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Clinical Immunology in Chromatinopathies: A Scoping Review

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 December 2025 and was last updated on 18 December 2025.

INTRODUCTION

Review question / Objective This scoping review aims to synthesise clinical data on anomalies of the immune system, including laboratory values, infection history, autoimmunity, and immunodeficiency in individuals with mNDDs belonging to the subclass chromatinopathies (CP), to identify patterns and fill knowledge gaps.

Background Chromatinopathies (CP) are a subclass of monogenic neurodevelopmental disorders (mNDD) caused by germline mutations in genes involved in epigenetic regulation. Symptoms may include neurodevelopmental delay, intellectual disability, autism spectrum disorder, facial dysmorphisms, growth- and various congenital abnormalities. These disorders often also present with immunopathology. However, a clear insight into immune dysregulation in mNDDs belonging to the subclass CP is currently unavailable.

Rationale Epigenetic machinery is essential for proper functioning of the immune system. Numerous animal and in vitro studies have shown an important role of epigenetic enzymes, which are dysfunctional in chromatinopathies, in the regulation of immune cell development, differentiation and function. Although several chromatinopathies have been already classified as inborn error of immunity there is currently no understanding of how especially recently diagnosed chromatinopathies affect the functioning of the immune system and therefore the impact of the medical management of the syndromes.

METHODS

Strategy of data synthesis Articles on immunological aspects in individuals with mNDDs belonging to the subclass CP, caused by germline mutations affecting chromatin-modifying enzymes from the “writers” group, were included. Searches

were conducted using PubMed, Cochrane Library, and Web of Science.
Terms used:
#1 ("Kleefstra Syndrome"[Supplementary Concept] OR kleefstra-syndrom*[tiab] OR kleefstra[ti] OR EHMT1[tiab] OR EHMT-1[tiab] OR 9q34.3[tiab] OR 9q-Subtelomeric-Delet*[tiab] OR 9qSTDS[tiab] OR g9a-like protein[tiab] OR lysine methyltransferase 1[tiab] OR "Kabuki Syndrome"[Supplementary Concept] OR kabuki-syndrom*[tiab] OR kabuki[ti] OR KMT2D[tiab] OR lysine methyltransferase 2D[tiab] OR wiedemann-steiner syndrom*[tiab] OR wiedemann-steiner[ti] OR KMT2A[tiab] OR lysine methyltransferase 2A[tiab] OR kleefstra-syndrome type 2[tiab] OR KMT2C[tiab] OR lysine methyltransferase 2C[tiab] OR DNMT3A[tiab] OR Tatton-Brown-Rahman syndrome[tiab] or Tatton-Brown-Rahman[ti] OR Rubinstein-Taybi syndrom*[tiab] OR Rubinstein-Taybi[ti] OR CREBBP[tiab] OR SETD1A[tiab] OR DNMT3B[tiab] OR ASH1L[tiab] OR KMT2E[tiab] OR WHSC1[tiab] OR KAT6B[tiab] OR KAT6A[tiab] OR EP300[tiab] OR KMT2B[tiab] OR DNMT1[tiab] OR NSD1[tiab] OR EZH2[tiab] OR SETD2[tiab] OR KMT5B[tiab] OR PRDM5[tiab] OR PRDM16[tiab] OR PRDM12[tiab] OR SETD5[tiab])
#2 (immun*[MeSH Terms] OR immun*[tiab] OR hypogammaglobulinemia[tiab] OR hypergammaglobulinemia[tiab] OR gammaglobulin*[tiab] OR IgG[tiab] OR IgA[tiab] OR IgM[tiab] OR CD4[tiab] OR CD8[tiab] OR CD3[tiab] OR CD19[tiab] OR T lymphocyt*[tiab] or B lymphocyt*[tiab] OR T cell[tiab] OR B cell[tiab] OR inflammasom*[tiab] OR NLRP3[tiab] OR infection[tiab] OR inflammation[tiab])
#3 (neoplasms[MeSH] OR tumor[tiab] OR cancer[tiab] OR tumour[tiab] OR lymphoma[tiab] OR malignanc* OR leukemia[tiab] OR leukaemia[tiab] OR melanoma[tiab] OR carcinoma[tiab] OR sarcoma[tiab] OR "myelodysplastic syndrom*"[tiab] OR "clonal hematopoiesis"[tiab])
Strategy #1 AND #2 NOT #3
Filter Clinical Study, Clinical Trial, Case Report, Observational Study.

Eligibility criteria Individuals with molecular diagnosis of chromatinopathy resulting from mutations in epigenetic genes from the "writer" category.

Source of evidence screening and selection Search: To date there are 179 syndromes classified as CPs. In this scoping review, we focus on the “writer” category of epigenetic enzymes, the enzymes that imprint epigenetic marks on chromatin. The search of articles was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension for scoping reviews. PubMed, Cochrane Registry, and Web of Science were searched to identify relevant articles. First, the comprehensive search strategy was conducted. Secondly, individual search strategies were performed for each gene that was not represented in the initial results. This step excluded the immunology-specific terms from the search strategy and included manual full-text screening of all results for immunological data. To maintain feasibility, the study exclusively included genes from the writer category of the epigenetic machinery. Forty-one additional references were added through cross-referencing.
Screening: After completing the search, articles were screened by evaluation of titles and abstracts first, followed by the evaluation of the full text, considering inclusion and exclusion criteria. Articles were included if they reported data on immunological aspects – immunoglobulin (Ig) levels or lymphocyte counts and/or infection history or immunopathology – in individuals with mNDDs belonging to the subclass CP caused by mutations in epigenes belonging to the “writer” category, were written in English, published in peer-reviewed journals, and involved human individuals 3. Articles were excluded if they regarded animal studies, cell studies, or cancer studies; full text was unavailable in English; or if they did not provide clinical information about the immune system in individuals with mNDDs belonging to the subclass CP and no molecular diagnosis of patients was performed.

Data management Data collection: Primarily, data was collected on the number of individuals per article, age, location of medical center, gene, genetic variant, protein variant consequence, and functional consequence. Furthermore, levels of Igs (IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM) and frequencies of lymphocytes (T cells: CD3+, CD3+CD4+, CD3+CD8+, B cells: CD19+, total memory CD19+CD27+, memory IgD+CD27+, switched memory IgD-CD27+, plasma cells IgM-CD38++, naive IgM+/IgD+, CD21lowCD38low, NK cells: CD16+/CD56+) were recorded. Moreover, data on infection history, autoimmunity, and other immunopathology was recorded. In cases where the consequence of protein variants was not mentioned or unclear, this was further evaluated by use of ClinVar (www.ncbi.nlm.nih.gov/clinvar/) and Alamut (www.sophiagenetics.com/platform/alamut-visual-plus/).

Data analysis: Following data collection, descriptive statistics were performed to evaluate frequencies of lymphocytes and concentrations of Igs, as well as prevalence of infections and

immunopathology. Absolute lymphocyte counts were noted and manually calculated if only percentages were given for subpopulations but the absolute total lymphocyte count was provided. All lymphocyte values were manually compared to the age-dependent reference values from Comans-Bitter et al.. However, these reference values could not be used in cases where only percentages for subpopulations were provided. In these cases, the conclusions of the article itself were used instead. Ig values were compared with Sanquin age-dependent references (www.sanquin.org).

Language restriction English only.

Country(ies) involved Germany and Netherlands.

Keywords Immunology, infection, autoimmunity, chromatin, epigenetics, neurodevelopmental disorders, hypogammaglobulinemia, histone modifications, epigenetic enzymes.

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