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Integration of genomic databases and bioinformatic approach to identify genomic variants for sjogren's syndrome on multiple continents

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ABSTRACT

An autoimmune disorder is an abnormality that causes a disease. It is caused by a weakened immune system. One of the autoimmune diseases is Sjogren's syndrome, which affects the salivary and lacrimal glands and causes dry mouth, dry eyes, and dry skin. Sjogren's syndrome influences humans of every age, with the symptoms occurring at the age of 45–55 years and rarely in children. One of the factors causing Sjogren's syndrome is genetic disorders. To identify genes that can influence Sjogren's syndrome in this study, we used several databases, including GWAS Catalog, HaploReg Version 4.1, GTEX portal, and Ensembl, particularly to identify the gene expression profiles of *TNIP1*, *TNFAIP3,* and *IRF5* and the quantitative properties of locus' expression. This research showed that the missense variants and splice donor rs2233290, rs2230926, and rs2004640 influenced the susceptibility of autoimmune diseases, especially Sjogren's syndrome, in the fibroblast tissue, sigmoid tissue, sigmoid colon, skin, esophagus, and adrenal glands. The allele frequency of each variant was then assessed in African, American, European, and Asian populations. Our data showed that *TNIP1, TNFAIP3,* and *IRF5* genes in African and American populations had higher frequencies than in the Asian population. This implies that the last of the aforementioned populations might be relatively susceptible to the autoimmune disease Sjogren's syndrome.

1. Introduction

Sjogren's syndrome is an autoimmune condition characterized by the lymphocytic infiltration of the exocrine glands, causing dysfunction and destruction. The salivary and lacrimal glands are most affected, giving rise to dry eyes and mouth. Sjogren's syndrome is associated with an increased risk of lymphoid malignancies (Rhodus, 2017). Sjogren's syndrome is classified into primary Sjogren's syndrome and secondary Sjogren's syndrome, occurring with other systemic autoimmune diseases, most commonly rheumatoid arthritis, systemic lupus erythematosus, or scleroderma (Rhodus, 2017).

The prevalence of primary Sjogren's syndrome less often happens, occurring in 61/100.000 of populations, with the highest prevalence being in Europe (Qin et al., 2015). Meanwhile, secondary Sjogren's syndrome happens more often, assumed at least in 0.4% of populations (Qin et al., 2015; Stefanski et al., 2017).

Sjogren's syndrome is caused by several factors, including genetics and environment (Ciccacci et al., 2019). Many genetic factors have been identified to be related to susceptibility to autoimmune diseases although, until recently, the number of loci related to Sjogren's syndrome was much lower (Teos & Alevizos, 2017). The use of drugs, smoking, stress, and diabetes are common causes of non-specific dryness symptoms. The development of Sjogren's syndrome affects groups of people of all ages, with symptoms appearing at the age of 45–55 years and rarely occurring in children (Alani et al., 2018). Women experience Sjogren's syndrome more often than men, with the first symptoms occurring many years before diagnosis (Stefanski et al., 2017).

Some of Sjogren's syndrome symptoms also frequently occur in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (Burbelo et al., 2014). Therefore, to detect the symptoms of Sjogren's syndrome specifically, one can have a deoxyribonucleic acid (DNA) examination. Gene variation frequently links disease progression and pathogenesis, including Sjogren syndrome. One website that covers gene variation is Genome-Wide Association Studies (GWAS) (Furqan et al., 2020). GWAS is a database with single nucleotide polymorphism (SNP) search results in the genomes of several humans as genetic markers that are used in predicting a disease disorder (Bush & Moore, 2012). The collection of databases from the GWAS Catalog is very useful for identifying the SNP type responsible for Sjogren's syndrome.

Human genetic identification aims to identify inherited genetic risk factors for diseases such as Sjogren's syndrome. Despite extensive research into the underlying causes of Sjogren's syndrome, this disease remains unclear. Broadly, its pathogenesis is multifactorial; environmental factors are thought to trigger the appearance of Sjogren's syndrome symptoms in individuals with a genetic predisposition for the disorder (García-Carrasco et al., 2006). Therefore, this research tried to map the types of genes from gene variations in several populations that play an important role in the pathogenesis of Sjogren's syndrome by utilizing the GWAS database. The end of this research will prioritize the most influential gene variations based on function in protein changes.

2. Materials and Methods

An overview of the research design is shown in Figure 1. Sjogren's syndrome-associated SNPs were obtained from the National Human Genome Research Institute (NHGRI) GWAS Catalog database http://www.ebi.ac.uk/gwas (access date 2021-12-1) and developed using HaploReg (version 4.1). The p-value < 10^{-8} threshold was employed to establish statistical significance with a GWAS catalog inclusion requirement, which could limit the discovery of false positive associations (Chen et al., 2021). To examine further whether the prioritized genetic variant showed a clinical significant correlation. From HaploReg (version 4.1) data, we found a missense or nonsense gene mutation. To evaluate genetic variant and gene expression profile, expression quantitative trait locus (e-QTL) analysis of Sjogren's syndrome was carried out using the GTEX http://www.gtexportal.org/home/ (access date 2022-02-23) database, which compiles gene expressions in some tissues. The genetic variation of Sjogren's syndrome was obtained from the GTEX portal database and confirmed by Ensembl Genome Browser http://www.ensembl.org/index.html_(access date 2022-02-23). Allele frequencies among European, African, American, and Asian populations were extracted from Ensembl Genome Browser (access date 2022-02-23) http://www.ensembl.org/Homo_sapiens/Variation. Annotation, such as location or variant type, was taken from Ensembl Genome Browser (access date 2022-02-23) http://www.ensembl.org/Homo_sapiens/Variation. A similar method was used by Irham LM et al. to identify genomic variants for the *TMPRSS2* gene in COVID-19 (Irham et al., 2020).

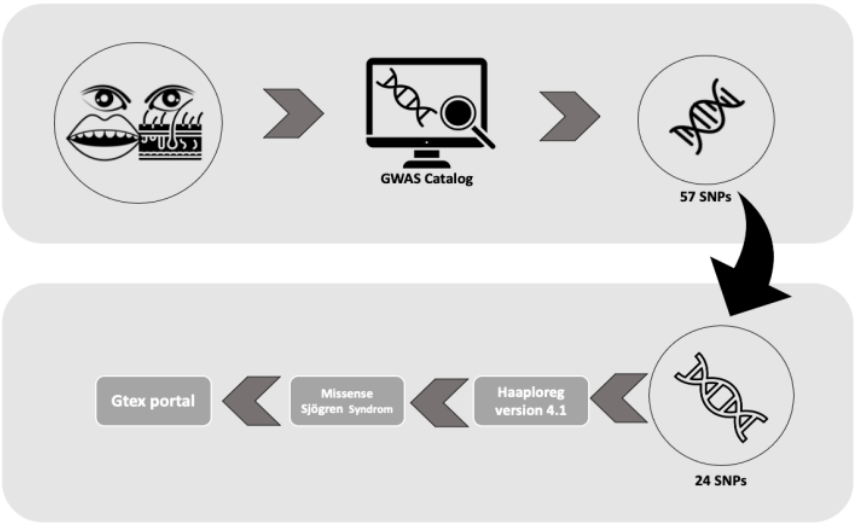

Fig 1. This schematic model shows that genome-based information can be integrated into genes influencing Sjogren's syndrome

3. Results and Discussion

3.1. Identification of Genomic variants of Sjogren's-syndrome

We obtained Sjogren's syndrome-associated SNPs through the GWAS Catalog database. Fifty-seven Sjogren's syndrome-associated SNPs were collected (**Supplementary Table 1**). We finally obtained 24 Sjogren's syndrome-associated SNPs with the removal of duplicate SNPs (**Table 1**). Then, the number of SNPs was expanded using HaploReg ver. 4.1, with a *p*-value of $< 10^{-8}$, and as a result, three Sjogren's syndrome risk genes were obtained.

In this study, we examined the expression of tissues influencing Sjogren's syndrome with missense variants (*TNIP1* and *TNFAIP3*) and splice donor interferon regulatory factor 5 (*IRF5*). Sjogren's syndrome is characterized by the dysfunction of the exocrine glands, causing functional impairments such as dry eyes, dry mouth, and dry skin (Kittridge et al., 2011). Genes that influence Sjogren's syndrome, *TNIP1,* and *TNFAIP3*, have recently been reported to be potential in various autoimmune diseases (Shamilov & Aneskievich, 2018) (Table 2). An autoimmune disease is a complex disease characterized by persistent or repeated inflammation, changes in immune response, and specific autoantibody production (Ciccacci et al., 2019). *TNIP1* can be associated with increased activation of immune cells and infiltration, leading to tissue-specific defects. It functions as a negative modulator downstream of certain cell membrane receptors, and its dysfunction may lead to the initiation and preservation of the autoimmune phenotype (Shamilov & Aneskievich, 2018).

This autoimmune disease has several clinical characteristics and some loci are at risk with susceptibility to Sjogren's syndrome. The GWAS reported the correlation of tumor necrosis factor, alpha-induced protein 3 genes (*TNFAIP3*) with Sjogren's syndrome (Ciccacci et al., 2019). *TNFAIP3* codes a protein named A20, which is the negative regulator of NF-kappa b. Its drawback in immune cells has been linked to inflammation and autoimmunity associated with Sjogren's syndrome (Catrysse et al., 2014). Besides, the locus related to Sjogren's syndrome is the *IRF5* at the 7q32 chromosome, which is also related to primary Sjogren's syndrome (Burbelo et al., 2014; Nordmark et al., 2009; Shamilov & Aneskievich, 2018).

Table 1. GWAS catalog result the duplicates removed are obtained 24 SNPs with signification $<10^{-8}$

Variant and risk allele	*p*-value
rs7574865	2×10^{-8}
rs17074492	6×10^{-8}
rs7119038	1×10^{-8}
rs6579837	3×10^{-8}
rs6933404	7×10^{-8}
rs5029939	8×10^{-9}
rs4731532	1×10^{-9}
rs11889341	9×10^{-10}
rs485497	1×10^{-10}
rs2736345	5×10^{-10}
rs56036302	6×10^{-10}
rs3823536	7×10^{-11}
rs10553577	7×10^{-15}
rs117026326	1×10^{-15}
rs17339836	2×10^{-16}
rs10168266	2×10^{-17}
rs3757387	3×10^{-19}
rs4282438	9×10^{-25}
rs2523571	6×10^{-28}
rs9271573	3×10^{-34}
rs9271588	9×10^{-37}
rs116232857	1×10^{-96}
rs3135394	5×10^{-113}
rs115575857	8 x 10-114

Table 2. Varian risk allele which codes three gen

Variant risk allele	variants near risk allele $r^2 > 0,8$	*p*-value	Gencode	Allele location
rs6579837	rs2233290	3×10^{-8}	*TNIP1*	Missense
rs5029939	rs2230926	8×10^{-9}	*TNFAIP3*	Missense
rs4731532	rs2004640	1×10^{-9}	*IRF5*	Splice donor

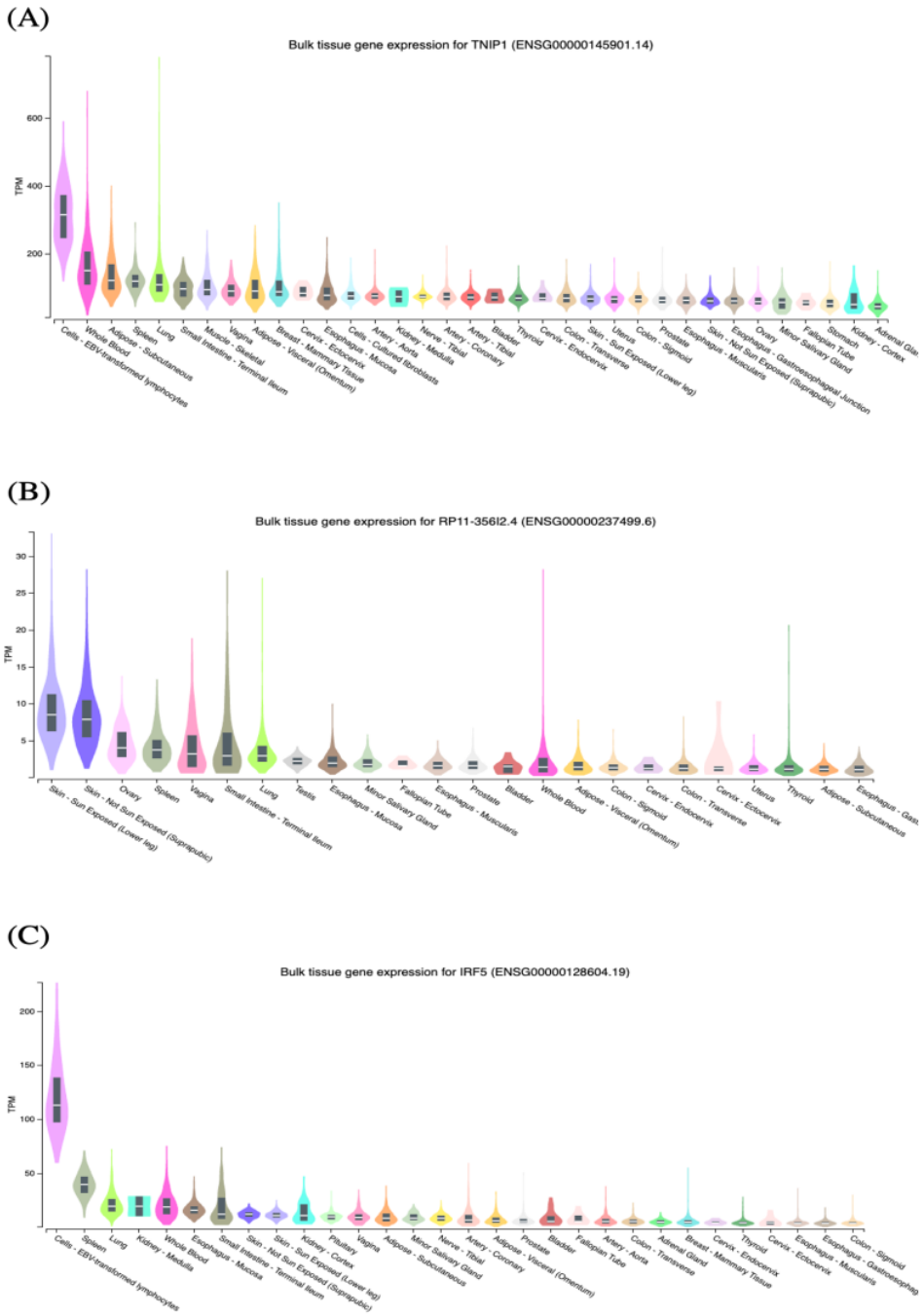

Fig. 2. Expression of SNPs associated with Sjogren's syndrome in different human tissue according to the database GTEX portal; TNIP1 (A), RP11-356I2.4 (B), IRF5 (C)

3.2. Sjogren's syndrome gene expression in various tissues

To evaluate the genetic variation of Sjogren's syndrome in human tissues, we used expression quantitative trait loci (eQTL) via the GTEX portal database http://www.gtexportal.org/home/ (access date 2022-02-23), which contains the expression levels of genes in various tissues. eQTL analysis requires genetic markers that can be genotyped in all individuals in the analyzed population. The observed eQTL represents the position of a locus controlling the expression of target genes (Yao et al., 2017). The database found three gene symbols, *TNIP1, RP11-356I2.4 (TNFAIP3)*, and *IFR5*, which showed expression in the skin and mucosa. *RP11-356I2.4* regulates *TNFAIP3* and correlates highly with the predicted *TNFAIP3* target genes (Lei et al., 2017). The skin and mucosa are closely related to complaints often expressed by patients with Sjogren's syndrome. We used publicly available databases to examine the genetic variant of Sjogren's syndrome. Genes related to Sjogren's syndromes such as *TNIP1*, *TNFAIP3,* and *IRF5,* which influence the occurrence of this autoimmune disease, can especially explain other symptoms of Sjogren's syndrome, such as dry eyes, dry mouth, and dry skin (Burbelo et al., 2014; Rhodus, 2017; Shamilov & Aneskievich, 2018).

3.3. The correlation between gene expression and eQTL

Besides, to identify the eQTL associated with the gene expression of Sjogren's syndrome, the publicly available GTEX portal database was used. We identified minor alleles rs2233290, rs2230926, and rs2004640 at *TNIP1*, *RP11*, and *IRF5*, respectively, were linked to Sjogren's syndrome. As shown in Table 3 and Figure 3, the GG genotype of rs2230926 was associated with a higher expression of *TNIP1* in the fibroblast culture tissue and the sigmoid colon compared to the CC genotype. Meanwhile, the TT genotype of rs2230926 had a higher expression of *RP11* in the skin than the TG and GG genotypes. In the rs2004640, the TG genotype showed a higher expression in *IRF5* in the esophagus (mucosa-muscularis-gastroesophageal junction) and in the adrenal glands than the other genotypes, TT and GG.

Table 3. e-QTL's result for the Sjogren's syndrome from GTEX portal database

ID SNP	Gencode ID (ENSG000 00-)	Gene Symbol	*p*-value	Effect size	Tissue	Actions
rs2233290	145901.14	*TNIP1*	1.3e-7	0.24	Cells - Cultured fibroblasts	GG>GC>CC
	145901.14	*TNIP1*	0.0000046	0.23	Colon - Sigmoid	GG>GC>CC
rs2230926	237499.6	*RP11*	0.000026	0.24	Skin - Sun Exposed (Lower leg)	TT>TG>GG
	237499.6	*RP11*	0.000098	0.23	Skin - Not Sun Exposed (Suprapubic)	TT>TG>GG
	128604.19	*IRF5*	5.6e-41	-0.40	Esophagus - Mucosa	TG>TT>GG
	128604.19	*IRF5*	9.2e-18	-0.23	Esophagus - Muscularis	TG>TT>GG
rs2004640	128604.19	*IRF5*	1.2e-15	-0.33	Adrenal Gland	TG>GG>TT
	28604.19	*IRF5*	5.7e-8	-0.18	Esophagus - Gastroesophageal Junction	TG>TT>GG

This research found that three variants—rs2233290 at *TNIP1*, rs2230926 at *TNFAIP3*, and rs2004640 at *IRF5*—were related to Sjogren's syndrome. Furthermore, rs2233290 coded the missense mutation, and the GG genotype had the highest expression of *TNIP1* in fibroblast culture cells and the sigmoid colon, with the heterozygote GC carrier showing middle expression and the CC genotype showing the lowest expression (Figure 3). Based on this discovery, rs2233290 was potentially linked to susceptibility to Sjogren's syndrome. We hypothesized that the CC genotype, with the highest expression of rs2233290, might be associated with higher susceptibility to Sjogren's syndrome. The research by Gregersen et al. (Gregersen et al., 2012) showed that the rs2233290 SNP influenced autoimmune diseases such as systemic lupus erythematosus and systemic sclerosis.

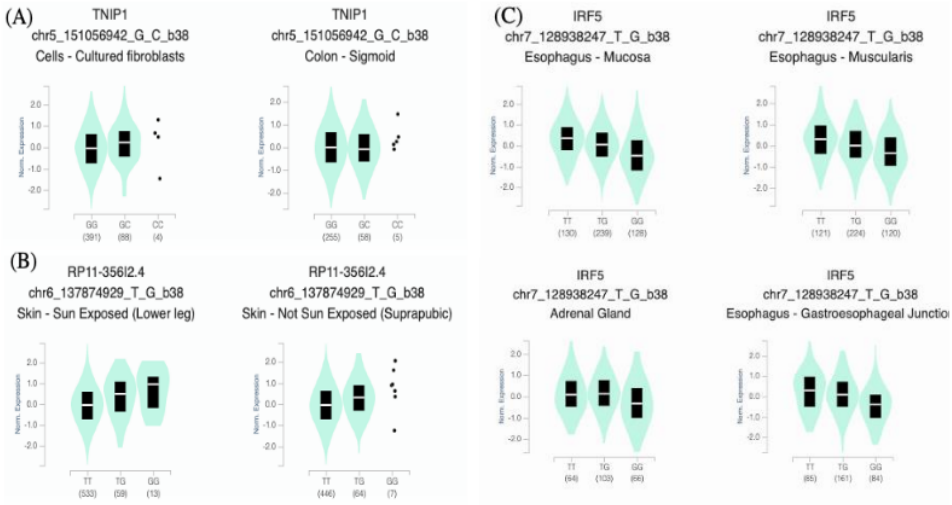

Fig. 3. Plot show the expression of SNPs for each genotype; rs2233290(A), rs2230926(B), rs2004640(C)

Moreover, previous research claimed that rs2230923 is associated with increased susceptibility to Sjogren's syndrome in younger patients (< 40 years) with lymphoma complications (Nezos et al., 2018) and rheumatoid arthritis (Hao et al., 2014). The SNP we found linked with the Sjogren's syndrome rs2230926 had a higher expression in the skin of the homozygous TT genotype compared to heterozygous TG (intermediate expression) and homozygous GG (lowest expression). Meanwhile, in other research, rs2004640 is associated with susceptibility to other autoimmune diseases, like systemic sclerosis (Dieudé et al., 2009). The rs2004640 SNP associated with Sjogren's syndrome showed a higher expression of TG heterozygous genotype of *IRF5* in the esophagus and adrenal glands than GG homozygous (intermediate expression) and TT homozygous genotypes (lowest expression).

3.4. **The allele frequencies of the candidate variants in different populations**

After identifying variants related to Sjogren's syndrome expression, we were interested in knowing allele frequencies in diverse populations. As shown in Table 4, allele variant frequencies were evaluated in diverse populations from Europe, America, East Asia, South Asia, and Africa. The allele frequencies were extracted from Ensembl Genome Browser http://www.ensembl.org/Homo_sapiens/Variation (access 2022-02-23). The allele frequencies across the populations differed for each SNP, as shown in Table 4 and Figure 4. The frequency of the C allele at rs2233290, which is associated with high expression in *TNIP1* in Sjogren's syndrome, was much lower in the East Asian (0%) population than in South Asians (5%), Europeans (8%),

Americans (9%), and Africans (21%). The G allele's frequency at each of rs2230926 (*TNFAIP3*) and rs2004640 *(IRF5*) was lower in European population (rs2230926 2% and rs2004640 47%) than in populations in South Asia (rs2230926 3% and rs2004640 49%), East Asia (rs2230926 5% and rs2004640 75%), America (rs2230926 8% and rs2004640 63%), and Africa (rs2230926 41% and rs2004640 60%) (Figure 4). Overall, the allele variants (rs2233290, rs2230926, and rs2004640) were linked to Sjogren's syndrome, showing a lower frequency in European populations than in African and American populations. Thus, African and American populations were possibly linked more to *TNFAIP3* and *IRF5* expressions and consequently to higher susceptibility to Sjogren's syndrome. Genomic variants are not only important for the identification of susceptibility of the disease but also it can be used to drive drug discovery (Adikusuma et al., 2021, 2022; Irham et al., 2020, 2022).

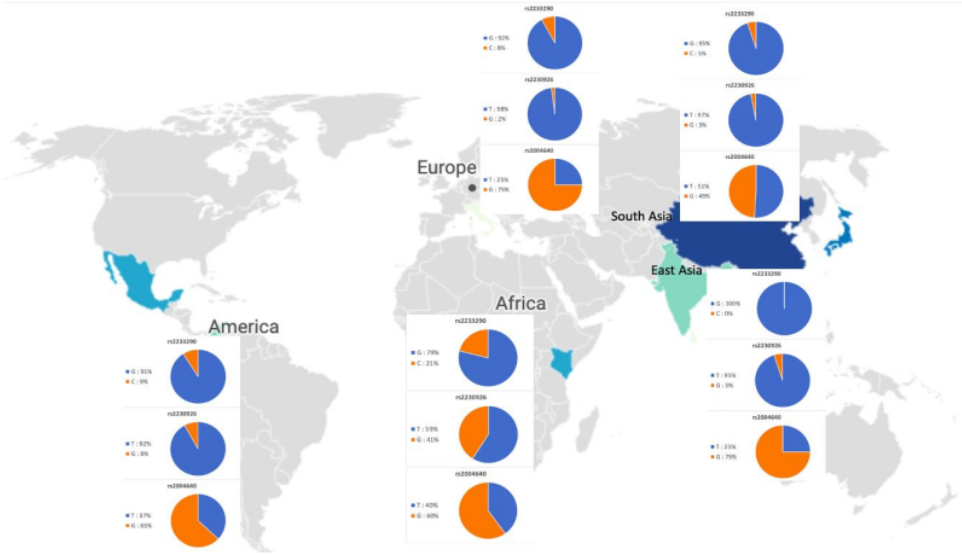

Fig. 4. The distribution of allele frequencies influences *TNIP1, TNFAIP3*, and *IRF5* in various populations. EUR, European; AFR, African; SAS, Southeast Asian; EAS, East Asian. Shows the distribution of three variants (rs2233290, rs2230926, dan rs2004640)

Table 4. Allele frequencies for SNPs examined in this study

SNP	Position	Gene	Location	Allele		Allele Frequencies (N)				
				Ref	Eff*	AFR	AMR	EAS	EUR	SAS
rs2233290	Chr 5:151056942	*TNIP1*	Missense	G	C	C: 0.213 (282)	C: 0.091 (63)	C: 0.003 (3)	C: 0.083 (83)	C: 0.047 (46)
rs2230926	Chr 6:137874929	*RP11*	Missense	T	G	G: 0.409 (541)	G: 0.078 (54)	G: 0.051 (51)	G: 0.024 (24)	G: 0.030 (29)
rs2004640	Chr 7:128938247	*IRF5*	Splice donor	T	G	G: 0.596 (788)	G: 0.634 (440)	G: 0.749 (755)	G: 0.468 (471)	G: 0.494 (483)

AFR, Africa; AMR, America; EAS, East Asian; EUR, European; SAS, Southeast Asian; N, the total number of samples; Ref, Reference; Eff, Effect allele of AFR, AMR, EAS, EUR, SAS were extracted from the Ensembl.org (http://www.ensembl.org/Homo_sapiens/Variation). *Effect allele is associated with higher expression in *TNIP1, TNFAIP3, IRF5*.

4. Conclusion

Our identification of the genetic variants influencing Sjogren's syndrome showed the highest expressions of *TNIP1, TNFAIP3*, and *IRF5* in the fibroblast tissue, sigmoid colon, skin, esophagus, and adrenal glands, which poses a risk for Sjogren's syndrome in individuals and populations. We emphasized that three variants, rs2233290, rs2230926, and rs2004640, affect *TNIP1, TNFAIP3*, and *IRF5* expressions; they also occur at various populations' frequencies. Based on these results, future studies may examine these variants in early symptom onset and initiate whether any are associated with disease susceptibility and severity.

Supplementary Materials

Supplementary Table 1. A total of fifty-seven Sjogren's syndrome-associated SNPs were collected

Author Contributions: Anisa Nova Puspitaningrum, Lalu Muhammad Irham conceived and designed the study. Anisa Nova Puspitaningrum, Lalu Muhammad Irham performed all data analyses. Anisa Nova Puspitaningrum, Lalu Muhammad Irham interpreted the results. Anisa Nova Puspitaningrum, Dyah Aryani Perwitasari, Wirawan Adikusuma, Gina Noor Djalilah, Haafizah Dania, Rita Maliza, Imaniar Noor Faridah, Made Ary Sarasmita, Melodia Rezadhini, Rocky Cheung, Lalu Muhammad Irham review, revise and editing. Anisa Nova Puspitaningrum wrote the manuscript. Lalu Muhammad Irham supervised this manuscript. All authors read and approved the final manuscript.

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Competing Interests

The authors declare no conflict of interest.

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