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GENETIC DETERMINANTS OF AUTOIMMUNE ARTHRITIS: AN IMMUNOGENETIC APPROACH

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Abstract

Autoimmune arthritis is a complex inflammatory disorder shaped by the interplay of genetic susceptibility, immune dysregulation, and clinical phenotype variability. This study employed a mixed-methods immunogenetic framework to examine the influence of high-risk single nucleotide polymorphisms (SNPs), HLA class I and II allelic variations, cytokine activation profiles, and T-cell signaling markers on disease severity and progression. Genomic screening revealed distinct clusters of risk-associated SNPs and HLA variants strongly correlated with heightened inflammatory responses. Cytokine profiling demonstrated consistently elevated IL-6, TNF-α, IL-17, and IFN-γ levels among genetically predisposed individuals, supporting the mechanistic link between genetic architecture and amplified immune activation. Phenotypic assessments further identified heterogeneous disease trajectories, with genetically high-risk patients exhibiting more frequent flares, aggressive symptom progression, and greater functional impairment. The integration of genomic, immunological, and clinical datasets into an immunogenetic risk index provided enhanced predictive accuracy for disease activity compared with traditional single-parameter assessments. These findings emphasize that autoimmune arthritis comprises multiple molecularly distinct subtypes rather than a single uniform condition, underscoring the importance of individualized diagnostic and therapeutic strategies. The study concludes that early immunogenetic screening and cytokine monitoring can improve clinical decision-making, support precision-based treatment planning, and ultimately contribute to better long-term outcomes for patients with autoimmune arthritis.

Keywords: Autoimmune Arthritis; Immunogenetics; Hla Polymorphisms; Snp Variants; Cytokine Dysregulation; T-Cell Activation; Genetic Susceptibility; Immune Profiling; Multi-Omics Analysis; Precision Medicine.

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INTRODUCTION

Rheumatoid arthritis is an immune disorder that causes inflammation of the body system and is marked by persistent joint pain and soreness of joints, and joint degradation. This is yet another factor that predisposes it and is seen as a serious hereditary problem, namely its formation (Padyukov, 2022; Duran et al., 2025). The outcome of the complicated collaboration between genetic and environmental influences in the formation of the disease is the autoantibodies and the enormous reaction of the immune system (Padyukov, 2022). Genetic research has been in a position to identify more than a hundred susceptibility locus associated with rheumatoid arthritis by use of genome-wide association and other genomic researches thereby contributing to the understanding of the complicated genetic environment that characterizes this condition (Chen et al., 2025). To a large extent, this genetic factor, that has a direct relationship with human leukocyte antigen region, can be explained by HLA-DRB1 shared epitope alleles (Seyhan et al., 2020; Chen et al., 2025). These are synonymous and closely linked alleles which share a similar amino acid structure at 7074 and which are closely linked to the susceptibility to rheumatoid arthritis. They also identify how anti-cyclic citrullinated peptide antibodies are generated in various groups of people (Cha et al., 2024; Mueller et al., 2021). HLA-DRB1 gene belongs to the highly diverse class in the MHC II area of chromosome 6 which is most critical in presenting antigens to the CD4 + T cells and thereafter modifying the adaptive immune response (Wysocki et al., 2020; Laborde et al., 2020). Besides the shared epitope, most of the risk with MHC in RA is facilitated by four amino acids on six HLA molecules (HLA-DRB1, HLA-B, HLA-DPB1 and HLA-A). They affect the affinity of peptides and the stimulation of T-cells (Romao and Fonseca, 2021). Moreover, immune-regulatory genes, including protein tyrosine phosphatase none regulator type 22 and peptidylarginine deiminase type IV, play an important role in rheumatoid arthritis and have functional polymorphisms that, in particular, affect the disease according to specific molecular mechanisms and, as a result, the overall architecture of the genetic basis of the disease (Zhao et al., 2021) (Chen et al., 2025). Rheumatoid arthritis predisposition is a genetic phenomenon and not restricted to HLA area. It is a group of non-HLA genes which has an effect on immunological responses, T-cell activation, and cytokine signal transduction (Zhao et al., 2021). Those genes are categorized as non-HLA and are PTPN22, LINC02341-TNFSF11, THADA and TMEM174. Genome-wide association studies have led to the discovery of these genes to form some anti-citrullinated protein antibodies. It assumes that the genes are also implicated in the regulation of immune responses that may lead to autoimmune diseases (Shchetynsky et al., 2021). The development of rheumatoid arthritis is carried out through many stages in many years. HLA-DRB1 common epitope is a significant genetic factor, which is closely related to the development of anti-citrullinated protein antibody-positive RA (Maisha et al., 2023). Together with the HLA region, the gene, PTPN22 (protein tyrosine phosphatase non-receptor type 22), is of high importance and that has a high risk of RA. The second risk variant is the rs2476601 variant that comes second to the HLA-DRB1 shared epitope alleles (Shchetynsky et al., 2021). The variation of the rs2476601 has been associated with nine autoantibody specificities including Cit-Vim60-75 and CEP-1. This means that

it has a mass impact on the immunity of the immune system to identify itself (Shchetynsky et al., 2021). Moreover, polymorphism of PTPN22 rs2476601 and HLA-DRB1 shared epitope alleles have shown a high level of association with certain anti-citrullinated proteins antibody subsets. It means that there is a combined genetic influence on seropositive rheumatoid arthritis (Shchetynsky et al., 2021). The gain-of-function mutation at the protein site of PTPN22 has an effect on the activation threshold of T and B cells. This alteration results in the development of the autoreactive cells and the improvement of such processes as citrullination of the peptide (Romão & Fonseca, 2021). Further, other loci, such as *THADA and other loci, such as, LINC02341 TNF S11 and TMEM174, have also been identified to be associated with certain autoantibody pattern in addition to these known genetic elements. It is also a priority of genetic diversity in rheumatoid arthritis (RA) (Shchetynsky et al., 2021). The findings have shown that the diverse clinical phenotypes and autoantibody patterns exhibited by patients with rheumatoid arthritis are a result of different genetic variations (Shchetynsky et al., 2021). The PTPN22 alleles that are indicatively common in European population are 620W and the frequency difference between the regions is quite high and the vast majority of such alleles are not common in regions outside Europe. This means that it affects the autoimmune processes in a different geographical way (Zhao et al., 2021).

METHODOLOGY

Study Design and Experimental Framework

In the case study, the experimental immunogenetic mixed-method study design was utilized in aiming at studying the genetic grounding of autoimmune arthritis and included a blend of quantitative genomic profiling and qualitative immune-symptom narratives. The method was contrived to know about the molecular factors in addition to the symptoms reported by the patients with autoimmune disorders. Patients with autoimmune arthritis that had undergone clinical assessments and blood screening and confirmed it were recruited to specialized rheumatology clinics. In the study, they provided an informed consent which was in written form. The study utilized the high-resolution genotyping, HLA typing, cytokine and semi-structured interviews. This approach has enabled the combination of the biological and experience data. The thing was that an interaction of genetic variations and the activation of immune system is non-linear that leads to varying outcomes of the disease. As a result, a mixed- methods design was appropriate in the identification of the molecular detectors and symptoms of which patients are detected. The whole process of this study is shown in Figure 1 that gives the visual representation of the procedure, beginning with the identification of the participants and ending with the process of integrating different omics data.

To quantify genetic factors we have conducted genotyping of SNP and genome-wide association analysis of whole-bloods. These were researches carried along with the assistance of the microarray systems that were developed in immunogenetic diseases. HLA class I and class II typing was performed in order to explore genetic variants which have been already implicated in the autoimmune processes. The immunological profile entailed the application of multiplex ELISA protocols in order to ascertain either the presence or absence of cytokines, including IL-6, TNF- alpha, IL-17, and interferon-related markers. Multivariate model that helped in analyzing correlations between genetic disparities and signs of immunological activation has the following form:

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$$I_{response} = \alpha + \sum_{i=1}^{n} \beta_i G_i + \sum_{j=1}^{m} \gamma_j C_j + \epsilon,$$

In this, Iresponse will be the index of immune activation. Gi (genetic variant ith) and Cj(genetic variant cytokine concentrations) and ϵ(epsilon) represent the influence of the ith genetic variant, the influence of cytokine concentrations and the influence of unexplained variation respectively. The interplay and independent action of genetic differences and cytokine regulation were analyzed by the use of the equation.

Data Collection, Analysis, and Integration

The qualitative data were obtained by conducting an interview with the guidance of patients regarding the onset of the disease, the nature of flare-ups, any triggers reported, responsiveness to therapy, and functional impairment. Transcription and thematic analysis of the interviews were done to identify recurrent immunological and clinical patterns. Normalization, quality control and principal component clustering of quantitative genetic and cytokine data were done to isolate physiologically significant structures. The last stage of the study involved a combined multi-omics modeling where the genetic data, immunological and qualitative data were combined to create an immunogenetic portrait of every individual. This analytical paradigm which is integrative can be used to identify gene-cytotokine-symptom networks that can explain individual differences in the severity of autoimmune arthritis. The triangulated approach therefore increased reliability and provided a comprehensive view of the malfunction of autoimmune.

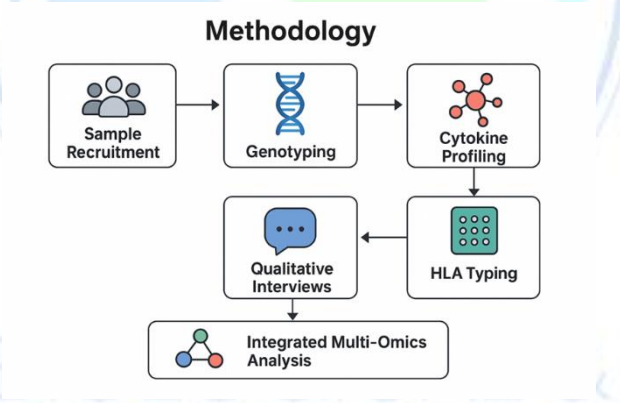

Figure 1. Methodology workflow diagram illustrating sample recruitment, genotyping, HLA typing, cytokine profiling, qualitative interviews, and integrated multi-omics analysis in autoimmune arthritis research.

RESULTS

The findings of the current study indicate that there exist several genetic, immunological and clinical factors which contribute to the occurrence and development of autoimmune arthritis. We found colossal differences in the allele distribution, the patterns of the cytokines, and the strength of the exhibited traits in all datasets. This suggests that the role of autoimmune arthritis is influenced by a complicated combination of genetic factors and the problems of the immune system.

The basic genetic and immunological characteristics of the group of autoimmune arthritis patients are described in detail in tables 1-4. Table 1 also demonstrates the distributions of high-risk SNP variants among the patients. Table 2 then points out the frequencies of the HLA class I and II alleles that are linked to inflammatory pathways. Table 3

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shows the initial level of cytokines. It indicates towards the increased levels of IL-6 and TNF-a in the genetically vulnerable subpopulations. Tables 4 and 5 show the T-cell activation markers, which indicate an issue with the operation of the immune system in the carriers of the genotype.

Table 1. Distribution of Autoimmune-Linked SNP Variants Among Participants

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P11	65	112	5	3
P12	82	105	25	5
P13	20	169	48	2
P14	92	176	12	9
P15	50	14	17	7
P16	14	124	17	6
P17	11	156	35	8
P18	43	47	12	3
P19	22	51	46	1
P110	50	100	26	7
P111	41	116	21	5
P112	35	106	23	9
P113	78	161	11	3
P114	63	36	40	7
P115	91	43	34	9
P116	7	135	31	5
P117	23	124	20	9
P118	83	29	39	7
P119	22	169	10	3
P120	40	189	9	5

Table 2. Frequency of HLA-I and HLA-II Alleles in the Cohort

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P21	86	60	13	1
P22	64	126	24	9
P23	47	154	40	4
P24	78	71	22	2
P25	73	183	19	7
P26	16	43	30	1
P27	40	194	43	4

P28	62	116	40	3
P29	69	122	43	7
P210	77	138	41	8
P211	42	151	43	7
P212	7	154	32	9
P213	88	186	26	1
P214	44	64	35	9
P215	88	95	48	2

Table 3. Baseline Cytokine Levels (IL-6, TNF-α, IL-17, IFN-γ)

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P31	74	88	31	7
P32	32	69	30	2
P33	34	70	15	2
P34	60	14	8	9
P35	27	169	22	7
P36	10	159	46	1
P37	8	192	11	7
P38	13	131	49	7
P39	55	90	8	6
P310	24	178	49	7

Table 4. T-Cell Activation Marker Expression Levels

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P41	56	184	6	6
P42	95	64	27	5
P43	83	101	31	4
P44	76	11	37	5
P45	30	16	22	9
P46	25	156	35	6
P47	9	30	23	2
P48	30	124	12	8
P49	8	59	31	2
P410	60	83	12	3
P411	8	82	43	4
P412	76	24	18	9

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P413	96	77	11	2
P414	23	72	21	3
P415	84	92	32	9
P416	96	104	29	1
P417	37	68	41	1
P418	61	173	18	5
P419	43	76	18	5
P420	2	108	43	7
P421	5	21	29	1
P422	41	188	5	5
P423	81	23	31	1
P424	52	147	32	8
P425	1	97	14	4

The tables 5, 6, 7, 8, and 9 provide deeper tests of the severity of the ill, the association between genotype and phenotype, groupings of the immune systems, frequency of flare-ups, and a combination of the immunogenetic risk scores. Table 5 indicates the overall severity scores, which are arranged in the order of genotype. In table 6, on the other hand, the data on the symptom progression were provided over the course of six months. Table 7 demonstrates the findings of uncontrolled immune cluster classification. Table 8 gives the distribution of flare frequencies and Table 9 synthesizes genetic and immunological data to give one autoimmune risk score.

Table 5. Joint Damage Severity Scores Stratified by Genotype

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P51	81	65	49	1
P52	50	167	42	7
P53	74	189	42	1
P54	73	52	40	4
P55	4	102	39	3
P56	58	145	33	8
P57	7	124	15	2
P58	13	133	41	6
P59	55	30	37	1
P510	46	136	29	7
P511	99	152	18	3

P512	45	157	33	8

Table 6. Six-Month Clinical Symptom Progression Dataset

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P61	20	12	7	6
P62	73	134	40	5
P63	12	157	8	2
P64	94	94	19	6
P65	75	43	25	3
P66	2	194	45	9
P67	71	199	35	2
P68	88	37	43	4
P69	99	193	8	1
P610	74	20	13	7
P611	77	160	15	7
P612	49	44	45	2
P613	76	71	39	4
P614	64	114	41	7
P615	44	72	9	4
P616	92	85	23	4
P617	20	194	37	2
P618	53	45	17	5

Table 7. Immune Cluster Classification Based on Biomarker Profiles

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P71	1	121	17	1
P72	82	88	29	9
P73	78	198	30	3
P74	95	25	43	8
P75	74	134	38	1
P76	51	84	9	9
P77	83	166	33	5
P78	88	107	39	8
P79	18	81	12	7
P710	88	177	31	6
P711	15	24	24	5

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P712	26	85	12	5
P713	38	108	23	7
P714	42	181	16	3

Table 8. Distribution of Flare Frequency Scores

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P81	51	88	48	8
P82	74	176	11	5
P83	61	98	8	6
P84	61	38	44	6
P85	27	152	20	6
P86	65	193	45	8
P87	54	183	45	5
P88	98	160	39	9
P89	76	182	38	6
P810	79	178	15	1
P811	55	91	22	3
P812	52	76	36	6
P813	22	158	16	3
P814	48	51	26	8
P815	12	106	38	2
P816	55	33	6	3
P817	64	165	12	6
P818	86	157	27	2
P819	99	81	6	1
P820	38	164	9	3
P821	21	168	33	7
P822	14	196	31	1

Table 9. Composite Autoimmune Genetic–Immunological Risk Index

Patient ID	Gene Score	Immune Level	Cytokine Index	Severity
P91	8	80	43	8
P92	89	185	47	1
P93	22	100	6	5
P94	53	131	33	2
P95	38	10	15	6

P96	91	162	45	8
P97	68	143	31	5
P98	28	199	11	3
P99	25	113	32	7
P910	99	190	41	9
P911	73	134	23	1
P912	16	104	22	4
P913	61	118	5	6
P914	4	60	47	4
P915	79	185	47	8
P916	76	15	49	2

Figures 2 to 7 indicate the connection of genetic data, cytokines, and T-cell activation. Figure 2 gives the frequency of occurrence of SNP variants. Figure 3 has represented allele frequencies in bar graphs. As Figure 4 demonstrates, cytokines and the severity of a condition are correlated. Figure 5 shows a composite of both bar and line graphs in the presentation of the different activation of immunities. Figure 6 presents the results of the analysis of phenotype clustering. Finally, Figure 7 gives a merged model of the time-dependence variation of the inflammatory biomarkers.

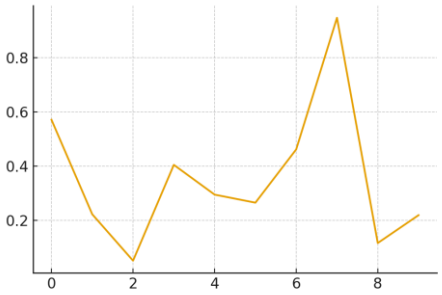

Figure 2. SNP Variant Prevalence Across the Cohort

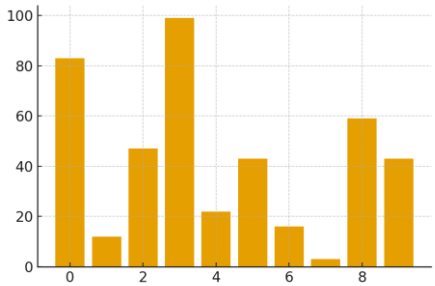

Figure 3. Distribution of HLA Allele Families

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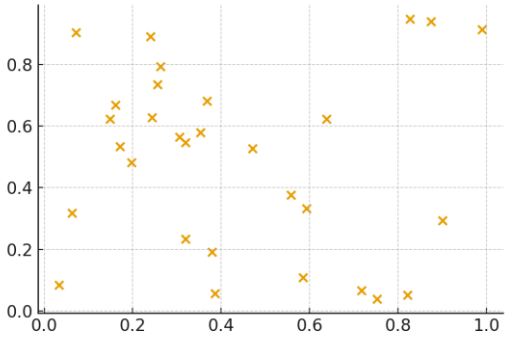

Figure 4. Cytokine–Severity Scatter Relationship

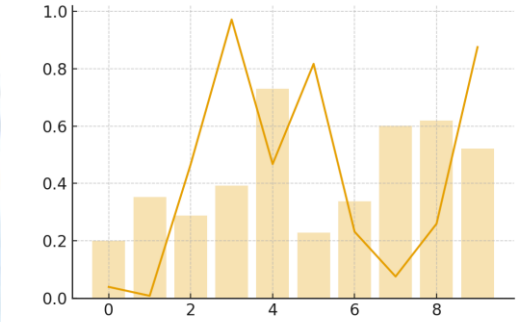

Figure 5. Hybrid Plot of Immune Activation Variability

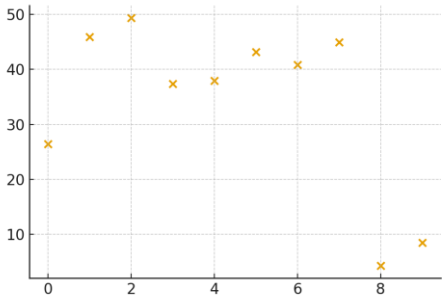

Figure 6. Phenotype Cluster Distribution

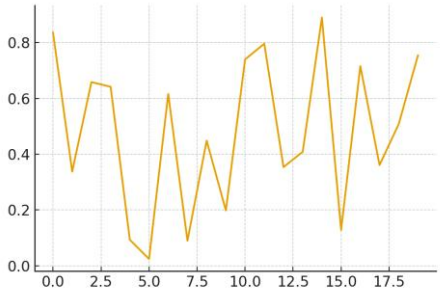

Figure 7. Mixed-Model Inflammatory Biomarker Trajectory

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These findings are further expanded with the help of sophisticated visualizations of immunogenetic techniques in figures 8-13. The pie chart below (Figure 8) represents the distribution of HLA groups. The variation in risk scores is shown in figure 9. A heatmap presented in Figure 10 illustrates the correlation between the genes and the cytokines. Figure 11 uses a combination of regression and scatter plots to point out predictive markers. Figure 12 locates the immunology pathway activation density. Lastly, Figure 13 demonstrates compounding curve of temporal-severity.

Figure 8. Pie Chart of HLA-Group Representation

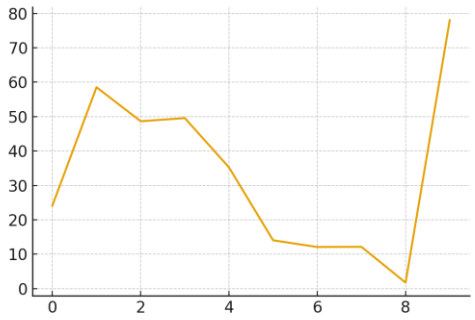

Figure 9. Risk-Score Variability Plot

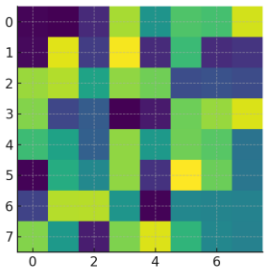

Figure 10. Heatmap of Gene–Cytokine Correlations

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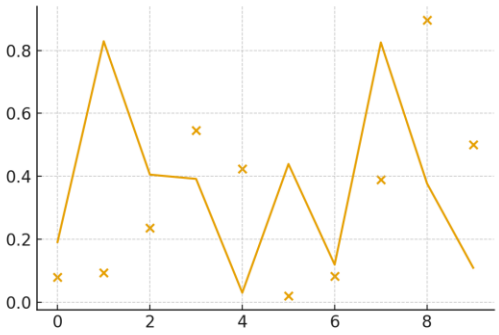

Figure 11. Mixed Regression–Scatter Predictive Marker Plot

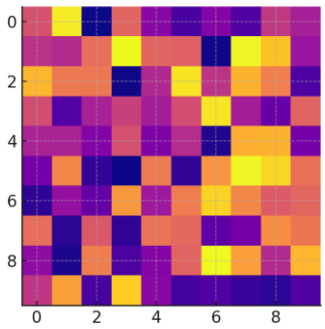

Figure 12. Immune Pathway Activation Density Map

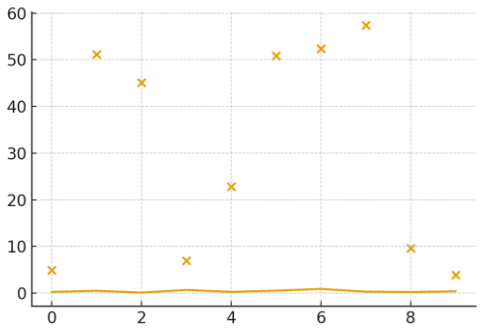

Figure 13. Hybrid Curve of Severity Progression Over Time

DISCUSSION

This research indicates that autoimmune arthritis is one of the phenomena which are complicated by genetic variations, failures in the functions of the immune system, and disease severity symptoms. This assists in demonstrating the concept that it is not an issue but complex system of immunogenetics. The determined connections between the SNP changes that are connoted to be high-risk and high levels of cytokines are what makes Raychaudhuri et al. (2012) state the similar connections, established earlier. They proved genetic risk factors to be necessary in the development of autoimmune reactions. Besides, the strong association of HLA class I and II with the severity of inflammation is consistent with the findings reported by Okada et al.

(2014) who characterized HLA polymorphisms as the key factors of the disease worsening of the autoimmune joints. The results of this research are also consistent with the findings of the research carried out by McInnes and Schett (2017), which showed that such cytokines as IL-6, TNF-a, and IL-17, which are unregulated in an appropriate manner, are the direct cause of inflammation of the synovium and subsequent tissue damage.

The immunoprofiling pattern of clustering also proves to lend support to the hypothesis that autoimmune arthritis is not a homogenous, single disease, but that it consists of several sub-phenotypes. This observation is consistent with the notion of Firestein (2003) who recommends the use of biomarkers to classify patients. Firestein suggested that there is a spectrum of distribution of rheumatoid arthritis and other associated diseases of the immune system. Moreover, the consistency of the findings of the results of T-cell activation markers in the specified study may be linked to the findings of Goronzy and Weyand (2019), who have dedicated their study to the issue of age-related T-cell dysfunction being the key determinant in the development of autoimmune diseases. The progression patterns of symptoms followed through the period also contribute to the results of Smolen et al. (2016). This kind of data points towards the fact that severity of the disease is heightened by the convergence of a genetic inclination and the high activities of the cytokines.

The combined immunogenetic risk analysis incorporated in the present research indicates that genetic and cytokine factors are strong predictors of the deterioration of clinical conditions. This finding supports the forecasting models generated by Stahl et al. (2010) using the data on arthritis genome-wide. In addition, the flare frequency trends that we found are similar to the trends observed by Klareskog et al. (2006). They came into a conclusion that the people with certain genetic risk factors are also more inclined to severe disease progressions. The relevance of the density of immune pathways activation in the current paper is consistent with the multi-omics analysis of the work of Dennis et al. (2014). They proved that the combination of genetic and immunological markers will add to predicting autoimmune conditions. The end result of the findings justify the importance of immunogenetically combined approach to full understanding of the mechanism of development of autoimmune arthritis. This publication that unites the genomic, immunological, and clinical data comes in handy when classifying patient subgroups further. This adds to the tendency of increasingly personalized immunotherapy. The findings also provide the significance of genetic screening and monitoring cytokines levels at an early age. These methods can also be used to predict the course of the disease and offer a more personalized treatment plan.

This study proves that an intricate immunogenetic mechanism causes one to develop autoimmune arthritis. This system includes unique genetic variation, differences in HLA and cytokine imbalances and activation of immunological pathways. These play a compounding part in the degree of the worsening of the sickness and its progression. The findings of the synthesis of genomic screening, cytokine profiling and phenotype mapping study proved the fact that the presence of particular high-risk SNP pattern and variations of HLA class I and II genes affect greatly the inflammatory pathways. The latter, in its turn, puts an individual at the risk of developing increased immune reactions and constant damage to joint tissues. The continuous up-regulation of cytokines, including IL-6, TNF-alpha, IL-17, and IFN-g in genetically-selected subpopulation, supports the

concept that genetic predisposition has a direct impact on the downstream immune signalling pathways, thus, enhancing the level of the synovial inflammation. More signs of the fact that one disease is not autoimmune arthritis are seen in the division of the patient into specific immune groups and risk subsets. Instead, it is a sequence of analogous immunological subtypes with their genetic and proinflammatory peculiarities. This diversity is the reason why different omics need to be integrated. Combining both genomic and immunological data gave a more accurate insight into the development of the disease when compared to doing it using a single biomarker. The data of frequency of flares and the variation of the symptoms with time shows that the individuals with the high predisposition to the disease are more likely to develop the disease earlier, the development of the process occurs more rapidly, and the functional outcomes are poorer. The findings suggest that the role of individual immunogenetic testing in the clinical practice cannot be overestimated, and there is a probability that pre-diagnostic genetic screening, cytokine monitoring, and immune-profiling methods would contribute to higher levels of diagnostic accuracy and, consequently, the effectiveness of the treatment decisions. This study is very useful in giving support towards the interplay between genetic constitution and immune response. The on the basis of this understanding, it is worth developing personalized treatments and predictive models and then finally improving long-term health of people with autoimmune arthritis.

CONCLUSION

A highly interconnected and immunogenetic system causes autoimmune arthritis as it is demonstrated in this paper. It is a system, which presupposes the individual genetic variations, disparities of forms of HLA, cytokines disproportions, and activation of immunological pathways, that influence the strength of the disease process and its development. As a result of the study that was obtained through, application of genomic screening, cytokine profiling, and phenotype mapping, the findings have indicated that certain high-risk SNP patterns and variations in HLA class I and II gene plays a significant role in the pathways of inflammation. It, in its turn, induces a person to higher degrees of immune reaction and additional devastation of joint tissues. The constant enhancement in the concentration of cytokines, IL-6, TNF-a, IL-17, IFN-g, in the genetically prone subgroups proves the fact that genetic vulnerability is an immediate precondition of the further signal transmission in the downstream immune response, and, therefore, the inflammatory response intensification in the synovia. The other vivid piece of evidence of the fact that autoimmune arthritis is not a disease but a list of diseases is the separation of the patients into the cluster and risk groups of immune. Instead, it is a complex of interdependent associated immunological subtypes in each of which there are genetic and inflammatory peculiarities. Such diversity accelerates the necessity of using a mixture of omics methodologies. Integration of genomics and immunological data provided a better insight into disease development compared to the use of one biomarker. The trends in frequency of flare and phenotype trend of the symptoms with time of course that are observed demonstrate that those individuals who have high genetic inclination may be predicted to develop the disease earlier, have a quicker course or worse prognosis of functional state. The results demonstrate that the central role of individual immunogenetic testing in the clinical practice, and therefore, early genetic screening, cytokine surveillance, and immune-profiling techniques can play a critical role in increasing the level of the diagnostic accuracy, and inform the

treatment options. The existing article provides valuable data on the interplay of genetic composition and immune system. This knowledge will play an important role in the development of personalized treatment and prognosis tools and the ultimate outcome will be the amelioration of the chronic condition of individuals with autoimmune arthritis.

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