Journal of Dermatological Science 99 (2020) 2–8

Contents lists available at ScienceDirect

Journal of Dermatological Science

journal homepage: www.jdsjournal.com

Invited review article

The current landscape of psoriasis genetics in 2020

Kotaro Ogawa[a,b], Yukinori Okada[a,c,d,*]

[a] Department of Statistical Genetics, Osaka University Graduate School of Medicine, Suita, Japan
[b] Department of Neurology, Osaka University Graduate School of Medicine, Suita, Japan
[c] Laboratory of Statistical Immunology Frontier Research Center (WPI-IFReC), Osaka University, Suita, Japan
[d] Integrated Frontier Research for Medical Science Division, Institute for Open and Transdisciplinary Research Initiatives, Osaka University, Suita, Japan

ARTICLE INFO

Article history:
Received 13 March 2020
Received in revised form 19 May 2020
Accepted 20 May 2020

Keywords:
psoriasis
genome-wide association study
HLA
Mendelian randomization
drug repositioning

ABSTRACT

Psoriasis is an immune-mediated disease associated with skin and joint inflammation that affects large proportions of populations worldwide. It is a heritable disease: individuals' genetic backgrounds modulate their susceptibility. In genetics, multiple human leukocyte antigen (HLA) genes are most strongly associated with the risk of psoriasis, especially HLA-C*06:02. In the last 10 years, large-scale genome-wide association studies (GWASs) of psoriasis have been conducted in multiple populations, and these have substantially increased the number of genetic loci associated with psoriasis susceptibility (n > 80). Understanding the genetic background of psoriasis is important for understanding the disease's biology, identifying clinical biomarkers, discovering novel drug targets, and accelerating the journey towards personalized medicine. However, the application of whole-genome and long-read sequencing technology in psoriasis genetic analysis is still developing. Moreover, achieving practical strategies for translating psoriasis risk-associated genetic variants into functional annotations and clinical applications remains challenging. In this review, we detail the current and future landscape of psoriasis genetics and introduce the cutting-edge use of large-scale GWAS data, especially in the Japanese population.

1. Introduction

Psoriasis is a chronic inflammatory disease of the skin and joints that is strongly associated with the major histocompatibility complex (MHC) region [1]; it is estimated to affect more than 125 million people worldwide [2]. The most common type of psoriasis is chronic plaque psoriasis (also known as psoriasis vulgaris: PV), which accounts for about 90 % of cases [1]. Approximately 6 %–42 % of psoriasis patients are also affected by chronic arthritis (psoriatic arthritis: PsA) in their lifetime [3]. Worldwide, the prevalence of psoriasis is about 2 %; however, prevalence varies by population [4]. For example, the prevalence of psoriasis in Europe is 1.3 %–11.4 % [5], whereas the prevalence in Japan is substantially lower at about 0.3 %–0.4 % [6]. In Europeans, the rate of psoriasis is much the same between males and females [4]; however, in Japan, the prevalence of psoriasis is higher in males, especially in older patients (male to female ratio: 1.44) [7]. The majority of epidemiological differences for psoriasis apparently originate from the genetic background of those affected. Large-scale genome studies have been conducted, and the genetic basis of psoriasis in Europeans has been summarized in previous reviews [8]. However, the genetic basis of psoriasis in non-European populations has yet to be reviewed in detail. Thus, the purpose of the present review is to discuss recent research on the genetics of psoriasis in multiple populations, especially in the Japanese population.

2. The genetic basis of psoriasis

Psoriasis is a multifactorial genetic disease for which the genetic factors explain about 70 % of disease susceptibility [9]. A higher incidence of psoriasis within families has been reported worldwide [10]. In twin studies, monozygotic twins have a susceptibility to psoriasis that is 2–3 times higher than that of

* Corresponding author at: Department of Statistical Genetics, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Osaka, Japan.
E-mail addresses: kogawa@sg.med.osaka-u.ac.jp (K. Ogawa), yokada@sg.med.osaka-u.ac.jp (Y. Okada).

https://doi.org/10.1016/j.jdermsci.2020.05.008

double zygotic twins [9]. Lonnberg et al. conducted a large-scale twin study, including 10,725 twin pairs in Denmark [9]; they found that about 4 % of participants had a lifetime history of psoriasis. Moreover, the concordance rate for psoriasis was 17 % in double zygotic twins and 33 % in monozygotic twins. These results demonstrate the familial aggregation of psoriasis. Early-stage genetic studies for psoriasis were conducted using linkage analysis in familial psoriasis [11]. From linkage analysis, nine loci (*PSORS1* to *PSORS9*) were associated with psoriasis [1]. Of these loci, *PSORS1* is known to be the major determinant of psoriasis susceptibility; it is in the MHC region, it explains about 35 %–50 % of the heritability of psoriasis [12], and it is associated with early-onset psoriasis. With recent research, *HLA-Cw6* has been identified as the susceptibility allele of *PSORS1,* and the general importance of identifying human leukocyte antigen (HLA) alleles associated with psoriasis has been recognized [13].

Currently, the genetic background of psoriasis is a key target for developing psoriasis treatments. With advances in single nucleotide polymorphism (SNP) microarray technology and the expansion of large-scale genome databases such as the International HapMap Project and 1000 Genomes Project, genome-wide association studies (GWASs) have been conducted to investigate multiple traits and diseases. Since 2007, many GWASs have investigated psoriasis in Europeans and East Asians; to date, more than 80 loci have been associated with psoriasis risk [8].

3. GWASs for psoriasis

3.1. Psoriasis GWASs in Europeans

The first large-scale GWAS for psoriasis was conducted in 2007 (Table 1) [14]. This study collected 1446 cases and 1432 controls in Europeans and genotyped 25,215 SNPs genome-wide. The results showed that the variants at *IL12B* and *IL23R* were significantly associated with psoriasis susceptibility. Similarly, the *IL12B* variant was associated with psoriasis in a Japanese study of 143 psoriasis patients and 100 healthy controls [15]. In 2010, the Wellcome Trust Centre conducted a GWAS that included 2622 psoriasis patients and 5667 controls [16]. They replicated the nine loci identified in the previous studies and found eight novel loci associated with PV. In 2010, Huffmeier et al. conducted a GWAS of PsA in Germany in which they recruited 609 PsA patients and 990 controls and replicated the results in six European trials. This study associated *TRAF3IP2* with PsA in Europeans [17]; this association had not been reported in previous family linkage studies, which demonstrates the usefulness of GWASs for detecting unknown variants associated with psoriasis. *TRAF3IP2* encodes a protein involved in IL-17 signaling [18]; the IL-17-induced T-cell immune system is thought to be important in the pathogenesis of psoriasis.

The sample size of a GWAS is an important factor that defines the statistical power of the study to identify novel loci. A meta-analysis of multiple GWASs is an efficient approach for increasing sample size. In 2012, Tsoi et al. conducted a large-scale GWAS meta-analysis that included 10,588 cases and 22,806 controls in Europeans [19]. They identified 15 new susceptibility loci and, therefore, increased the number of psoriasis-associated loci in Europeans to 36. In 2015, a large GWAS of psoriasis and PsA were conducted in which 1430 PsA patients and 1417 unaffected individuals were recruited [20]. The results of this study were meta-analyzed with those from previous studies; thus, the total number of European “subjects” was as follows: 9293 PV cases, 3061 PsA cases, 3110 cutaneous psoriasis (PsC) cases, and 13,670 unaffected control subjects. The meta-analysis detected 10 regions associated with PsA and 11 with PsC at a genome-wide significance level. In 2017, Tsoi et al. conducted the largest GWAS for psoriasis to date: it included >39,000 effective samples and identified 16 new loci associated with PV (taking the total number of associated loci to 63) [21]. The loci identified in this study explained up to 28 % of the genetic heritability in PV. This study also included drug-repositioning analysis using the GWAS data and drug databases: seven genes from six novel loci were found to be targets for 18 different drugs, most of which are currently used for psoriasis treatment.

3.2. Psoriasis GWASs in non-Europeans and future directions

To date, the majority of the GWASs in non-Europeans have been conducted in East Asia. In 2009, Zhang et al. conducted a GWAS for psoriasis in Han Chinese [22]; they reported that *IL12B*, *LCE3A*, and *LCE3D* were significantly associated with PV susceptibility in this population. In 2010, Sun et al. conducted a large-scale GWAS that included 8312 psoriasis cases and 12,919 controls from China; they identified six genes (*ERAP1*, *PTTG1*, *CSMD1*, *GJB2*, *SERPINB8*, and *ZNF816A*) associated with PV susceptibility [23]. This study also included a replication analysis of a European-ancestry GWAS that included 3293 cases and 4188 controls from Germany, as well as 254 nuclear families from the USA. Similar to results from China, *ZNF816A* and *GJB2* were also associated with PV in Europeans; however, *ERAP1*, *PTTG1*, *CSMD1,* and *SERPINB8* were not associated with Europeans. This study, therefore, demonstrated the heterogeneity of PV susceptibility between Chinese and European populations. In 2014, Tang et al. conducted a whole exome sequencing study and identified two independent missense variants in *IL23R* and *GJB2* and common missense single number variants in *LCE3D*, *ERAP1*, *CARD14,* and *ZNF816A* [24]. Although many drugs are used to treat psoriasis, the determinants of drug sensitivity have not been fully studied.

In 2016, Nishikawa et al. conducted the first Japanese GWAS for psoriasis [25]; the study focused on the susceptibility of psoriasis to anti-TNF-α therapy, which has been conducted in severe psoriasis patients. They recruited 65 patients and evaluated the severity of their psoriasis and the areas of disease following 12 weeks of anti-TNF-α treatment. A total of 731,442 SNPs were genotyped, and a GWAS for drug sensitivity was conducted. Ten SNPs associated with the treatment response were identified, including *JAG2* and *ADRA2A*. This study highlighted the importance of genetic background for the appropriate selection of psoriasis treatment drugs.

In 2018, Hirata et al. conducted the first large-scale Japanese GWAS for PV. They recruited 606 Japanese PV cases and 2052 controls and identified significant associations with TNFAIP3-interacting protein 1 (*TNIP1*) and the MHC region [26]. *TNIP1* was reported to be associated with PV susceptibility in a previous Japanese genome study [27] and we replicated the result. *TNIP1* has also been associated with PV in Europeans GWAS studies [17]. *TNIP1* controls inflammation in multiple immune-related diseases via a complex with MyD88, an essential signal transducer in the Toll-like receptor (TLR) signaling pathway. Taken together, these results suggest that the regulation of Toll-like receptor signaling is closely related to the pathogenesis of PV across worldwide populations.

Recently, a trans-ethnic meta-analysis of GWASs has been conducted in a variety of complex diseases. For example, Okada et al. conducted a trans-ethnic meta-analysis for rheumatoid arthritis; it included 68,695 Europeans and 35,778 Asians, and it integrated more than 25 groups from several countries [28]. In total, 101 rheumatoid arthritis risk loci were identified; furthermore, correlations of risk allele frequencies and odds ratios of risk loci were found between populations, suggesting that the genetic risk of rheumatoid arthritis is generally shared between Europeans and Asians. At present, the majority of GWASs for psoriasis have

Table 1
Genome-wide association studies for psoriasis.

Publication year	Trait	Ethnicity	Number of participants	Representative findings in PV research	Reference
2007	PV	European	2878	Identification of *IL12B* and *IL23R*	[24]
2009	PV	Chinese	15,332	Identification of *LCE3A* and *LCE3D*	[32]
2010	PV	Chinese and European	29,700	Identification of six risk genes	[33]
2010	PV	European	8289	Identification of eight new risk loci associated with PV	[26]
2010	PsA	European	7087	Identification of *TRAF3IP2* associated with PsA	[27]
2012	PV	European	33,394	Identification of 15 new risk loci	[29]
2014	PV	Chinese	21,309	Identification of two missense SNVs and five common missense SNVs	[34]
2015	PsA and PsC	European	29,134	Identification of 10 loci associated with PsA and 11 loci associated with PsC	[30]
2016	PV	Japanese	65	Identification of 10 SNPs associated with TNFα therapy response	[35]
2017	PV	European	39,498	Identification of 16 new risk loci	[31]
2018	PV	Japanese	2658	HLA-A*02:07 association with PV in Japanese	[36]

PV: psoriasis vulgaris; PsA: psoriatic arthritis; PsC: cutaneous psoriasis.

been conducted in a single ancestry. To understand the mechanisms of psoriasis in multiple ethnic groups, future trans-ethnic studies of worldwide populations are warranted.

4. Psoriasis genetic risk of HLA gene

The MHC region located at 6p21 confers a strong genetic risk of psoriasis [8]. Within the MHC region, the class I HLA gene *HLA-C* has a strong association with susceptibility to psoriasis [13]. In particular, the HLA-C*06:02 allele, which was the first risk allele detected, is known to be strongly associated with psoriasis both in Europeans and Chinese [29]. Direct HLA genotyping is technically challenging because of the complexity of polymorphic alleles and structural variances. Thus, the classical HLA typing method utilizes sequence-specific primers and oligonucleotides. Although these methods are accurate, they are also relatively expensive; consequently, HLA analysis has not been conducted comprehensively.

In 2012, Raychaudhuri et al. created a computational method for detecting the details of the MHC region using SNP array genotyping data [30]. They computationally imputed HLA alleles and amino acid sequences using reference data collected by the Type 1 Diabetes Genetics Consortium, which contained directly genotyped HLA alleles and densely genotyped SNPs within the entire MHC region; this method was named “HLA imputation.” HLA imputation enables estimation of HLA allele genotypes and dosages using only SNP microarray data; thus, by applying this method, information about HLA alleles and amino acid polymorphisms of HLA genes can be obtained at zero cost. However, the HLA imputation method requires the creation of population-specific HLA reference panels. For example, a Japanese-specific reference panel for HLA imputation has been developed using 900 healthy cohort samples [31].

In 2014, HLA imputation was used for fine mapping of the MHC's association with psoriasis in Europeans [32]. In this study, 9247 PV patients and 13,589 controls were recruited, and HLA association analysis was conducted using SNP genotyping data. HLA-C*06:02 was found to be most strongly associated with psoriasis susceptibility; stepwise conditional analysis showed that HLA-C*12:03, HLA-B amino acid position 67 and 9, HLA-A amino acid position 95, and HLA-DQα1 amino acid position 53 also had significant associations with psoriasis independently. Further HLA analysis of PsA and PsC revealed that HLA-B amino acid position 45 was a key risk factor of PsA and PsC in Europeans. Therefore, the genetic factors that underlie psoriasis risk can differ among psoriasis subtypes.

In 2016, Zhou et al. conducted deep sequencing of the MHC region in Han Chinese [33]. They sequenced the MHC region in 20,635 individuals, including 9946 psoriasis patients and 10,689 controls, and conducted fine mapping of the MHC region. In agreement with the previous HLA study in Europeans [32], HLA-C*06:02 was the allele most strongly associated with psoriasis. Multivariate HLA analysis also showed that HLA-C*07*04; rs118179173; HLA-B amino acid position 9, amino acid position 67, and amino acid position 116; HLA-DPB1*05:01; *BTNL2* amino acid position 281; and HLA-A amino acid position 95 were independently associated with psoriasis. HLA allele frequencies in the Chinese and European populations were also compared and there was a significant difference between them ($P = 5.9 \times 10^{-7}$). The HLA genetic background of psoriasis is therefore heterogeneous between populations.

In 2017, we performed fine mapping of the HLA variants associated with PV in the Japanese population [26] and found that HLA-A*02:07 (HLA-A 99Cys), HLA-C*06*02, and HLA-DQβ1 57Asp were significantly associated with PV. Although HLA-C*06:02 was the allele most strongly associated with psoriasis in other populations, in the Japanese population, HLA-C*06:02 is rarely associated with psoriasis because it is hardly found in Japanese people (at a rate of <0.5 %). The association of HLA-A*02:07, however, has also been reported in previous Japanese psoriasis studies [34]. The PV risk-associated amino acid polymorphisms are known to be located in the peptide-binding pockets of HLA-A and HLA-DQ molecules (Fig. 1), which suggests that structural changes may influence the antigen-presenting function.

5. Mendelian randomization reveals the causal factors of psoriasis

Several epidemiological studies have reported that body mass index (BMI), a widely used metric for obesity, is elevated in psoriasis patients in comparison to healthy controls [35]. To test whether or not BMI is a causal factor of psoriasis, statistical analysis is required: a method known as Mendelian randomization is considered an effective statistical approach to such problems. Mendelian randomization is an instrumental variable method that uses genetic variants to determine whether an association between a factor and an outcome is consistent with a causal relationship [36]. Given the progress of GWASs, SNPs with genome-wide significance can now be used as instrumental variables in Mendelian randomization. While the correlations between psoriasis and obesity [35] or high BMI [37] have been reported in many studies, a causal relationship had not previously been clarified due to the existence of many confounding factors. In 2019, however, two studies independently reported a causal relationship between obesity and psoriasis. In one study, Budu-Aggrey et al. conducted Mendelian randomization to test for the causality of BMI with psoriasis in Europeans [38]. They conducted one-sample Mendelian randomization using the UK Biobank study genotype data and HUNT study data. They also conducted two-sample Mendelian randomization using the GWAS summary

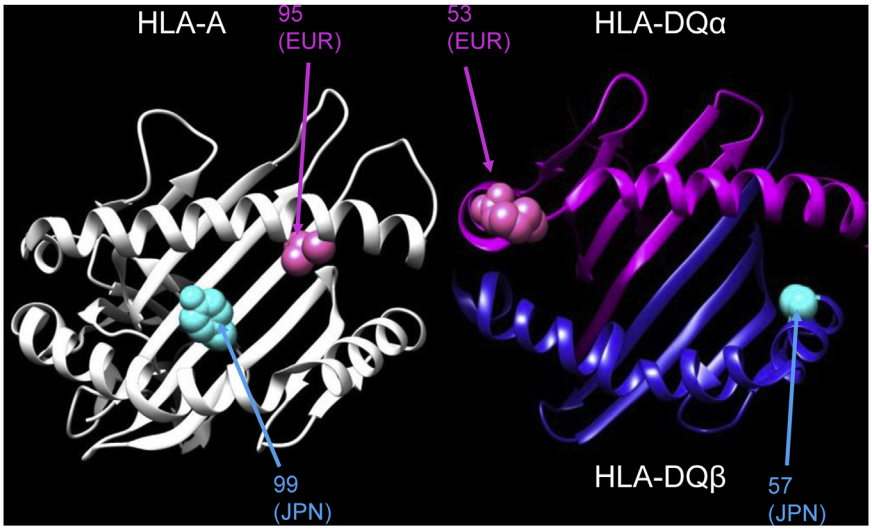


Fig. 1. Psoriasis vulgaris risk-associated amino acid positions of HLA genes in Japanese and Europeans shown in three-dimensional ribbon models. HLA amino acid positions associated with psoriasis vulgaris risk in HLA-A and HLA-DQ molecules are placed in three-dimensional models. The protein structures of HLA-A and HLA-DQ are based on Protein Data Bank entries, 1 × 7q and 1jk8, respectively. This figure was created using UCSF Chimera (version 1.14).

statistics of BMI and psoriasis. Ultimately, they found that a higher BMI is a causal risk factor for psoriasis. In addition, our group conducted a trans-ethnic Mendelian randomization study using nine metabolic traits potentially linked with psoriasis in Europeans and Japanese: BMI, triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, blood sugar, HbA1c, systolic blood pressure, and diastolic blood pressure [39]. We found that obesity is a causal risk factor for psoriasis in both Japanese and Europeans. Interestingly, no other metabolic traits were significantly associated with psoriasis susceptibility. Based on these findings, patients can now be advised with confidence to lose weight in order to avoid worsening psoriasis. Therefore, this study represents a successful example of applying a Mendelian randomization approach in clinical medicine.

6. Drug repositioning from GWAS data

To date, multiple GWASs have been conducted worldwide, and more than 80 loci have been identified. However, a method for translating GWAS results into applications for clinical medicine has proved to be elusive. The key issue is how we use identified genetic variants effectively in medicine. One potential solution is drug repositioning, which is a method for finding new usages for existing drugs outside the scope of the original medical indication. Today, the world's pharmaceutical companies spend more than 10 billion US dollars per year on research, and the cost of developing a new drug is about 2.9 billion US dollars [40]. Therefore, identifying and using drugs that have already been developed to treat other diseases is a more cost-effective approach.

In 2014, Okada et al. conducted the first GWAS-based drug repositioning study [28]. Using the results of a trans-ethnic rheumatoid arthritis GWAS meta-analysis, they conducted *in silico* drug screening with protein–protein interaction networks and drug databases. Their results identified CDK4/CDK6 inhibitors, which had previously been used for breast cancer treatment, as candidate novel drugs for rheumatoid arthritis treatment. Indeed, this drug has been shown to improve rheumatoid arthritis symptoms in some animal models [41]. Following Okada et al., drug-repositioning studies using GWAS summary statistics have also been conducted for type 2 diabetes [42] and Parkinson's disease [43]. In 2019, Sakaue et al. constructed the Python software GREP (Genome for REPositioning drugs), which contains databases of drugs, diseases, and ICD codes, for *in silico* drug screening [44]. GREP can quantify the enrichment of a user-selected set of genes in the targets of clinical categories and, thereby, capture potential drugs; it also automatically conducts drug discovery analysis from the GWAS resources. In fact, GREP needs only GWAS summary statistics for this analysis. Genomic drug discovery is a promising cost-effective approach that has attracted attention from pharmaceutical companies. In Fig. 2, we show the results of the GREP analysis in which the latest psoriasis GWAS data was used. Many drugs that are already used for the treatment of psoriasis are included in the results; in addition, new candidate drugs are identified, and further validation of these drugs may contribute to the treatment of psoriasis.

7. Limitations of current genome analysis strategies and future perspectives

Due to the success of GWAS analysis, the translational application of GWAS data is receiving substantial attention. To date, more than 10,000 loci have been identified from GWASs [45]. However, the genetic component (i.e., the heritability) currently explained by such large-scale GWAS data is not in agreement with that found in twin studies. For example, the heritability explained by the latest PV GWAS data is about 30 % of all heritability [21]. One reason for this discrepancy is the GWAS sample size, which is currently insufficient for identifying true heritability. Another reason is that GWASs do not cover all possible genetic variants. Most GWASs use tag SNPs and short indels. Commercial SNP microarrays include up to one million variants, and SNP genotype imputation, which uses population-specific genome references, is widely used to impute variants in the range of 5–10 million. However, the majority of these variants are SNPs; structural variants are not covered. To increase coverage of the variants, GWAS should be conducted based on whole genome sequencing (WGS) data. Currently, with the progress of next-generation sequencing technology, the cost of WGS has greatly decreased [46]. The cost of WGS is <500 US dollars per sample at present. On the other hand, SNP microarray genotyping costs just 50 dollars, approximately, per sample, i.e., 10 times less than WGS. Such a cost difference remains substantial, and the majority of large-scale GWASs are still based on SNP microarrays. Further advances in sequencing technology are, therefore, needed before large-scale

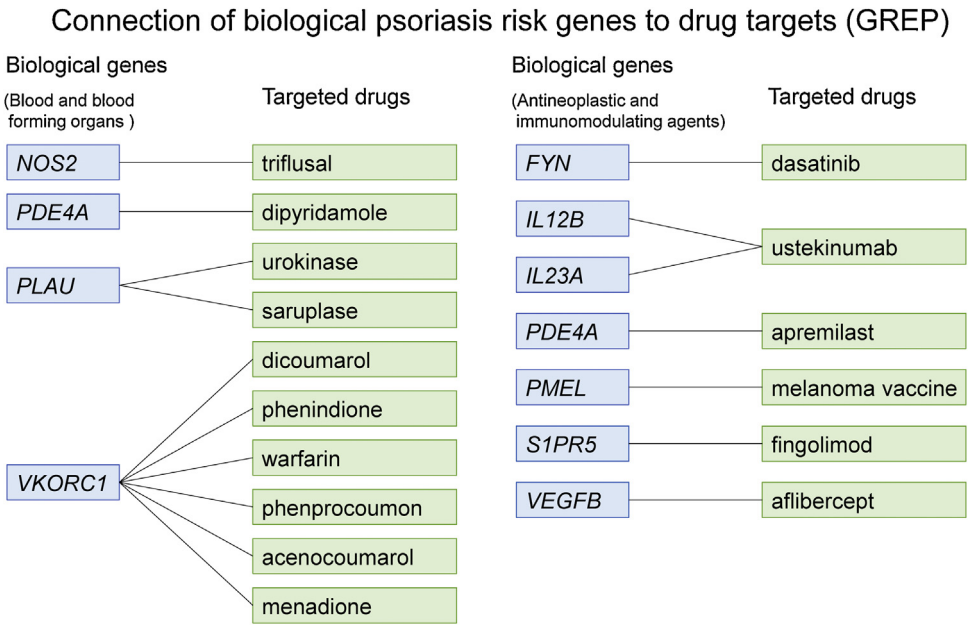


Fig. 2. Psoriasis drug repositioning results obtained using GREP. A European GWAS summary, which included 34,772 persons, was used for analysis. The connections between psoriasis risk genes and approved drugs were detected by GREP software. The connections among biological psoriasis risk genes and individual targeted drugs are shown.

GWASs can be routinely conducted via WGS. Furthermore, most of the next-generation sequencers used today are short read-based (i.e., the sequencing read length is 100–200 bases) and not suitable for detecting variants with repeats or complex structural variation. As alternatives, long-read sequencers, such as PacBio [47] or Nanopore [48], can be employed. These technologies produce long reads ranging from 10,000 to 40,000 bases; thus, the detection of long repeat variants in genome sequences becomes simple. For example, facioscapulohumeral muscular dystrophy has been associated with the D4Z4 repeat that is 3300 bases in length. This repeat was detected by southern blotting and fully sequenced using Nanopore-based sequencing technology [49]. While the cost of long-read sequencing is currently high, several initial large-scale studies have been reported. In 2019, Beyter et al. conducted long-read sequencing of 1817 Icelanders and identified around 23,000 autosomal structural variants [50]. They found that rare structural variants were larger in size and more likely to impact protein function than common structural variants. Although long-read sequencing is a promising method for detecting structural variants, the accuracy of this method can be as low as 90 % [47]. Thus, where finances allow, the combination of short read- and long read-based sequencing would currently represent the best approach.

8. Conclusion

In this review, we summarized the current landscape of psoriasis genetics, and we proposed future steps in psoriasis genomics analysis. With the progress of genome sequencing technologies, researchers have discovered a large number of variants associated with psoriasis susceptibility. However, the functional annotations and clinical applications of the identified risk variants have not been fully elucidated or exploited. The genetic basis of psoriasis in non-European populations, including the Japanese population, has yet to be revealed in full. Therefore, the implementation of nationwide and trans-ethnic large-scale psoriasis genetic studies is warranted.

Funding sources

This research was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (15H05911, 19H01021), AMED (JP19gm6010001, JP19ek0410041, JP19ek0109413, and JP19km0405211).

Declaration of Competing Interest

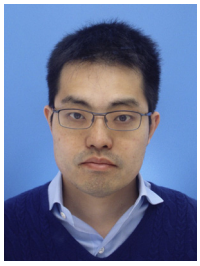
The authors have no conflicts of interest to declare.

References

[1] C.E. Griffiths, J.N. Barker, Pathogenesis and clinical features of psoriasis, Lancet 370 (9583) (2007) 263–271.
[2] J.E. Greb, A.M. Goldminz, J.T. Elder, M.G. Lebwohl, D.D. Gladman, J.J. Wu, N.N. Mehta, A.Y. Finlay, A.B. Gottlieb, Psoriasis, Nat. Rev. Dis. Primers 2 (2016) 16082.
[3] D.D. Gladman, Psoriatic arthritis, Dermatol. Ther. 22 (1) (2009) 40–55.
[4] S.P. Raychaudhuri, E.M. Farber, The prevalence of psoriasis in the world, J. Eur. Acad. Dermatol. Venereol. 15 (1) (2001) 16–17.
[5] I.M. Michalek, B. Loring, S.M. John, A systematic review of worldwide epidemiology of psoriasis, J. Eur. Acad. Dermatol. Venereol. 31 (2) (2017) 205–212.
[6] M. Furue, S. Yamazaki, K. Jimbow, T. Tsuchida, M. Amagai, T. Tanaka, K. Matsunaga, M. Muto, E. Morita, M. Akiyama, Y. Soma, T. Terui, M. Manabe, Prevalence of dermatological disorders in Japan: a nationwide, cross-sectional, seasonal, multicenter, hospital-based study, J. Dermatol. 38 (4) (2011) 310–320.
[7] K. Kubota, Y. Kamijima, T. Sato, N. Ooba, D. Koide, H. Iizuka, H. Nakagawa, Epidemiology of psoriasis and palmoplantar pustulosis: a nationwide study using the Japanese national claims database, BMJ Open 5 (1) (2015) e006450.
[8] S.T. Hwang, T. Nijsten, J.T. Elder, Recent highlights in psoriasis research, J. Invest. Dermatol. 137 (3) (2017) 550–556.
[9] A.S. Lonnberg, L. Skov, A. Skytthe, K.O. Kyvik, O.B. Pedersen, S.F. Thomsen, Heritability of psoriasis in a large twin sample, Br. J. Dermatol. 169 (2) (2013) 412–416.
[10] Y.H. Huang, C.F. Kuo, L.H. Huang, M.Y. Hsieh, Familial aggregation of psoriasis and co-aggregation of autoimmune diseases in affected families, J. Clin. Med. 8 (1) (2019).
[11] F. Enlund, L. Samuelsson, C. Enerback, A. Inerot, J. Wahlstrom, M. Yhr, A. Torinsson, T. Martinsson, G. Swanbeck, Analysis of three suggested psoriasis susceptibility loci in a large Swedish set of families: confirmation of linkage to chromosome 6p (HLA region), and to 17q, but not to 4q, Hum. Hered. 49 (1) (1999) 2–8.

[12] M.H. Allen, H. Ameen, C. Veal, J. Evans, V.S. Ramrakha-Jones, A.M. Marsland, A. D. Burden, C.E. Griffiths, R.C. Trembath, J.N. Barker, The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis, J. Invest. Dermatol. 124 (1) (2005) 103–106.
[13] R.P. Nair, P.E. Stuart, I. Nistor, R. Hiremagalore, N.V.C. Chia, S. Jenisch, M. Weichenthal, G.R. Abecasis, H.W. Lim, E. Christophers, J.J. Voorhees, J.T. Elder, Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene, Am. J. Hum. Genet. 78 (5) (2006) 827–851.
[14] M. Cargill, S.J. Schrodi, M. Chang, V.E. Garcia, R. Brandon, K.P. Callis, N. Matsunami, K.G. Ardlie, D. Civello, J.J. Catanese, D.U. Leong, J.M. Panko, L.B. McAllister, C.B. Hansen, J. Papenfuss, S.M. Prescott, T.J. White, M.F. Leppert, G.G. Krueger, A.B. Begovich, A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes, Am. J. Hum. Genet. 80 (2) (2007) 273–290.
[15] Y. Tsunemi, H. Saeki, K. Nakamura, T. Sekiya, K. Hirai, H. Fujita, N. Asano, M. Kishimoto, Y. Tanida, T. Kakinuma, H. Mitsui, Y. Tada, M. Wakugawa, H. Torii, M. Komine, A. Asahina, K. Tamaki, Interleukin-12 p40 gene (IL12B) 3'-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris, J. Dermatol. Sci. 30 (2) (2002) 161–166.
[16] Genetic Analysis of Psoriasis Consortium & the Wellcome Trust Case Control Consortium 2, A. Strange, F. Capon, C.C. Spencer, J. Knight, M.E. Weale, M.H. Allen, A. Barton, G. Band, C. Bellenguez, J.G. Bergboer, J.M. Blackwell, E. Bramon, S.J. Bumpstead, J.P. Casas, M.J. Cork, A. Corvin, P. Deloukas, A. Dilthey, A. Duncanson, S. Edkins, X. Estivill, O. Fitzgerald, C. Freeman, E. Giardina, E. Gray, A. Hofer, U. Huffmeier, S.E. Hunt, A.D. Irvine, J. Jankowski, B. Kirby, C. Langford, J. Lascorz, J. Leman, S. Leslie, L. Mallbris, H.S. Markus, C.G. Mathew, W.H. McLean, R. McManus, R. Mossner, L. Moutsianas, A.T. Naluai, F.O. Nestle, G. Novelli, A. Onoufriadis, C.N. Palmer, C. Perricone, M. Pirinen, R. Plomin, S.C. Potter, R.M. Pujol, A. Rautanen, E. Riveira-Munoz, A.W. Ryan, W. Salmhofer, L. Samuelsson, S.J. Sawcer, J. Schalkwijk, C.H. Smith, M. Stahle, Z. Su, R. Tazi-Ahnini, H. Traupe, A.C. Viswanathan, R.B. Warren, W. Weger, K. Wolk, N. Wood, J. Worthington, H.S. Young, P.L. Zeeuwen, A. Hayday, A.D. Burden, C.E. Griffiths, J. Kere, A. Reis, G. McVean, D.M. Evans, M.A. Brown, J.N. Barker, L. Peltonen, P. Donnelly, R.C. Trembath, A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1, Nat. Genet. 42 (11) (2010) 985–990.
[17] U. Huffmeier, S. Uebe, A.B. Ekici, J. Bowes, E. Giardina, E. Korendowych, K. Juneblad, M. Apel, R. McManus, P. Ho, I.N. Bruce, A.W. Ryan, F. Behrens, J. Lascorz, B. Bohm, H. Traupe, J. Lohmann, C. Gieger, H.E. Wichmann, C. Herold, M. Steffens, L. Klareskog, T.F. Wienker, O. Fitzgerald, G.M. Alenius, N.J. McHugh, G. Novelli, H. Burkhardt, A. Barton, A. Reis, Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis, Nat. Genet. 42 (11) (2010) 996–999.
[18] J. Nititham, C. Fergusson, C. Palmer, W. Liao, J. Foerster, Candidate long-range regulatory sites acting on the IL17 pathway genes TRAF3IP2 and IL17RA are associated with psoriasis, Exp. Dermatol. 27 (11) (2018) 1294–1297.
[19] L.C. Tsoi, S.L. Spain, J. Knight, E. Ellinghaus, P.E. Stuart, F. Capon, J. Ding, Y. Li, T. Tejasvi, J.E. Gudjonsson, H.M. Kang, M.H. Allen, R. McManus, G. Novelli, L. Samuelsson, J. Schalkwijk, M. Stahle, A.D. Burden, C.H. Smith, M.J. Cork, X. Estivill, A.M. Bowcock, G.G. Krueger, W. Weger, J. Worthington, R. Tazi-Ahnini, F.O. Nestle, A. Hayday, P. Hoffmann, J. Winkelmann, C. Wijmenga, C. Langford, S. Edkins, R. Andrews, H. Blackburn, A. Strange, G. Band, R.D. Pearson, D. Vukcevic, C.C. Spencer, P. Deloukas, U. Mrowietz, S. Schreiber, S. Weidinger, S. Koks, K. Kingo, T. Esko, A. Metspalu, H.W. Lim, J.J. Voorhees, M. Weichenthal, H. E. Wichmann, V. Chandran, C.F. Rosen, P. Rahman, D.D. Gladman, C.E. Griffiths, A. Reis, J. Kere, Collaborative Association Study of Psoriasis (CASP), Genetic Analysis of Psoriasis Consortium; Psoriasis Association Genetics Extension, Wellcome Trust Case Control Consortium 2, R.P. Nair, A. Franke, J.N. Barker, G.R. Abecasis, J.T. Elder, R.C. Trembath, Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity, Nat. Genet. 44 (12) (2012) 1341–1348.
[20] P.E. Stuart, R.P. Nair, L.C. Tsoi, T. Tejasvi, S. Das, H.M. Kang, E. Ellinghaus, V. Chandran, K. Callis-Duffin, R. Ike, Y. Li, X. Wen, C. Enerback, J.E. Gudjonsson, S. Koks, K. Kingo, T. Esko, U. Mrowietz, A. Reis, H.E. Wichmann, C. Gieger, P. Hoffmann, M.M. Nothen, J. Winkelmann, M. Kunz, E.G. Moreta, P.J. Mease, C.T. Ritchlin, A.M. Bowcock, G.G. Krueger, H.W. Lim, S. Weidinger, M. Weichenthal, J.J. Voorhees, P. Rahman, P.K. Gregersen, A. Franke, D.D. Gladman, G.R. Abecasis, J.T. Elder, Genome-wide association analysis of psoriatic arthritis and cutaneous psoriasis reveals differences in their genetic architecture, Am. J. Hum. Genet. 97 (6) (2015) 816–836.
[21] L.C. Tsoi, P.E. Stuart, C. Tian, J.E. Gudjonsson, S. Das, M. Zawistowski, E. Ellinghaus, J.N. Barker, V. Chandran, N. Dand, K.C. Duffin, C. Enerback, T. Esko, A. Franke, D.D. Gladman, P. Hoffmann, K. Kingo, S. Koks, G.G. Krueger, H.W. Lim, A. Metspalu, U. Mrowietz, S. Mucha, P. Rahman, A. Reis, T. Tejasvi, R. Trembath, J.J. Voorhees, S. Weidinger, M. Weichenthal, X. Wen, N. Eriksson, H.M. Kang, D. A. Hinds, R.P. Nair, G.R. Abecasis, J.T. Elder, Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants, Nat. Commun. 8 (2017) 15382.
[22] X.J. Zhang, W. Huang, S. Yang, L.D. Sun, F.Y. Zhang, Q.X. Zhu, F.R. Zhang, C. Zhang, W.H. Du, X.M. Pu, H. Li, F.L. Xiao, Z.X. Wang, Y. Cui, F. Hao, J. Zheng, X.Q. Yang, H. Cheng, C.D. He, X.M. Liu, L.M. Xu, H.F. Zheng, S.M. Zhang, J.Z. Zhang, H. Y. Wang, Y.L. Cheng, B.H. Ji, Q.Y. Fang, Y.Z. Li, F.S. Zhou, J.W. Han, C. Quan, B. Chen, J.L. Liu, D. Lin, L. Fan, A.P. Zhang, S.X. Liu, C.J. Yang, P.G. Wang, W.M. Zhou, G.S. Lin, W.D. Wu, X. Fan, M. Gao, B.Q. Yang, W.S. Lu, Z. Zhang, K.J. Zhu, S.K. Shen, M. Li, X.Y. Zhang, T.T. Cao, W. Ren, X. Zhang, J. He, X.F. Tang, S. Lu, J.Q. Yang, L. Zhang, D.N. Wang, F. Yuan, X.Y. Yin, H.J. Huang, H.F. Wang, X.Y. Lin, J.J. Liu, Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21, Nat. Genet. 41 (2) (2009) 205–210.
[23] L.D. Sun, H. Cheng, Z.X. Wang, A.P. Zhang, P.G. Wang, J.H. Xu, Q.X. Zhu, H.S. Zhou, E. Ellinghaus, F.R. Zhang, X.M. Pu, X.Q. Yang, J.Z. Zhang, A.E. Xu, R.N. Wu, L.M. Xu, L. Peng, C.A. Helms, Y.Q. Ren, C. Zhang, S.M. Zhang, R.P. Nair, H.Y. Wang, G.S. Lin, P.E. Stuart, X. Fan, G. Chen, T. Tejasvi, P. Li, J. Zhu, Z.M. Li, H.M. Ge, M. Weichenthal, W.Z. Ye, C. Zhang, S.K. Shen, B.Q. Yang, Y.Y. Sun, S.S. Li, Y. Lin, J.H. Jiang, C.T. Li, R.X. Chen, J. Cheng, X. Jiang, P. Zhang, W.M. Song, J. Tang, H.Q. Zhang, L. Sun, J. Cui, L.J. Zhang, B. Tang, F. Huang, Q. Qin, X.P. Pei, A.M. Zhou, L.M. Shao, J.L. Liu, F.Y. Zhang, W.D. Du, A. Franke, A.M. Bowcock, J.T. Elder, J.J. Liu, S. Yang, X.J. Zhang, Association analyses identify six new psoriasis susceptibility loci in the Chinese population, Nat. Genet. 42 (11) (2010) 1005–1009.
[24] H. Tang, X. Jin, Y. Li, H. Jiang, X. Tang, X. Yang, H. Cheng, Y. Qiu, G. Chen, J. Mei, F. Zhou, R. Wu, X. Zuo, Y. Zhang, X. Zheng, Q. Cai, X. Yin, C. Quan, H. Shao, Y. Cui, F. Tian, X. Zhao, H. Liu, F. Xiao, F. Xu, J. Han, D. Shi, A. Zhang, C. Zhou, Q. Li, X. Fan, L. Lin, H. Tian, Z. Wang, H. Fu, F. Wang, B. Yang, S. Huang, B. Liang, X. Xie, Y. Ren, Q. Gu, G. Wen, Y. Sun, X. Wu, L. Dang, M. Xia, J. Shan, T. Li, L. Yang, X. Zhang, Y. Li, C. He, A. Xu, L. Wei, X. Zhao, X. Gao, J. Xu, F. Zhang, J. Zhang, Y. Li, L. Sun, J. Liu, R. Chen, S. Yang, J. Wang, X. Zhang, A large-scale screen for coding variants predisposing to psoriasis, Nat. Genet. 46 (1) (2014) 45–50.
[25] R. Nishikawa, H. Nagai, T. Bito, T. Ikeda, T. Horikawa, A. Adachi, T. Matsubara, C. Nishigori, Genetic prediction of the effectiveness of biologics for psoriasis treatment, J. Dermatol. 43 (11) (2016) 1273–1277.
[26] J. Hirata, T. Hirota, T. Ozeki, M. Kanai, T. Sudo, T. Tanaka, N. Hizawa, H. Nakagawa, S. Sato, T. Mushiroda, H. Saeki, M. Tamari, Y. Okada, Variants at HLA-A, HLA-C, and HLA-DQB1 confer risk of psoriasis vulgaris in Japanese, J. Invest. Dermatol. 138 (3) (2018) 542–548.
[27] M. Tamari, H. Saeki, M. Hayashi, Y. Umezawa, T. Ito, O. Fukuchi, Y. Nobeyama, K. Yanaba, H. Nakagawa, Y. Tsunemi, T. Kato, S. Shibata, M. Sugaya, S. Sato, Y. Tada, S. Doi, A. Miyatake, K. Ebe, E. Noguchi, S. Fujieda, T. Ebihara, M. Amagai, H. Esaki, S. Takeuchi, M. Furue, T. Hirota, An association study of 36 psoriasis susceptibility loci for psoriasis vulgaris and atopic dermatitis in a Japanese population, J. Dermatol. Sci. 76 (2) (2014) 156–157.
[28] Y. Okada, D. Wu, G. Trynka, T. Raj, C. Terao, K. Ikari, Y. Kochi, K. Ohmura, A. Suzuki, S. Yoshida, R.R. Graham, A. Manoharan, W. Ortmann, T. Bhangale, J.C. Denny, R.J. Carroll, A.E. Eyler, J.D. Greenberg, J.M. Kremer, D.A. Pappas, L. Jiang, J. Yin, L. Ye, D.F. Su, J. Yang, G. Xie, E. Keystone, H.J. Westra, T. Esko, A. Metspalu, X. Zhou, N. Gupta, D. Mirel, E.A. Stahl, D. Diogo, J. Cui, K. Liao, M.H. Guo, K. Myouzen, T. Kawaguchi, M.J. Coenen, P.L. van Riel, M.A. van de Laar, H.J. Guchelaar, T.W. Huizinga, P. Dieude, X. Mariette, S.L. Bridges Jr, A. Zhernakova, R.E. Toes, P.P. Tak, C. Miceli-Richard, S.Y. Bang, H.S. Lee, J. Martin, M.A. Gonzalez-Gay, L. Rodriguez-Rodriguez, S. Rantapaa-Dahlqvist, L. Arlestig, H.K. Choi, Y. Kamatani, P. Galan, M. Lathrop, R. Consortium, G. Consortium, S. Eyre, J. Bowes, A. Barton, N. de Vries, L.W. Moreland, L.A. Criswell, E.W. Karlson, A. Taniguchi, R. Yamada, M. Kubo, J.S. Liu, S.C. Bae, J. Worthington, L. Padyukov, L. Klareskog, P.K. Gregersen, S. Raychaudhuri, B.E. Stranger, P.L. De Jager, L. Franke, P.M. Visscher, M.A. Brown, H. Yamanaka, T. Mimori, A. Takahashi, H. Xu, T.W. Behrens, K.A. Siminovitch, S. Momohara, F. Matsuda, K. Yamamoto, R.M. Plenge, Genetics of rheumatoid arthritis contributes to biology and drug discovery, Nature 506 (7488) (2014) 376–381.
[29] L. Chen, T.F. Tsai, HLA-Cw6 and psoriasis, Br. J. Dermatol. 178 (4) (2018) 854–862.
[30] S. Raychaudhuri, C. Sandor, E.A. Stahl, J. Freudenberg, H.S. Lee, X. Jia, L. Alfredsson, L. Padyukov, L. Klareskog, J. Worthington, K.A. Siminovitch, S.C. Bae, R.M. Plenge, P.K. Gregersen, P.I. de Bakker, Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis, Nat. Genet. 44 (3) (2012) 291–296.
[31] Y. Okada, Y. Momozawa, K. Ashikawa, M. Kanai, K. Matsuda, Y. Kamatani, A. Takahashi, M. Kubo, Construction of a population-specific HLA imputation reference panel and its application to Graves' disease risk in Japanese, Nat. Genet. 47 (7) (2015) 798–802.
[32] Y. Okada, B. Han, L.C. Tsoi, P.E. Stuart, E. Ellinghaus, T. Tejasvi, V. Chandran, F. Pellett, R. Pollock, A.M. Bowcock, G.G. Krueger, M. Weichenthal, J.J. Voorhees, P. Rahman, P.K. Gregersen, A. Franke, R.P. Nair, G.R. Abecasis, D.D. Gladman, J.T. Elder, P.I. de Bakker, S. Raychaudhuri, Fine mapping major histocompatibility complex associations in psoriasis and its clinical subtypes, Am. J. Hum. Genet. 95 (2) (2014) 162–172.
[33] F. Zhou, H. Cao, X. Zuo, T. Zhang, X. Zhang, X. Liu, R. Xu, G. Chen, Y. Zhang, X. Zheng, X. Jin, J. Gao, J. Mei, Y. Sheng, Q. Li, B. Liang, J. Shen, C. Shen, H. Jiang, C. Zhu, X. Fan, F. Xu, M. Yue, X. Yin, C. Ye, C. Zhang, X. Liu, L. Yu, J. Wu, M. Chen, X. Zhuang, L. Tang, H. Shao, L. Wu, J. Li, Y. Xu, Y. Zhang, S. Zhao, Y. Wang, G. Li, H. Xu, L. Zeng, J. Wang, M. Bai, Y. Chen, W. Chen, T. Kang, Y. Wu, X. Xu, Z. Zhu, Y. Cui, Z. Wang, C. Yang, P. Wang, L. Xiang, X. Chen, A. Zhang, X. Gao, F. Zhang, J. Xu, M. Zheng, J. Zheng, J. Zhang, X. Yu, Y. Li, S. Yang, H. Yang, J. Wang, J. Liu, L. Hammarstrom, L. Sun, J. Wang, X. Zhang, Deep sequencing of the MHC region in the Chinese population contributes to studies of complex disease, Nat. Genet. 48 (7) (2016) 740–746.
[34] M. Muto, Y. Date, M. Ichimiya, Y. Moriwaki, K. Mori, N. Kamikawaji, A. Kimura, T. Sasazuki, C. Asagami, Significance of antibodies to streptococcal M protein in psoriatic arthritis and their association with HLA-A*0207, Tissue Antigens 48 (6) (1996) 645–650.
[35] I. Snekvik, C.H. Smith, T.I.L. Nilsen, S.M. Langan, E.H. Modalsli, P.R. Romundstad, M. Saunes, Obesity, waist circumference, weight change, and risk of incident psoriasis: prospective data from the HUNT Study, J. Invest. Dermatol. 137 (12) (2017) 2484–2490.
[36] C.A. Emdin, A.V. Khera, S. Kathiresan, Mendelian randomization, JAMA 318 (19) (2017) 1925–1926.

[37] R. Naito, S. Imafuku, Distinguishing features of body mass index and psoriasis in men and women in Japan: a hospital-based case-control study, J. Dermatol. 43 (12) (2016) 1406–1411.
[38] A. Budu-Aggrey, B. Brumpton, J. Tyrrell, S. Watkins, E.H. Modalsli, C. Celis-Morales, L.D. Ferguson, G.A. Vie, T. Palmer, L.G. Fritsche, M. Loset, J.B. Nielsen, W. Zhou, L.C. Tsoi, A.R. Wood, S.E. Jones, R. Beaumont, M. Saunes, P.R. Romundstad, S. Siebert, I.B. McInnes, J.T. Elder, G. Davey Smith, T.M. Frayling, B. O. Asvold, S.J. Brown, N. Sattar, L. Paternoster, Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study, PLoS Med. 16 (1) (2019) e1002739.
[39] K. Ogawa, P.E. Stuart, L.C. Tsoi, K. Suzuki, R.P. Nair, H. Mochizuki, J.T. Elder, Y. Okada, A transethnic Mendelian randomization study identifies causality of obesity on risk of psoriasis, J. Invest. Dermatol. 139 (6) (2019) 1397–1400.
[40] J.A. DiMasi, H.G. Grabowski, R.W. Hansen, Innovation in the pharmaceutical industry: new estimates of R&D costs, J. Health Econ. 47 (2016) 20–33.
[41] T. Hosoya, H. Iwai, Y. Yamaguchi, K. Kawahata, N. Miyasaka, H. Kohsaka, Cell cycle regulation therapy combined with cytokine blockade enhances antiarthritic effects without increasing immune suppression, Ann. Rheum. Dis. 75 (1) (2016) 253–259.
[42] M. Imamura, A. Takahashi, T. Yamauchi, K. Hara, K. Yasuda, N. Grarup, W. Zhao, X. Wang, A. Huerta-Chagoya, C. Hu, S. Moon, J. Long, S.H. Kwak, A. Rasheed, R. Saxena, R.C. Ma, Y. Okada, M. Iwata, J. Hosoe, N. Shojima, M. Iwasaki, H. Fujita, K. Suzuki, J. Danesh, T. Jorgensen, M.E. Jorgensen, D.R. Witte, I. Brandslund, C. Christensen, T. Hansen, J.M. Mercader, J. Flannick, H. Moreno-Macias, N.P. Burtt, R. Zhang, Y.J. Kim, W. Zheng, J.R. Singh, C.H. Tam, H. Hirose, H. Maegawa, C. Ito, K. Kaku, H. Watada, Y. Tanaka, K. Tobe, R. Kawamori, M. Kubo, Y.S. Cho, J.C. Chan, D. Sanghera, P. Frossard, K.S. Park, X.O. Shu, B.J. Kim, J.C. Florez, T. Tusie-Luna, W. Jia, E.S. Tai, O. Pedersen, D. Saleheen, S. Maeda, T. Kadowaki, Genome-wide association studies in the Japanese population identify seven novel loci for type 2 diabetes, Nat. Commun. 7 (2016) 10531.
[43] T. Uenaka, W. Satake, P.C. Cha, H. Hayakawa, K. Baba, S. Jiang, K. Kobayashi, M. Kanagawa, Y. Okada, H. Mochizuki, T. Toda, In silico drug screening by using genome-wide association study data repurposed dabrafenib, an anti-melanoma drug, for Parkinson's disease, Hum. Mol. Genet. 27 (22) (2018) 3974–3985.
[44] S. Sakaue, Y. Okada, GREP: genome for REPositioning drugs, Bioinformatics 35 (19) (2019) 3821–3823.
[45] M.C. Mills, C. Rahal, A scientometric review of genome-wide association studies, Commun. Biol. 2 (2019) 9.
[46] E.C. Hayden, Technology: the $1,000 genome, Nature 507 (7492) (2014) 294–295.
[47] A. Rhoads, K.F. Au, PacBio sequencing and its applications, Genom. Proteom. Bioinf. 13 (5) (2015) 278–289.
[48] M. Jain, S. Koren, K.H. Miga, J. Quick, A.C. Rand, T.A. Sasani, J.R. Tyson, A.D. Beggs, A.T. Dilthey, I.T. Fiddes, S. Malla, H. Marriott, T. Nieto, J. O'Grady, H.E. Olsen, B.S. Pedersen, A. Rhie, H. Richardson, A.R. Quinlan, T.P. Snutch, L. Tee, B. Paten, A.M. Phillippy, J.T. Simpson, N.J. Loman, M. Loose, Nanopore sequencing and assembly of a human genome with ultra-long reads, Nat. Biotechnol. 36 (4) (2018) 338–345.
[49] S. Mitsuhashi, S. Nakagawa, M. Takahashi Ueda, T. Imanishi, M.C. Frith, H. Mitsuhashi, Nanopore-based single molecule sequencing of the D4Z4 array responsible for facioscapulohumeral muscular dystrophy, Sci. Rep. 7 (1) (2017) 14789.
[50] D. Beyter, H. Ingimundardottir, H.P. Eggertsson, E. Bjornsson, S. Kristmundsdottir, S. Mehringer, H. Jonsson, M.T. Hardarson, D.N. Magnusdottir, R.P. Kristjansson, S.A. Gudjonsson, S.T. Sverrisson, G. Holley, G. Eyjolfsson, I. Olafsson, O. Sigurdardottir, G. Masson, U. Thorsteinsdottir, D.F. Gudbjartsson, P. Sulem, O.T. Magnusson, B.V. Halldorsson, K. Stefansson, Long read sequencing of 1,817 Icelanders provides insight into the role of structural variants in human disease, Biorxiv (2020), doi:http://dx.doi.org/10.1101/848366.



Kotaro Ogawa, MD, is a graduate student in the department of Statistical Genetics at Osaka University. He graduated from Osaka University Medical School in 2011. He worked as a clinician in Kinki Central Hospital and Toyonaka Municipal Hospital. After clinical training, he entered Graduate School of Medicine, Osaka University in 2016. He has engaged in the genetic study of immune diseases, such as multiple sclerosis and psoriasis. His recent focus is translating GWAS results into applications for clinical medicine.