autoimmune syndromes in 35% of cases [82]. Ahmad et al. (2013), retrospective analysis, 401 adults, various autoimmune syndromes in 14.2% of cases [219]. Mandl et al. (2004), prospective single-center study, 80 adults with anti-SSA + pSS. ICD4 + TL in 16% of cases [220]. Kirtava et al. (1995), prospective single-center study, 115 adults with pSS. ICD4 + TL in 5.2% of cases [221].	2B (moderate strength)
MPOD	Phagocytosis	1:2000-4000 in Europe and the USA	Activity < 18 conventional units (CU) for ELISA	Small controlled clinical trials and case reports—RF [222], RA [223], MS [224], AT [225].	2C (low strength)
NKD	Cellular branch of innate immunity	Unspecified	< 5% of the total blood lymphocyte pool for cNCD	Green et al. (2005), case-control study, nSLE = 64, nRA = 17. Moderate NKD in 20% of women and 75% of men with SLE, in 35% of women with RA. Profound NKD in 25% of women with SLE. Moderate NKD in 10% of healthy women and 29% of healthy men from families with SLE [125]. Villanueva et al. (2005), case-control study, 20 children, NKD in 50% of cases in JIA [226]. Gascón et al. (1986), case-control study, 43 adults. NKD in 76% of cases in AA [227].	1C (low strength)
NKTD	Cellular branch of innate immunity	Unspecified	Deficiency criterion: < 3% of the total lymphocyte pool for cNKTD	Tudhope et al. (2010), a prospective single-center study. 43 adults with RA and 23 controls. Lower iNKT numbers (median 0.001% vs. 0.021%, $p < 0.001$) and poorer response to α-GalCer (median fold-expansion 31 vs. 121, $p = 0.037$) in RA. Profound NKTD in RA. Association of NKTD with CRP levels [124]. Lee et al. (2010), a prospective single-center study, 20 adults, adult-onset Still's Disease. Reduced iNKT numbers and response to α-GalCer. Secondary NK functional impairment [228]. Cho et al. (2012), a prospective single-center study, 128 adults, 92 healthy controls. Reduced iNKT numbers and response to α-GalCer in SLE. Correlation with SLEDAI [48]. Wither et al. (2008), a prospective single-center study, 367 adults, first-degree relatives with SLE, and 102 healthy individuals. NKTCD is associated with ANA in families with SLE. Correlation of results in parents, siblings and probands - NKTD heritability [229]. Kojo et al. (2001), a prospective single-center study, included adults with RA (n = 20), SLE (n = 18), SSc (n = 13), SS (n = 17), BS (n = 20) and healthy subjects (n = 13). Quantitative NKTD—48.6%, qualitative NKTD—48.6% of cases with autoimmunity, except BS. Impact of NKTD on prognosis and response to treatment [173].	1C (low strength)
CIE	Phagocytosis	1:1000	<0.015 × 10(9)/L	Magen et al. (2024), a large population-based study, 12,140 adults with ICE, control group—24,280 people. Increased frequency of various autoimmune syndromes [46].	2B (moderate strength)

As **Table 5** shows, PMDs form associations with autoimmune syndromes in a variable manner, most consistent with the principle of a universal relationship. However, according to the current evidence base, it is still possible to identify the closest associations between some forms of PMDs and autoimmune syndromes (**Table 6**).

Table 6. Some of the closest associations between PMDs and autoimmune syndromes.

No.	PMD Category	Autoimmune Syndrome	Strength of Evidence (Centre for Evidence-Based Medicine)
1	MBLD	SLE, RA [21,162]	2A (high strength)
2	SIgAD	CeD, CD, NUC, RA, JIA, AT, DM1T [22]	3A (high strength)
3	ICD4 + TL	RA, CD, AA, DM1T, pSS [82,217,218].	2B (moderate strength)
4	SIgGSD	SLE, SV, AC, pSS, DM1T [118,136,204]	2B (moderate strength)
5	SIgED	SLE, AC, RA, AT [72,212,213]	1B (moderate strength)

6.3. Integral Concept of PMDs in Autoimmune Syndromes and Rethinking of Therapy

It turns out that PMD is an ambivalent phenomenon. It includes, on the one hand, a decrease in immunoresistance due to the lack of a certain immune factor with the associated activation of microbial triggers [24]. And, on the other hand, it can be due to immune dysregulation with secondary reciprocal hyperactivation of the part of the immune system not involved in the PMD phenotype. It can result in the generation of an autoimmune syndrome [1] (**Figure 6**). Building a holistic picture of the pathogenesis of an integral disease with the definition of at least three key components—the causal immunodeficiency, the relevant microbial trigger and the associated autoimmune syndrome is important for achieving complete, comprehensive control over the immune-dependent pathological process. And, accordingly to the clinical picture, total control is possible through triple therapy: immunotherapy of immunodeficiency as an etiological factor and, at the same time, the initial link in pathogenesis, antimicrobial therapy to eliminate the trigger as a conductor and modulator of autoimmunity (intermediate link in pathogenesis) and immunosuppressive therapy for autoimmunity itself (effector link in pathogenesis of the disease) (**Figure 6**) [230]. Interestingly, immunotherapy, which can currently be recommended for the treatment of PMDs, often turns out to be effective for the treatment of associated microbial triggers and autoimmune diseases. Thus, it demonstrates an integral polymodal immunomodulatory therapeutic effect, which may be a guide to rational monotherapy of a complex pathogenetically structured immune-dependent human pathology. So, in this way, we can avoid polypharmacy. Given this data, it is difficult to overestimate the ability of a physician to correctly select a particular immunotherapeutic agent for an immunocompromised patient with PMD with clinically manifest microbe-induced autoimmunity.

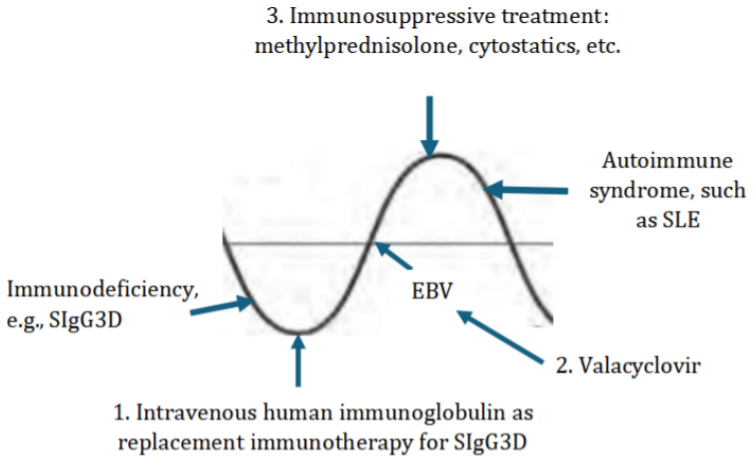

Figure 6. Wave model of immunodeficiency with microbe-induced associated autoimmune syndrome as an ambivalent phenomenon and the principle of oppositely directed integral therapeutic interventions (on the example of the pathogenetic triad "SIgG3SD + EBV + SLE").

Figure 6 demonstrates a basic model of the functional state of the immune system in PMDs in light of associated autoimmune syndromes. It illustrates the paradoxically ambivalent state of the immune system in PMDs. Some im-

mune factors are deficient (for example, IgG3 subclass in SIgG3SD), creating a state of reduced immune resistance predisposing to the reactivation of certain opportunistic microbial triggers of autoimmunity, such as EBV. At the same time, the other non-affected part of the immune system, due to the loss of reciprocal suppressive effects from lost immune cells or proteins, is in a state of hyperactivation and can be involved in the development of an autoimmune reaction by a microbial trigger (for example, SLE). This ambivalent state, modulated by a microbial trigger, is best described by a wave model, since a physical wave also has two opposing phases, which inseparably constitute its essence. The wave model of PMDs explains the need for effective ambivalent immunomodulatory therapeutic approaches with paradoxically multidirectional influences that simultaneously aim at weakening immune factors (substitutional IVIG for SIgG3SD) and suppressing abnormally activated ones (chemical immunosuppressants for SLE).

Thus, intravenous normal human immunoglobulin (IVIG) is the standard of treatment for humoral PMDs in which serum IgG molecules are deficient [231,232]. It can provide temporary direct and complete replacement of serum antibody deficiency [39,233]. In SIgMD and SIgAD, IVIG preparations containing only IgG molecules, but not IgM and IgA, can be used for surrogate replacement. The clinical benefit of such therapy has been demonstrated in the results of some clinical trials [234]. However, in SIgMD and SIgAD, direct replacement of the immune factor deficiency is also possible through the use of a special IVIG preparation enriched with IgM and IgA molecules [235]. The benefit of such interventions has also been demonstrated in some clinical trials [20,236]. Although the data for the routine use of this approach are currently insufficient. Kaveri SV et al. rightly note that immunoglobulin therapy for humoral PID is more than mere replacement therapy. It can additionally eliminate the manifestations of associated autoimmune and allergic syndromes [237]. Thus, Kim JH et al. in a specially designed study demonstrated the complete elimination of clinical manifestations of bronchial asthma during intravenous immunoglobulin replacement therapy for SIgGSD without the need for additional use of glucocorticosteroids [238]. Indeed, AP [123] and AC [77], in the structure of associated PMDs in which humoral immunity disorders play a large role, respond better to IVIG. It is currently the first line of therapy for many of these autoimmune syndromes. However, in other forms of autoimmunity, where the proportion of complement defects, phagocytosis and/or cellular immunodeficiencies is higher (for example, in SLE, RA, BC and Churg-Strauss syndrome), IVIG is less effective. Thus, in CVID, associated LN can respond dramatically to IVIG [239]. These indirect data indicate a high probability that immunotherapy of the causative PID also affects the associated autoimmune syndrome. It should be tested in further clinical trials. Such insights will open the way to an in-depth personalized multidisciplinary treatment of autoimmune syndromes. We must take into account the PMDs that underlie them. The clinical potential of this approach was reported by Kojo S et al. in 2001 based on the results of a study of autoimmune manifestations of NKTD [173]. Although in the case of cellular immunodeficiency, recombinant human interleukin 2 (hr-IL2) may be more useful [240]. Su G et al. demonstrated the benefit of a differentiated approach to the treatment of SLE depending on the nature of the PID underlying the autoimmune syndrome [241]. Fata F et al. reported the complete elimination of not only the laboratory phenotype of CyN, but also the clinical and histological manifestations of associated CD after immunotherapy with recombinant granulocyte colony-stimulating factor (hrG-CSF) as the basic therapy of CyN [242]. Eradication of the associated autoimmune syndrome by treatment with PMDs has also been demonstrated in animal models [243].

Similar to IVIG in humoral PID, cytokine therapy including recombinant human interferons -alpha, -beta, -gamma (hrIFN -α, -β, -γ), hr-IL2, hrG-CSF, and thymosin-α1 (th-α1) peptide therapy, has shown effectiveness in cellular immune diseases. It also has cross-therapeutic effects on associated microbial triggers and autoimmune syndromes [240] (**Table 7**). There are even reports of the combined use of different immunotherapeutic agents in autoimmune syndromes, for example, IVIG and hrIFN-alpha in AH [244].

It is advisable to select an immunotherapy agent not only according to PMDs, but also to take into account the immunomodulatory effect of this agent on the associated microbial trigger and autoimmune syndrome, which differ in different immunotherapeutic drugs. Conversely, when choosing a basic therapy for autoimmunity, it is advisable to take into account not only the form of the autoimmune syndrome itself, but also the features of the associated PMDs and the probable microbial trigger of the breakdown of immune tolerance to autoantigens of the human body.

It seems rational to try to use only one immunotherapeutic agent, which, due to its simultaneous polymodal immunomodulatory action, would provide an integral therapeutic effect on all three key components of the pathogenesis of a complex clinical phenomenon: PMD, microbial trigger and autoimmune reaction. It would minimize the use of drugs by eliminating the need for additional therapy. An example of such an approach is the use of IVIG

at a dose of 2 g/kg/month for CMV-induced Guillain-Barré syndrome in a patient with SIgGSD or SIgMD [200].

Table 7. Cross-therapeutic activity of immunotherapeutic agents for PMD and autoimmune syndromes.

Immunotherapeutic Agent	PMD	Autoimmune Syndromes
IVIG	SIgGSD, SIgGD, SPAD, UH, THI [39]	Kawasaki syndrome, GBS, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, ITP, DM, MG, PV [237]
hrIFN-alpha	NKD [47], NKCD [245], ICD4 + TCD [246]	BS [247,248], Charge-Strauss syndrome [249] (eosinophilic granulomatosis with polyangiitis) [250], AU [251], DM1T [252]
hrIFN-beta	NKTCD [253]	MS [253]
hrIFN-gamma	NKD [47], NKTD [254], ICD4 + TCD [255], PPD [52], MPOD [225]	RA [256]
Th-α1	ICD4 + TCD [257], NKCD [258]	CD, ITP, autoimmunity after COVID-19 vaccination [259]
hr-IL2	NKD [47], ICD4 + TCD [82]	SLE [260,261], LN [240]
hrG-CSF, hrGM-CSF	FBN, CyN, CIN [242]	RA [262], CD [263]

Ignoring the causal PMDs leads to adverse clinical effects in medical practice, when, despite compensation for the associated autoimmune syndrome, the patient further develops new clinical manifestations of PMD. Thus, Narsai T et al. reported the transformation of EBV-induced autoimmune gastritis into EBV-induced gastric adenocarcinoma in a patient with SIgMD in the case of isolated use of autoimmune syndrome therapy without affecting the viral trigger and PMD [264]. Ignoring the causal PMD can also lead to iatrogenic effects due to the influence of the applied immunosuppressive therapy for autoimmunity on the natural course of the immune system disease. Thus, Ajao SO et al. reported the development of iatrogenic Kaposi's sarcoma after the use of vedolizumab for NUC due to ignoring the causal immunodeficiency that led to inflammatory bowel disease [265].

Kurobane et al. first reported the complete resolution of SIgAD after allogeneic bone marrow transplantation [266]. However, it remains an open question whether the autoimmune syndromes associated with PMD will disappear. For example, Hadžić N et al. demonstrated that primary sclerosing cholangitis can be completely resolved after allogeneic hematopoietic stem cell transplantation for the treatment of cellular immunodeficiency in patients [267].

6.4. Ways to Correct Current Errors

Barreto ICDP et al. state that PIDs are much more common phenomena in the human population than it seems at first glance. They should become part of the routine work of general practitioners [268]. Accordingly, Shin JJ et al. indicate a significant expansion of ideas about the spectrum of clinical manifestations of diseases of the immune system in humans, which goes far beyond the well-known infectious syndrome [206]. Autoimmunity is a typical manifestation of PMD [167], and therefore Sogkas G et al. call for more persistent attempts to search for inborn errors in immunity in rheumatic diseases, given the known close relationship between them [269].

The lack of awareness among physicians and a certain bias in the scientific community regarding the problem of PMD is a serious obstacle both to conducting further clinical studies and to the application of the evidence obtained in the course of such studies in wide clinical practice. It is not without reason that the titles of articles on PMD often use such emotional epithets as forgotten [270], ignored [271], underestimated [272] or undervalued [120] immune system disease. And Vo Ngoc DT et al., considering the problem of SIgAD, speak of "the long and winding road" of scientific research and clinical understanding of the phenomenology of SIgAD in humans [273]. Ignoring a number of clinically significant PMDs leads to both distortion of the modern doctrine of immune-dependent manifestations of immune system diseases and, probably, inaccuracies in statistical data on their prevalence in the modern human population. Thus, Stiehm RE. et al., summarizing the results of the work of immunological centers, state the 4 most common PIDs in children, in particular, THI, SIgGSD, SIgAD and SPAD [274]. Although in fact the most common forms of PID in the pediatric population are MBLD (5–10%) [21], SIgDD (6–9%) [74], SIgED (3%) [72] and SIgGSD (at least 1% of people) [37].

The lack of understanding of the clinical significance of PMDs in humans is one of the main reasons for ignoring these diseases by scientists and clinicians. Accordingly, Al S et al., conducting a population-based study of SIgED,

asked a key fundamental question: "is there a clinical significance of very low serum immunoglobulin E level?" They ultimately demonstrated a sharp increase in the frequency of allergic, autoimmune and oncological syndromes in individuals with this PMD [212]. However, SIgED, as well as a number of other PMDs, is still not included in many PID registries in humans [31]. Even small deviations of immunological parameters from the normative values in PMDs can be clinically significant. Thus, severe clinical consequences of mild hypogammaglobulinemia [38], subnormal forms of SIgG1SD [37], SIgG2SD [66], SIgG3SD [67] and even SIgG4SD [68] have been demonstrated.

The use of too strict, even reductionist, diagnostic criteria that do not take into account the diversity of the described forms of PMDs and the known evolutionary scenarios of their development is also a serious obstacle to a full understanding of the depth of the problem. It damages the proper clinical application of the obtained scientific evidence. Thus, Janssen LMA et al., using the example of SIgMD, claim a large number of so-called unclassified forms of PMDs (unPMD), which, however, can have severe clinical manifestations [143]. In particular, partial forms of PMD are often ignored. Accordingly, Jamee M. et al. substantiated the distinction between total (serum IgA concentration less than <7 mg/dL; so-called "selective IgA deficiency" (SIgAD)) and partial IgA deficiency (serum IgA concentration less than the lower limit of normal, but above 7 mg/dL; so-called "partial IgA deficiency" (PIgAD)). They demonstrated that in both forms of this PMD, an abnormally increased number of cases of respiratory infections, autoimmune polyendocrinopathies, and other autoimmune syndromes are noted [275].

Although the emergence of autoimmune syndromes in PMDs is becoming an increasingly well-known phenomenon, their understanding may still remain rather superficial and incomplete. Are they "complete strangers" or "two sides of the same coin" [276]? Describing autoimmunity in PMDs solely as a "crossroads" between autoimmune reactions and immunodeficiency [12,26,277] is incomplete. These phenomena not only coexist in the same patient at a certain point in time, but are also interconnected in etiology and pathogenesis [22]. The alternative term "overlap" has the same gnoseological problem [278]. In fact, it is often the same process in different manifestations, and not a simple intersection of two independent diseases. It is also incorrect to present autoimmune syndromes as complications [168] or comorbidities [275] of PMDs. The autoimmunity itself is a clinical manifestation of immunodeficiency. Based on these positions, the ideas of Schmidt RE et al. that immunodeficiencies and associated autoimmune syndromes are different components of the one process ("two sides of the same coin") seem more correct [279]. Walter JE et al. noted that autoimmunity is not a random, but a regular and constant ("continuum") pathological process in immunocompromised individuals [280]. The same applies to the ideas about "crossovers" between primary and secondary immunosuppression in autoimmunity [104]. Secondary immunosuppression can be not only a separate clinical phenomenon independent of PID, but also a regular evolutionary continuation of the PMD phenotype under the influence of certain additional factors, including some immunosuppressive therapeutic interventions [177].

Certain terminological uncertainty and some reductionism in diagnostic criteria, insufficient understanding of the diversity of PMDs in terms of form, origin, evolutionary scenario of development, interaction with each other and with other diseases, poor understanding of the phenomena of heterogeneity of the clinical picture and variability of the clinical course of PMDs, imprecise distinction between PMD phenotypes and associated secondary immunosuppression, difficulty in assessing the correlations between PMD phenotypes and associated autoimmune syndromes are the conditions and factors that have led to both significant achievements, contradictions and gaps in modern science about PMDs. And, without a doubt, such subjective human factors as bias and lack of awareness are also present. So, modern scientific evidence of PMDs association with autoimmune syndromes is still incomplete. There are "evidence, controversies and gaps" by Taietti I et al. on the example of SIgMD [281]. This situation leads to the preservation of the currently outdated approach to diagnosing autoimmune syndromes, mostly as idiopathic phenomena, without the need to clarify the etiological factor and individual mechanism of development. It does not allow the use of available additional highly effective methods of personalized treatment, including immunotherapy of causal immunodeficiency and interventions aimed at the trigger of autoimmunity.

It is necessary to increase the awareness of scientists and doctors about the problem of PID on the basis of impartiality and priority of scientific evidence. It could ensure wider diagnosis of PMDs in patients with autoimmune pathology in clinical practice with the implementation of a progressive personalized multidisciplinary approach to patient management with the provision of etiotropic and deepening pathogenetic therapy of the disease. We can agree with the ideas of Hogendorf et al. [118] and Kojo et al. [173] regarding the need to stratify associated autoimmune syndromes according to the causes of PID. This would provide an impetus for further clinical research aimed

at studying the heterogeneity of PMDs in humans, the breadth of its clinical phenotype, evolutionary development scenarios, relevant and comprehensive diagnostic criteria, and the closeness of the association with various autoimmune and other immune-dependent syndromes. It can be due to the development of effective immunotherapeutic approaches to compensate for PMDs and, accordingly, the manifestations of associated autoimmunity.

6.5. Directions for Further Research

The accumulated evidence base of the Association of PMDs and Autoimmune Syndromes in Humans should be the basis for intensifying further clinical research in this direction. A wider coverage of PMDs nosologies is necessary when studying the relationship with immune-dependent pathology in order to correct the existing heterogeneity of the strength of evidence for different PMDs [282]. Implementation of large population studies involving medical data from tens and even hundreds of thousands of respondents, as has already been done with SIgED, will strengthen the position of the scientific statement that PMDs are associated with the phenomenon of autoimmunity in humans [283].

Separately, diagnostic searches should be directed at attempts to identify differences in clinical manifestations and/or laboratory markers in autoimmune syndrome depending on the associated PMDs [284]. In other words, it is necessary to clarify how the causal PMD affects the clinical and laboratory phenotype of the associated autoimmune syndrome [285]. Accumulated evidence to date suggests that SIgAD-mediated SLE and NKD-mediated SLE may differ in a number of key clinical and laboratory attributes [125]. So, we must take PMDs into account. It may lead to stratification of autoimmune syndromes by associated immune system diseases, thereby optimizing diagnostic and prognostic processes in the direction of personalized medicine. Bibliometrics of scientific biomedical publications on primary immunodeficiency diseases in the Arab world is a perfect example of the first step on this way [286].

The interplay between genetic and epigenetic factors in PMD manifestation must be studied properly [287,288].

The next area of clinical research should be to study the possible impact of causal PMDs on the sensitivity of the associated autoimmune syndrome to conventional immunosuppressive treatment, as well as to test the scientific hypothesis that basic therapy of causal PMDs may improve the results of conventional immunosuppressive treatment of associated autoimmune syndromes [289,290].

It is important to use the 5-year experience from the German Screening Program dedicated to syndromic inborn errors of immunity in TREC-Newborn Screening [291]. We have to find simple and informative biomarkers of PMDs in rheumatic patients for clinical practice [292]. Building alliances for early detection of PMDs from primary care to hematology and clinical immunology is very important to solve these problems [293]. A practical reference for the allergist/immunologist and the allergy-immunology fellow-in-training is necessary [294].

It may provide a more progressive personalized approach to diagnostic and therapy selection in many patients with PMDs.

6.6. Limitations

It is necessary to admit that PMDs are studied heterogeneously. Along with deeply studied immunodeficiencies, such as SIgAD and MBLD, there are nosologies that have been reported quite a bit, for example, EPOD and SIgDD. For some forms of PMDs, there are still no thorough reviews, systematic reviews, or meta-analyses. During the long period covered by this systematic review, different laboratory measurement methods, units, and different diagnostic criteria for some PMDs were used, which makes it difficult to compare and generalize the results.

Heterogeneity is also characteristic of autoimmune syndromes. The list of autoimmune diseases is constantly expanding, so some nosological forms were not covered in early studies. The diagnostic criteria of autoimmune diseases have changed over time, as well as laboratory methods of measuring biomarkers for diagnosis verification. There may be overlapping mechanisms of the development of different autoimmune syndromes, which creates difficulties in the interpretation of data in mixed syndromes.

Most cited data demonstrate association rather than causation. This fact leaves doubts about the existence of a cause-and-effect relationship. However, the mechanisms underlying the development of autoimmunity in most known PMDs are well understood, and a separate section of this review is devoted to them. Furthermore, there are no studies with negative results that would refute the association. Therefore, there is no controversy. Most likely, this is due to insufficient research in some areas.

Despite rigorous selection criteria, residual misdiagnosis cannot be completely excluded. In some studies, dif-

ferentiation between primary minor immunodeficiencies and subclinical immune variants, age-related immune dysfunction, or secondary immunosuppression may have been incomplete. Age-dependent immune immaturity or immunosenescence, transient immune alterations, and immune suppression related to chronic disease or immunomodulatory therapy could have been misclassified as primary immune defects. In addition, incomplete reporting of exclusion criteria in retrospective studies limited the ability to fully disentangle primary from secondary immune abnormalities. Such misclassification may have led to both overestimation and underestimation of PMD–autoimmunity associations. However, consistency of findings across multiple independent studies and immune pathways suggests that the principal conclusions remain robust.

Potential confounders (genetic susceptibility, environmental exposures, infections, treatment effects) are not systematically addressed.

Narrative synthesis limitations and the absence of pooled effect sizes are also present.

All these features create certain limitations in the systematization of knowledge about PMDs, and the correction of these shortcomings should be the subject of further clinical research.

7. Ethical Aspects

This study was conducted in accordance with established ethical standards for research involving human data. As a systematic review based exclusively on analysis of previously published, anonymized data, it did not involve direct contact with human participants, collection of identifiable personal information, or intervention. Therefore, approval from an institutional ethics committee and informed consent were not required.

The review adhered to principles of transparency, accuracy, and responsible reporting, including careful citation of original sources and critical appraisal of study quality. Potential ethical concerns related to misclassification or overinterpretation of findings were addressed through conservative evidence weighting and explicit acknowledgment of study limitations.

8. Conclusions

Until now, no attempt has been made to globally systematize data on the association between PMDs and autoimmune syndromes in humans, despite the accumulation of data over more than 45 years. This is the first systematic review on PMDs and autoimmunity, which shows the state of research on this topic to date over a long period of time. This became possible after clarification of the phenomenology of PMDs, the growth of scientific knowledge about the variety, frequency, and clinical significance of PMDs and the development of a clinical and laboratory classification of PMDs in humans, i.e., creation of the theoretical and methodological basis of PMDs.

As the results of this review show, PMDs are associated with the development of the whole spectrum of known autoimmune syndromes in humans on a population scale in a universal manner with some nosological prerogatives, age, ethnic, geographical and gender differences. Due to its diversity, widespread nature, and critical importance, PMDs are a fairly representative natural model of the development of various autoimmune syndromes in people at the expense of the entire population.

Obtained data can help to better understand the phenomenology and wide diversity of mechanisms of the development of immune-dependent syndromes, both on a population scale and in particular individuals, for fundamental medical sciences. Also this can improve diagnostic approaches, the selection of both immunosuppressive therapy for autoimmune manifestations and basic immunotherapy for underlying PMDs for practical medicine. So, we can provide a potentially more effective integrative personalized multidisciplinary approach to patient management with etiopropic influences [295–297]. Autoimmune diseases can be divided into subgroups depending on the associated PMDs in rheumatology. PMDs can be divided into associated autoimmune syndromes in clinical immunology [298, 299]. It becomes possible to establish the etiology of the so-called idiopathic syndromes and prescribe not only pathogenetic and symptomatic, but also etiotropic therapy [300,301]. It must take into account during conducting diagnostic searches and building a structure of clinical diagnoses in routine medical practice. Therefore, it is difficult to overestimate the data obtained in this review.

The identification of the relationship between PMDs and autoimmune syndromes contributes to progress in the diagnosis, clinical management and prognosis of patients suffering from heterogeneous autoimmune pathology. It allows the identification of the etiology of the existing immunodependent lesion, which opens the way to

personalized etiotropic treatment. Such therapy affects not only the pathogenesis of the disease, but also the cause of the development of the pathology. It also provides an opportunity to better predict complications and clinical consequences on an individual basis.

However, there are a number of limitations that could affect the final conclusion. There is extremely heterogeneous and, apparently, insufficient evidence base for a number of PMDs. It is advisable to conduct additional rationally designed clinical studies in the field of the association of PMDs with the phenomenon of autoimmunity. It is necessary to take into account reasonable observations and a number of potential errors and shortcomings. They are thoroughly discussed in this review. Key factors influencing clinical and epidemiological findings include terminological inconsistencies, multiple autoimmune pathways, heterogeneity of PMD origin and evolution, overlap with other immunodeficiencies and comorbidities, variability of clinical phenotypes and course, difficulties distinguishing PMDs from secondary immunosuppression, and the absence of standardized diagnostic criteria for many PMDs. Overlap with subclinical immunodeficiency, age-related immune dysfunction, and secondary immunosuppression remains unclear. Potential confounders (genetic susceptibility, environmental exposures, infections, treatment effects, etc.) are not absolutely excluded. The solving of these problems would allow us to clarify the role and place of PMDs in the development of autoimmune syndromes in humans. So, we will improve the clinical consequences of autoimmune syndromes in immunocompromised individuals.

At the same time, we did not find negative studies that would not encourage the association of PMDs and autoimmunity in humans. Thus, it is not a matter of controversy, but of insufficient study of some nosologic units. It is natural for such a variety of forms of PMDs and autoimmune syndromes. In addition, the association of a number of PMDs and autoimmune syndromes has been confirmed by the results of qualitative meta-analyses and systematic reviews. Fundamental science has demonstrated many pathogenetic mechanisms of breakdown of immune tolerance in PMDs. Immunotherapeutic agents used for the treatment of PMDs also help with many autoimmune syndromes that are associated with these PMDs. These data allow us to lean towards a cause-and-effect relationship, rather than a random combination or variable predisposition. However, the model of PMDs as a universal factor in the development of autoimmunity in humans undoubtedly requires further validation.

So, to avoid the overinterpretation of results, we should clearly distinguish exploratory findings from validated conclusions and explicitly acknowledge the limitations of in silico or indirect evidence. To achieve this goal, a large body of new, well-designed, high-quality clinical trials investigating the Association of PMDs and Autoimmune Syndromes in Humans is needed. The results of this systematic review should be viewed with caution as encouraging data that require further careful verification.

Thus, for the first time, data on the global association of PMDs with autoimmune syndromes in humans have been collected, which is significant for theoretical and practical medicine. It changes our fundamental knowledge about the nature of immunocompromise phenomenon in humans. This should be reflected in diagnostic and therapeutic recommendations for practicing doctors and become the subject of further clinical studies. However, we have to perform a philosophical rethinking of the problem of PMDs based on the scientific evidence accumulated to date. It is necessary to make related methodological changes in the organization of the research process. Without these transformations, it is hardly possible to achieve significant progress in the field of studying the Association of PMDs and Autoimmune Syndromes in Humans.

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During the preparation of this work the author used ChatGPT 4.0 for some tables and figures building. The author subsequently reviewed and edited content as necessary and take full responsibility for the final content of the publishing article.

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