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BRIEF REPORT

Autoantibody Response Toward Chromatin in Patients With Juvenile Idiopathic Arthritis

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Objective. Patients with juvenile idiopathic arthritis (JIA) frequently exhibit antinuclear antibodies (ANAs), but the specific antigen target recognized by them and the presence of additional autoantibody specificities in patients with JIA remains elusive.

Methods. Plasma samples from 110 untreated patients with active JIA, as well as from 14 children with unspecified arthritis and 151 age- and sex-matched healthy children, were analyzed with multiple modern clinical-grade autoantibody assays, including automated indirect immunofluorescence to screen for ANAs with HEp-2 cells, and specific immune assays to detect reactivity to individual autoantigens. In addition, a HuProt proteome microarray was used to screen for novel autoantibody targets in plasma samples from five patients with ANA-positive JIA and four ANA-negative healthy controls.

Results. Homogeneous nuclear ANA staining, indicating reactivity toward chromatin, was detected in most (61.8%) patients with JIA but rarely in healthy controls (2.6%; $P < 0.0001$). No antibody reactivity to specific nuclear antigens or other autoantigens associated with connective tissue diseases was detected. However, 20% of patients with JIA harbored antibodies against double-stranded DNA (dsDNA)–nucleosome complexes (compared with 2.6% of controls, $P < 0.0001$). Finally, the proteome microarray revealed core histone H2A variant H2AFY, part of the nucleosome, to be the most widely recognized human protein by autoantibodies of patients with JIA.

Conclusion. Autoantibody reactivity in JIA primarily targets chromatin, but the epitopes targeted are likely either posttranslationally modified or multimolecule epitopes, such as dsDNA–nucleosome complexes, rather than epitopes on individual native proteins or purified dsDNA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. It is a heterogeneous condition, likely of autoimmune origin, and is currently classified into seven different subtypes according to the International League of Associations for Rheumatology (ILAR) criteria. These subtypes are oligoarthritis, rheumatoid factor–negative polyarthritis (Poly RF–), rheumatoid factor–positive polyarthritis (Poly RF+), systemic JIA, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis.[1]

Approximately 30% to 60% of all patients with JIA test positive for antinuclear antibodies (ANAs).[2–5] ANA positivity is linked to specific JIA phenotypes and disease outcomes, such as early disease onset, female sex, oligoarthritis, and a higher risk of uveitis.[2–5] Based on this, ANA positivity has recently

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been proposed as a classification criteria for redefined JIA subgroups.[1]

ANA testing is currently poorly standardized, with significant variability in methods and cutoff values across different countries and laboratories, and specific nuclear staining patterns detected have rarely been reported in published studies.[2] Moreover, the exact autoantibody targets in JIA remain elusive. Reactivity to extractable nuclear antigens (ENAs), common autoantibody targets in other systemic rheumatic diseases, such as systemic lupus erythematosus (SLE), Sjögren disease, or systemic sclerosis, is rarely observed in patients with JIA.[5,6] However, the most common ANA staining pattern detected in patients with JIA appears to be homogeneous nuclear staining,[5] suggesting autoantibody reactivity against chromatin or its individual components: nucleosomes that further consist of double-stranded DNA (dsDNA) wrapped around histone proteins. In line with this, some earlier studies have reported increased reactivity to these structures in patients with JIA.[5,7,8]

In this study, we set out to explore the autoantibody reactivity in patients with JIA using a modern, highly standardizable automated immunofluorescence test system for ANA detection, several clinical-level antibody detection methods using well-defined autoantigens, and finally, a human protein microarray for unbiased discovery of autoantibody reactivity against the entire human proteome.

MATERIALS AND METHODS

Study participants. The study cohort included 110 pediatric patients, who met the ILAR criteria for JIA,[1] 151 healthy age- and sex-matched control children, and 14 children with the diagnosis of unspecified arthritis, that is, a single arthritis episode of unknown etiology not fulfilling the ILAR criteria for JIA (Supplementary Table 1). Patients with JIA were enrolled by pediatric rheumatologists at the Kuopio, Turku, and Oulu University Hospitals at the time of diagnosis or during clinical relapse after medication discontinuation. All patients with JIA either were treatment naive or had not used immunomodulatory medications for two months before the sampling. Healthy control children participated in the Finnish Type 1 Diabetes Prediction and Prevention follow-up study (http://dipp.utu.fi). Written informed consent was obtained from all study participants and/or their legal guardians, as mandated by the Declaration of Helsinki, and the study was approved by the ethics committees of the participating University Hospitals of Kuopio, Oulu, and Turku.

Samples. Peripheral blood samples from patients with JIA, healthy controls, and children with the diagnosis of unspecified arthritis were collected between May 2020 and October 2023 into lithium heparin blood collection tubes. The samples were centrifuged at 1,000 × *g* for 10 minutes, and plasma samples were collected and stored at –80 °C until analysis.

ANA detection by indirect immunofluorescence test. ANA measurements were performed using a fully automated indirect immunofluorescence test (IIFT) system. HEp-2 cell slides were stained using an IF Sprinter, and images were recorded with the Europattern Microscope Live automated microscope (both from Euroimmun AG). Plasma dilutions starting from 1:80 were used, and the immunofluorescence patterns were coded according to International Consensus on ANA Patterns (https://anapatterns.org/) recommendations. All samples were evaluated by a single laboratory physician with the aid of the Europattern Classifier software (Euroimmun AG).

Autoantibody assays. The anti–citrullinated protein/peptide (CCP) antibody and Phadia EliA connective tissue disease (CTD) screen assays (Thermo Fisher Scientific) were performed according to the manufacturer's instructions on a Phadia 250 instrument (Thermo Fisher Scientific). The individual antigens tested after a positive CTD screen were dsDNA, Sm, SSA/Ro52 and Ro60, SS-B/La, centromere B, Scl-70, Mi-2, RNA-Pol III, PM/Scl, Jo-1, PCNA, Ribosomal-P protein, U1-RNP (RNP-70, A, C), and fibrillarin. The Microblot-Array (MBA) ANA plus assay (TestLine Clinical Diagnostics), which detects 44 distinct autoantibodies using an immunoblot array in a microtiter format, was performed according to the manufacturer's instructions. Anti-dsDNA enzyme-linked immunosorbent assay (ELISA) (IgG), anti-dsDNA-NcX ELISA (IgG), anti-histone ELISA (IgG), and anti-nucleosomes ELISA (IgG) (all from Euroimmun AG) were performed according to the manufacturer's instructions.

HuProt proteome microarray. Five plasma samples from patients with ANA-positive JIA and four plasma samples from ANA-negative healthy control children were sent to Cambridge Protein Arrays Ltd for autoantibody profiling using the HuProt version 4.0 Human Proteome Microarray. For further details, please see Supplementary Methods.

Statistical analyses. GraphPad Prism software (version 10.4.1) was used for statistical analysis. Mann–Whitney U test, Kruskal-Wallis test with Dunn's posttest, Fisher's exact test, and McNemar test were used as indicated. A P value <0.05 was considered statistically significant.

RESULTS

Our study cohort included 110 children with JIA, sampled during active disease, either at diagnosis or during a disease relapse after medication discontinuation. As control groups, we had 14 children diagnosed with unspecified arthritis (disease controls) and 151 age- and sex-matched healthy control children. The majority of patients with JIA were diagnosed with Poly RF– (n = 38), oligoarthritis (n = 56), or enthesitis-related arthritis (n = 9), with the remaining patients diagnosed with Poly RF+

(n = 3), psoriatic arthritis (n = 2), or other juvenile arthritis (n = 2). The demographic and clinical characteristics of the study groups are detailed in Supplementary Table 1.

We first screened the plasma samples for ANAs using a highly standardized, fully automated IIFT method. ANA positivity at a titer of ≥1:160 was observed in 86 out of 110 (78.2%) patients with JIA, compared with 57 out of 151 (37.7%) healthy children and six out of 14 (42.9%) children with unspecified arthritis (Figure 1A). Several patients with JIA displayed ANA positivity at higher titers (≥1:640), which was not detected in the healthy children (Figure 1A). In addition to ANA titer, the staining pattern of ANA reactivity was determined. The majority of ANA-positive samples exhibited either a speckled or homogeneous nuclear staining pattern (Figure 1B). The speckled nuclear staining pattern, indicating autoantibody reactivity to nuclear proteins not part of the chromatin, was most commonly observed in healthy children. In contrast, the homogeneous nuclear staining pattern, indicating reactivity to chromatin, was dominant in patients with JIA

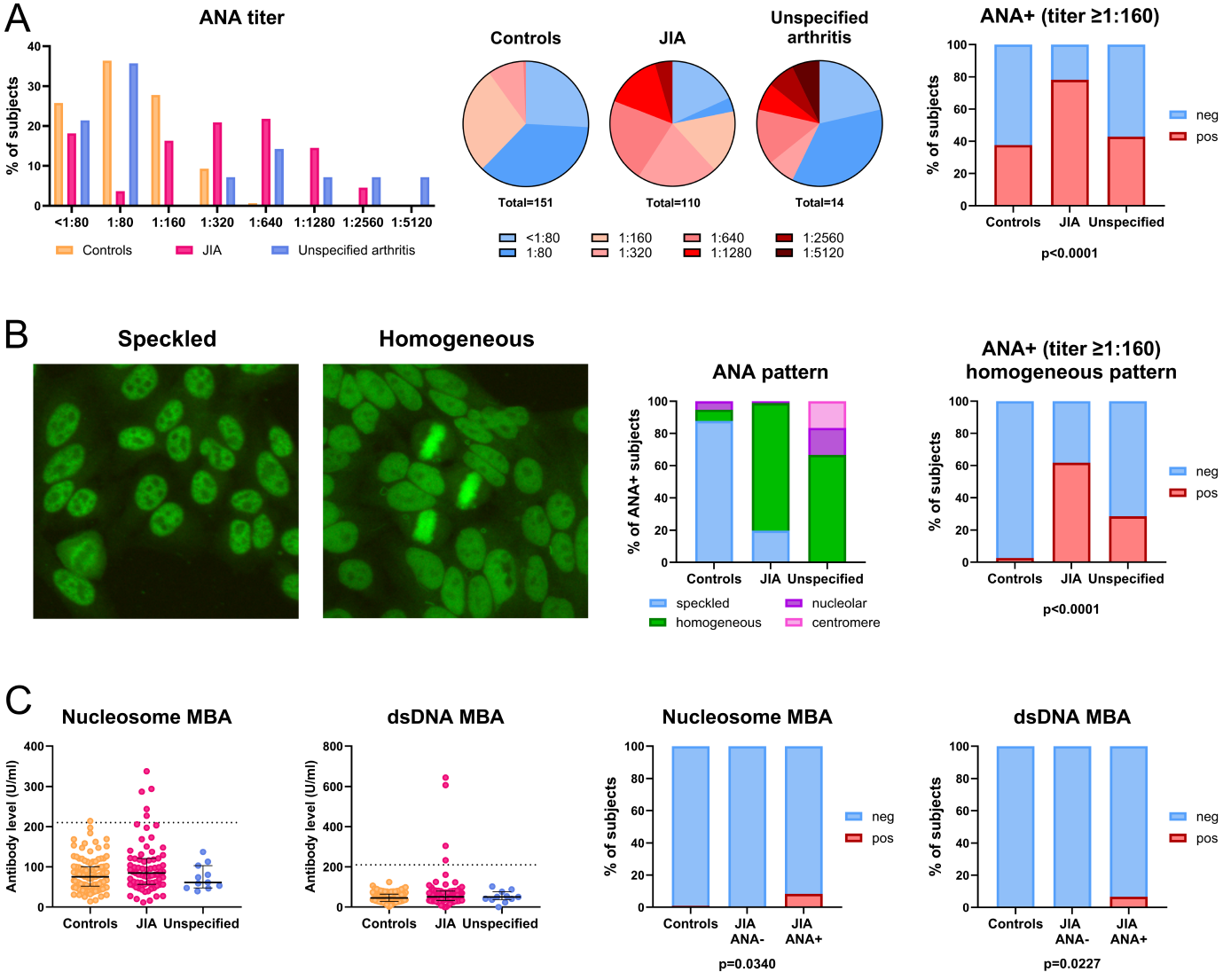

Figure 1. Homogeneous nuclear ANA staining in patients with JIA suggests autoantibody reactivity toward chromatin. (A) Frequency (left panel) and distribution (middle panel) of different ANA titers observed in the study groups using an IIFT. Frequency of ANA-positive subjects (ANA ≥1:160) in the different study groups (right panel). (B) Representative speckled and homogeneous nuclear ANA staining patterns in HEp-2 cells using IIFT (left panel). Distribution of nuclear ANA staining patterns in ANA-positive (ANA ≥1:160) subjects in the different study groups (middle panel). Frequency of ANA-positive subjects (ANA ≥1:160) with a homogeneous nuclear staining pattern in the different study groups (right panel). (C) Reactivity toward nucleosomes and dsDNA in the MBA presented as concentration (U/mL) of antibodies (left panels), with the error bars depicting concentration median and interquartile range. The frequency of subjects testing positive for nucleosomes or dsDNA at a cutoff value of 210 U/mL (dotted line) in the controls, and patients with ANA-negative (ANA <1:160) and ANA-positive (ANA ≥1:160) JIA (right panels). Fisher's exact test was used for statistical analysis. ANA, antinuclear antibody; dsDNA, double-stranded DNA; IIFT, indirect immunofluorescence test; JIA, juvenile idiopathic arthritis; MBA, Microblot-Array.

(Figure 1B). In fact, a homogeneous nuclear ANA staining result at a titer of ≥1:160 distinguished patients with JIA (68 out of 110; 61.8%) from healthy children (4 out of 151; 2.6%) more effectively than overall ANA positivity at the same titer ($P < 0.001$; McNemar test), with children with unspecified arthritis again falling in between (4 out of 14; 28.6%) (Figure 1B). Because our sampling period (2020–2023) spanned the COVID-19 pandemic, we also assessed the ANA results longitudinally. Interestingly, whereas the frequency of ANA positivity remained stable in patients with JIA, it increased in healthy controls from late 2021 onward (Supplementary Figure 1). This was driven by an increase in low-titer (1:160 or 1:320) ANA positivity with a speckled nuclear staining pattern. Consequently, no temporal shifts were observed when using ANA positivity at a titer of ≥1:160 with a homogeneous nuclear staining pattern as the criteria for positivity (Supplementary Figure 1).

Consistent with previous studies,[2–5] ANA positivity at a titer of ≥1:160, particularly with a homogeneous nuclear staining pattern, was associated with female sex, risk of uveitis, and younger age at disease onset in patients with JIA (Supplementary Figure 2). Moreover, higher erythrocyte sedimentation rate and C-reactive protein values were detected in patients with ANA-positive JIA at sampling, but no association with HLA-B27 positivity, number of active joints, Juvenile Arthritis Disease Activity Score 10, or cytomegalovirus seropositivity was detected (Supplementary Figure 2).

To further explore autoantibody reactivity in patients with JIA, we first screened the plasma samples for CCP antibodies, which are diagnostic of rheumatoid arthritis, and for 16 specific ENAs commonly observed in systemic autoimmune rheumatic diseases. CCPs were detected only in the three patients with JIA diagnosed with Poly RF+, as expected, and low levels of ENAs were detected only in a few isolated patients, with dsDNA antibodies being the most common finding (detected in four patients with JIA; Supplementary Table 2). We then performed a broader autoantibody screening using an immunoblot array (MBA), which allows probing autoantibody reactivity against 44 distinct autoantigens associated with different autoimmune diseases. Again, a few isolated patients with JIA displayed autoantibody reactivity against nucleosomes (5 out of 73; 6.8%) and dsDNA (4 out of 73, 5.5%) and even more rarely to the other 42 autoantigens tested (Figure 1C; Supplementary Table 3). Notably, all patients with JIA displaying reactivity against dsDNA or nucleosomes also showed ANA positivity in IIFT (Figure 1C).

Given the predominant homogeneous nuclear ANA staining pattern and the rare specific autoantibody reactivities to dsDNA or nucleosomes detected in patients with JIA, we further explored autoantibody reactivity to components of chromatin. Chromatin consists of linker dsDNA and repeating units of nucleosomes, that is, dsDNA coiled around an octamer of core histone proteins (Figure 2A). Therefore, the plasma samples were assayed with clinical-grade ELISAs detecting autoantibodies against purified dsDNA, histone, and nucleosomes, but no differences were observed between the study cohorts (Supplementary Figure 3). We also tested the samples with a dsDNA-NcX ELISA kit, which uses dsDNA complexed with nucleosomes, a more natural antigen structure compared with purified dsDNA or nucleosomes, and has shown better performance compared with dsDNA ELISAs in diagnosing SLE.[9] Surprisingly, samples from patients with JIA showed increased reactivity in this ELISA, with 22 out of 110 (20.0%) samples from patients with JIA positive using the manufacturer's cutoff compared with four out of 151 (2.6%) healthy children and none of 14 (0%) children with unspecified arthritis (Figure 2B). The dsDNA-NcX reactivity also strongly correlated with ANA positivity, with 21 out of 86 (24.4%) patients with ANA-positive JIA showing a positive response compared with only one out of 24 (4.2%) ANA-negative patients (Figure 2B).

Finally, to perform an unbiased screening for autoantibody targets, we used the HuProt human proteome microarray, which consists of more than 21,000 unique human proteins and isoform variants. For this exploratory study, we selected five samples from female patients with early-onset JIA exhibiting high-titer homogeneous nuclear ANA staining and compared them with four samples from age- and sex-matched, ANA-negative healthy controls. Interestingly, H2AFY (core histone macro-H2A) was identified as the most abundantly recognized autoantibody target in patients with JIA (Figure 2C). H2AFY is a variant of the H2A subunit of the nucleosome and subsequently part of the chromatin, making it a logical autoantigen hit given the homogeneous nuclear ANA staining pattern observed in the studied patients with JIA. Overall, between 50 and 103 individual proteins were identified as highly antibody-binding targets (Z score of >3) for each of the five JIA patient samples studied. Filtering these to proteins recognized with a Z score of >3 by at least three out of five patients with JIA but by none of the four healthy controls identified six additional proteins (in addition to H2AFY) as putative autoantibody targets: MAGI1 (membrane-associated guanylate kinase WW and PDZ domain–containing 1), KEAP1 (Kelch-like ECH-associated protein 1), CCNB2 (cyclin B2), MYOD1 (myogenic differentiation antigen 1), HSPA13 (heat shock protein 70 family A member 13), and NEDD9 (neural precursor cell expressed developmentally down-regulated protein 9) (Figure 2C).

DISCUSSION

In this study, we first confirmed using a highly standardized ANA IIFT method that the majority of children with JIA are positive for ANAs, with most displaying a homogeneous nuclear staining pattern. This pattern suggests the presence of autoantibodies targeting chromatin, which are rarely detected in healthy children. Using several clinical-grade autoantibody assays, we verified that this reactivity is not primarily due to autoantibodies against common nuclear antigens detected in other CTDs[5,6] or to individual components of chromatin, such as purified dsDNA, histone

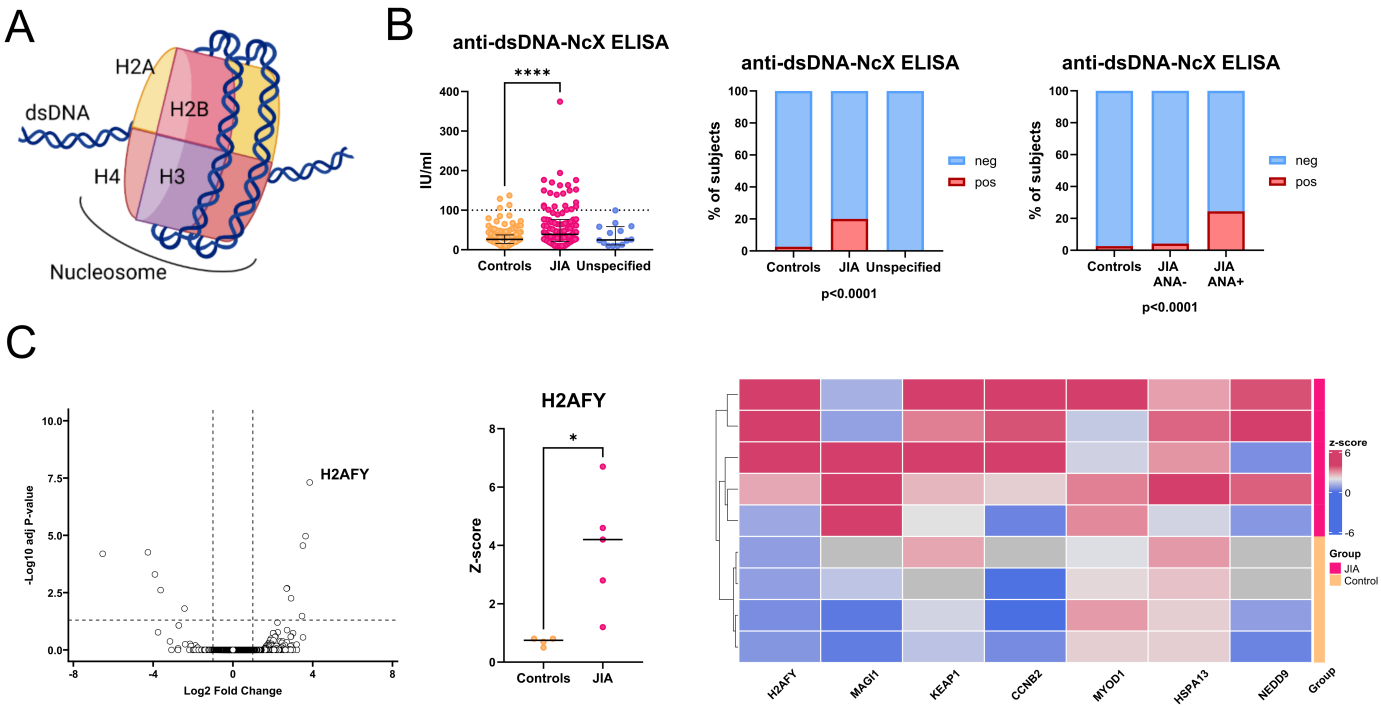

Figure 2. Patients with JIA show increased reactivity toward dsDNA-NcX. (A) A schematic representation of the basic structure of chromatin, which consists of linker dsDNA and repeating units of nucleosomes, that is, dsDNA coiled around an octamer consisting of two pairs of core histone proteins H2A, H2B, H3, and H4. Image created with BioRender.com. (B) Results from anti-dsDNA-NcX ELISA presented as concentration of antibodies (left panel), with the error bars depicting concentration median and interquartile range. Frequency of subjects testing positive at a cutoff value of 100 IU/mL (dotted line) in the different study groups (middle panel), and with patients with JIA separated into ANA-negative (<1:160) and ANA-positive (≥1:160) subgroups (right panel). Statistical testing was performed using Kruskal-Wallis test with Dunn's posttest (left panel) or Fisher's exact test (middle and right panels). (C) Differentially detected autoantibody targets in patients with JIA compared with controls depicted as a volcano plot of the HuProt microarray data (left panel). Z scores of H2AFY reactivity in healthy controls and patients with JIA (middle panel). Mann–Whitney U test was used for statistical testing. Heatmap visualization of reactivities (Z scores) of autoantibody targets recognized with a Z score of >3 by at least three out of five patients with JIA but by none of the four healthy controls. *$P < 0.05$, ****$P < 0.0001$. CCNB2, cyclin B2; dsDNA, double-stranded DNA; dsDNA-NcX, double-stranded DNA–nucleosome complexes; ELISA, enzyme-linked immunosorbent assay; H2A, histone H2A; H2AFY, histone 2A variant; H2B, histone H2B; H3, histone H3; H4, histone H4; HSPA13, heat shock protein family A member 13; KEAP1, Kelch-like ECH-associated protein 1; MAGI1, membrane associated guanylate kinase WW and PDZ domain containing 1; MYOD1, myogenic differentiation antigen 1; NEDD9, neural precursor cell expressed developmentally down-regulated protein 9.

proteins, or nucleosomes because reactivity to these was detected in only a small fraction of the patients in this study. In contrast, however, 20% of patients with JIA showed reactivity to dsDNA-NcX, which consists of dsDNA–nucleosome complexes. This structure likely represents a more natural antigen compared with purified dsDNA or nucleosomes because in vivo dsDNA is bound to nucleosomes within apoptotic cell fragments presented to the immune system.[9] Interestingly, a previous study assaying autoantibody reactivity to a different artificial histone-dsDNA construct reported highly similar results, with reactivity seen in 24% of patients with JIA but in none of the controls.[7] Collectively, these findings suggest that a major autoantibody target in JIA is a conformational epitope formed by a dsDNA–nucleosome complex rather than epitopes on dsDNA or individual histone proteins.

It is important to note the discrepancy between the level of reactivity to dsDNA-NcX (20%) and antichromatin reactivity observed in the IIFT assay (>60% at the titer of ≥160). This suggests that dsDNA-NcX may not contain all the conformational structures present in chromatin of intact HEp-2 cells used in the IIFT assay. Alternatively, chromatin proteins in HEp-2 cells may have undergone posttranslational modifications not present in the purified antigens used in laboratory assays. For example, some studies have suggested that citrullinated or carbamylated histone structures could be targets of autoantibodies in JIA.[10,11]

Besides autoantibodies against chromatin, there may be other autoantibody targets in JIA not detectable with HEp-2 IIFT. To investigate this, we conducted a human protein microarray screening for antibody reactivity to more than 21,000 distinct human proteins and isoform variants, the broadest autoantibody screening performed in JIA, to our knowledge. Interestingly, the most broadly recognized protein was H2AFY, a histone protein forming part of the nucleosome, reinforcing the central role of chromatin as the major autoantibody target in JIA. Previous studies exploring autoantibody reactivity in JIA using more limited protein microarrays or peptide libraries[12–15] have yielded highly variable results. A limitation of some of these previous studies is

that only linear, but not conformational, epitopes can be identified when using peptide fragments instead of whole proteins as targets. Moreover, the few potential protein targets, in addition to H2AFY, identified in our study were not part of the more restricted libraries screened in the previous studies, so their potential as autoantibody targets would need to be confirmed in future studies. An important limitation even of our large-scale proteome study using whole proteins is that conformational epitopes not part of individual proteins, such as the dsDNA-NcX structure, or posttranslationally modified protein epitopes would not be detected. However, overall, both our current and the previous screening studies suggest that no single natural protein target is likely recognized by the autoantibodies of a majority of the patients with JIA.

In this study, we noted that from late 2021 onward, healthy control children showed a rising incidence of low-titer ANA positivity with a speckled nuclear pattern. This phenomenon temporally coincides with the drastic increase in SARS-CoV-2 infections in children after relaxation of COVID-19 restrictions in Finland.[16] Several small studies have suggested that SARS-CoV-2 infections can lead to an increase in low-titer autoantibodies, including ANAs,[17] aligning with our findings. Importantly, however, the proportion of ANA-positive samples with a homogeneous nuclear pattern remained unchanged over time in both patients with JIA and controls, indicating that the chromatin-targeted autoantibody reactivity predominant in patients with JIA was stable and unaffected by the pandemic.

In conclusion, our comprehensive assessment of autoantibody reactivity in patients with JIA suggests that (1) chromatin is the main target of autoantibody reactivity in JIA and (2) the epitopes targeted are likely conformational structures formed by different molecules, such as the dsDNA-nucleosome complexes, and/or posttranslationally modified epitopes of chromatin proteins. The detection of a typical homogeneous nuclear staining pattern with a highly standardized ANA IIFT assay remains the best diagnostic modality to detect JIA-associated autoantibodies. However, our current data suggest that the dsDNA-NcX assay, or further modifications of it, could be used as a supporting method for a highly specific detection of JIA-associated anti–chromatin autoantibody reactivity.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Kinnunen confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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