Original article

Genetic association of IL2RA, IL17RA, IL23R, and IL31RA single nucleotide polymorphisms with alopecia areata

Mansour A. Alghamdi a,b, Laith N. AL-Eitan c,e, Hanan A. Aljamal c, Ayed A. Shati d, Mohammed A. Alshehri d

a Department of Anatomy, College of Medicine, King Khalid University, Abha 61421, Saudi Arabia
b Genomics and Personalized Medicine Unit, College of Medicine, King Khalid University, Abha 61421, Saudi Arabia
c Department of Biotechnology and Genetic Engineering, Jordan University of Science and Technology, Irbid 22110, Jordan
d Department of Child Health, College of Medicine, King Khalid University, Abha 61421, Saudi Arabia

A R T I C L E   I N F O

Article history:
Received 1 November 2021
Revised 26 August 2022
Accepted 21 September 2022
Available online 27 September 2022

Keywords:
Alopecia areata
Autoimmunity
Genetic predisposition
Hair disorders
Multifactorial disease

A B S T R A C T

The signalling of cytokine receptors plays a crucial role in regulating tolerance and immunity. Impaired immunological processes result in autoimmune inflammation that target the hair follicles, causing many hair disorders, mainly alopecia areata (AA). Therefore, polymorphisms in cytokine receptor genes are suggested to have a significant impact on the pathogenesis of AA, a disease with a multifactorial basis and uncertain etiology. In the present study, 152 AA patients of the Jordanian population were investigated for their genetic susceptibility to develop AA compared to 150 control subjects. Genomic DNA extraction and genotyping had conducted for IL17RA (rs879575, rs2229151, and rs4819554), IL2RA (rs3118470), IL23R (rs10889677), and IL31RA (rs161704) using the Sequenom MassARRAY® system. The allele frequency of IL17RA rs879575 is significantly higher in patients, while no statistical differences were found for IL2RA, IL23R, and IL31RA SNPs. Also, the recessive model of IL31RA rs161704 showing that AA genotype is significantly associated with AA development. To date, there is no published data regarding the association between AA and the selected genetic variants in our population. However, this study's findings assert that SNPs of IL17RA and IL31RA are linked to AA susceptibility in Jordanian patients.

© 2022 The Author(s). Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Increased daily hair loss (effluvium) and noticeable hairlessness (alopecia) are the most common symptoms of hair disorders with a variety range of pathogenesis (Courtois et al., 1996; Wolff et al., 2016). Alopecia areata (AA) is a tissue-specific, inflammatory disorder that targets hair follicles resulting in its loss (Wasserman et al., 2007; Miao et al., 2014; Pratt et al., 2017; Lee et al., 2018). AA features a sudden onset of patchy, non-scarring hair loss with a recurrent course (Alkhalifah et al., 2010; Biran et al., 2015; Villasante Fricke and Miteva, 2015; Pratt et al., 2017). Hair loss course has various patterns and severity, where some might develop into total scalp or entire body hair loss (Finner, 2011; Forstbauer et al., 2012; Strazzulla et al., 2017).

Although the exact etiology of AA is not fully elucidated, AA is considered to be a multifactorial disorder (Moravej et al., 2018; Olayinka and Richmond, 2021). Genetic predisposition, immunological and environmental factors are aggravating facets in the disease development (Islam et al., 2015; Biran et al., 2015; Pratt et al., 2017; Olayinka and Richmond, 2021). Recently, research unveiled a strong genetic association of AA based on genome-wide association studies (GWAS) and positive family history incidence (Alkhalifah et al., 2010; Olayinka and Richmond, 2021). The latter of which accounts for 10–42 % of patients with AA (Aytekin et al., 2015). Several genes encoding immune components are con-
tributed to the induction of AA, indicated its polygenic basis (Kalish and Gilhar, 2003; Olayinka and Richmond, 2021). Since there is evidence of hair follicle autoantigens attack mediated by T cells, genes and their corresponding variations encoded by T cells have reported to increase AA susceptibility.

Among those genes expressed by T cells, interleukin 2 receptor subunit alpha (IL2RA) that identified by several GWAS on selected cytokines genes associated with AA (Petukhova et al., 2010; Miao et al., 2014; Moravej et al., 2018; Olayinka and Richmond, 2021). IL2RA is constitutively expressed in regulatory T cells (Tregs), which promotes immunity homeostasis and suppression of autoantigen-mediated immune response (Malek and Castro 2010; Redler et al., 2012; Biran et al., 2015). IL17RA is another signature gene in AA development; a highly polymorphic gene that encodes Interleukin-17 receptor subunit alpha (IL17RA). This cytokine receptor has a role in inflammatory regulations and disease progression (Moseley et al., 2003; Korppi et al., 2020). Genetic variants in IL17RA have been associated with the risk of autoimmune disorders, as well as cancerous, inflammatory, and infectious conditions (McGovern et al., 2009; Lew et al., 2012; Catanoso et al., 2013; Jiang et al., 2015; Batalla et al., 2015). Furthermore, IL23 receptor (IL23R) which binds to its cytokine (IL23) is essential for inflammation and immune response mediated by T-helper 17 (Th17) cell (Jürgens et al., 2010; Lucàfò et al., 2018). Polymorphisms in IL23R gene encoding IL23 cytokine receptor plays an important role in the pathogenesis of several chronic diseases including AA (Bojko et al., 2018; Bojko et al., 2018; Mosallaeei et al., 2019; Ruysen-Witrand et al., 2019; Zhu et al., 2020; Tabatabaei-Panah et al., 2020). The newly discovered human IL-31RA gene, which encodes the inflammatory interleukin 31 receptor subunit alpha (IL-31RA), is participating in immune responses regulation (Zhang et al., 2008). IL-31RA is expressed by several cell types (Saito et al., 2017), however, the genetic variants of IL-31RA have not been well studied regarding its role in AA pathogenesis, yet there is several observations with other diseases (Lin et al., 2010; He et al., 2020) suggested its association with AA (Lee et al., 2013). Therefore, it would be of a great impact to investigate the genetic association of IL2RA, IL17RA, IL23R and IL31RA polymorphisms as pathogenic markers in AA patients compared with control cases in the Jordanian population.

2. Materials and methods

2.1. Study population and ethics

This study has conducted under the Human Ethics Standard and the IRB guidelines (Ref. 13/104/2017) of Jordan University of Science and Technology (JUST), King Abdullah University Hospital (KAUH), and Jordanian Royal Medical Services (JRMS). From dermatology clinics of JRMS and KAUH hospitals, blood samples, in addition to clinical data were collected after obtaining signed written informed consent from participants/their guardians. AA patients (n = 152) of both sexes; 107 males and 45 females (29.6 %) aged between 13 and 67 years have been assessed based on the standard evaluation guidelines for AA identification of Olsen et al. (2004). Meanwhile, 129 (86 %) control males and 21 (14 %) females with an age range between 17 and 64 years and no history of AA were recruited (they visited the dermatology clinics for other dermatological concerns).

2.2. Extraction and genotyping of genomic DNA

Upon research collaboration with Al-Eitan et al. (2019), Wizard® Genomic DNA Purification Kit (Qiagen, Germany) has supplied for genomic DNA (gDNA) isolation of 5 SNPs within three interleukin receptor genes. These genes and associated SNPs including IL17RA rs879575 (exon region), rs2229151 (exon region), and rs4819554 (promoter region); IL2RA rs3118470 (intron region); IL23R rs10889677 (3- untranslated region (UTR)); and IL31RA rs161704 (exon region). Upon partnership with the Australian Genome Research Facility (AGRF), genotyping was performed in duplicate (success rate ≥ 95 %) using the Sequenom MassARRAY® system (Sequenom, San Diego, CA, USA).

2.3. Statistical analysis

Statistical Package for the Social Sciences (SPSS) software version (v. 21.0; IBM Corporation, New York, USA) and the SNPStats web tool (https://www.snpstats.net/start.htm) are used for genotype, allele, and haplotype association and frequencies, including ascertainment bias examination, where deviations from Hardy-Weinberg equilibrium (HWE) has examined by the chi-square ($\chi^2$) test. A P-value lower than 0.05 is estimated to be a statistically significant value.

3. Results

The present study is a continuation study of a project that investigates the genetic association of candidate genes with AA and the related phenotypes among the Jordanian population (Al-Eitan et al., 2019). A total of 152 AA patients (107 males and 45 females) and 150 control subjects (129 males and 21 females) were participated in this study with age (mean ± SD) of 31.144 ± 12.41 and 33.9 ± 9.81, respectively. The onset age of AA was 27.328 ± 12.57 years, where patients divided into two age groups. Of which, 87 (57.3 %) were affected before reaching their thirty at young ages, while less than half (65, 42.7 %) were affected when they are thirty or older. Differences of both age and gender did not reach any statistical significance.

The clinical subtypes of AA were assessed based on the guidelines of Olsen et al. (2004). Accordingly, patients were classified into three categories: patchy alopecia (PA), alopecia totalis (AT), and alopecia universalis (AU). Most of the patients having mild (patchy) AA (137, 90.13 %), followed by far less common severe AA forms; AU (10, 6.57 %) and AT (5, 3.28 %). The AA sites were scalp in 92 patients (60.5 %), hair-bearing sites of the face (i.e., eyelashes, eyebrows, and beard) in 35 (23.02 %), scalp and face in 8 (5.3 %), and other body parts (i.e., axillary hair and pubic hair) in 4 (2.63 %). Nail changes such as pitting, brittleness, and striations were seen in 11 (7.3 %) patients, while the other 141 (92.7 %) patients reported no associated abnormalities. Moreover, about one-third (48, 31.6 %) of the patients have symptoms associated with the disease before hair loss begins, while the remaining 104 (68.4 %) cases were asymptomatic.

Allelic distributions of the studied SNPs were in HWE in all study population, except for the IL17RA rs879575 in the control group (Table 1). Differences in the distribution of both genotypes and alleles with AA development did not reveal any statistical significance (Table 2). The frequency of allele C in IL17RA was 92 % (238) in the patients compared to 91 % (228) among the control group (Table 2). In addition, genetic models (codominant, dominant, and recessive) were evaluated in both AA patients and control individuals (data shown for IL31RA rs161704 only). Among these, there was a statistically significant difference found in the recessive model of IL31RA rs161704 ($P = 0.032$, Table 3). Haplotype frequencies of the blocks were estimated for the IL17RA polymorphisms showing no association with AA susceptibility (Table 4).
Table 1
Minor allele frequencies and HWE P-values for AA cases and controls.

| Gene   | SNP       | Control (n = 150) | Case (n = 152) |
|--------|-----------|------------------|----------------|
|        | MA<sup>a</sup> | MAF<sup>b</sup> | HWE P-value | MA<sup>a</sup> | MAF<sup>b</sup> | HWE P-value |
| IL17RA | rs879575  | T 0.23           | 0.019        | T 0.22         | 0.23 |
|        | rs2229151 | A 0.0            | 1            | A 0.0          | 1 |
|        | rs4819554 | G 0.14           | 0.73         | G 0.12         | 1 |
| IL2RA  | rs3118470 | C 0.2            | 1            | C 0.25         | 0.83 |
| IL23R  | rs10889677| A 0.39           | 0.73         | A 0.39         | 0.49 |
| IL31RA | rs161704  | A 0.24           | 1            | A 0.31         | 0.09 |

<sup>a</sup> MA: Minor Allele.  
<sup>b</sup> MAF: Minor Allele Frequency.

Table 2
Association of IL17RA, IL2RA, IL23R and IL31RA with AA susceptibility.

| Gene   | SNP       | Allele/ genotype | Control (n, %) | Case (n, %) | P-value |
|--------|-----------|------------------|----------------|-------------|---------|
| IL17RA | rs879575  | C 228, 91        | 238, 92        | 0.80        |
|        |           | T 23, 9          | 22, 8          | 0.85        |
|        | rs2229151 | CC 93, 63        | 96, 63         |             |
|        |           | CT 42, 28        | 46, 30         |             |
|        | rs4819554 | TT 13, 9         | 10, 7          |             |
| IL2RA  | rs3118470 | A 256, 86        | 268, 88        | 0.67        |
|        |           | C 40, 14         | 36, 12         |             |
|        | rs10889677| AA 11, 75        | 118, 78        | 0.79        |
| IL31RA | rs161704  | AG 34, 23        | 32, 21         |             |
|        |           | GG 146, 99       | 151, 99        |             |
|        | rs2229151 | A 256, 86        | 268, 88        | 0.67        |
|        |           | G 40, 14         | 36, 12         |             |
|        |             | AA 11, 75        | 118, 78        | 0.79        |
|        | rs4819554  | GT 13, 9         | 10, 7          |             |
|        |           | CT 42, 28        | 46, 30         |             |
|        | IL23R     | TT 13, 9         | 10, 7          |             |
|        | rs10889677| A 256, 86        | 268, 88        | 0.67        |
|        |           | C 40, 14         | 36, 12         |             |
|        |             | AA 11, 75        | 118, 78        | 0.79        |
|        | rs161704   | AG 34, 23        | 32, 21         |             |
|        |           | GG 146, 99       | 151, 99        |             |

Table 3
Genetic model associated with AA susceptibility (data for IL31RA rs161704).

| Gene   | SNP       | Model       | Genotype | Controls (n, %) | Patients (n, %) | OR (95 % CI) | P-value |
|--------|-----------|-------------|----------|----------------|----------------|--------------|---------|
| IL31RA | rs161704  | Codominant  | G/G      | 84 (57.5 %)    | 77 (50.7 %)    | 1.00         | 0.089   |
|        |           |             | G/A      | 54 (37 %)      | 56 (36.8 %)    | 1.13 (0.70–1.84) |   |
|        |           |             | A/A      | 8 (5.5 %)      | 19 (12.5 %)    | 2.59 (1.07–6.26) |   |
|        |           | Dominant    | G/G      | 84 (57.5 %)    | 77 (50.7 %)    | 1.00         | 0.23    |
|        |           |             | G/A-A/A  | 62 (42.5 %)    | 75 (49.3 %)    | 1.32 (0.84–2.08) |   |
|        |           | Recessive   | G/G-G/A  | 138 (94.5 %)   | 133 (87.5 %)   | 1.00         | 0.032   |
|        |           |             | A/A      | 8 (5.5 %)      | 19 (12.5 %)    | 2.46 (1.04–5.82) |   |

Table 4
Haplotype frequencies of IL17RA gene variants (rs879575, rs2229151, rs4819554).

| Haplotype | Total | Control | Patient | OR (95 % CI) | P-value |
|-----------|-------|---------|---------|--------------|---------|
| CGA       | 0.6806| 0.6715  | 0.6881  | 1.00         | -       |
| TGA       | 0.1894| 0.19    | 0.1902  | 0.99 (0.65–1.51) | 0.98 |
| CGG       | 0.0927| 0.0954  | 0.0915  | 0.94 (0.51–1.74) | 0.86 |
| TGG       | 0.0339| 0.0398  | 0.0269  | 0.65 (0.20–2.07) | 0.46 |
4. Discussion

AA is one of the predominant autoimmune diseases, and the second among hair loss disorders following androgenetic alopecia. AA has complex and unclear pathomechanism, which may explain its varied epidemiology, clinical features, and treatment options (Villasante Fricke and Miteva, 2015). The disease can occur at any age, more frequently in the young population, which is the case in the current study where more than half of the patients younger than 30 years old (mean ± SD age at diagnosis 27.328 ± 1.257). According to a retrospective review of the Rochester Epidemiology Project (REP: 1990–2009) of AA patients, the men age at diagnosis was 3.63 years (Mirzoyev et al., 2014). Moreover, it found that 47.9 % of AA patients are in the range of 21 and 40-years of age, with 24.2 and 26.7 years as the mean age of onset for females and males, respectively (Tan et al., 2002). Several observations suggested that male patients are more likely to be diagnosed at an earlier age (less than 10 years) compared to females. Female patients are often diagnosed in adolescence (10–20 years) and showing a greater tendency for nail abnormalities and associated autoimmune diseases, particularly thyroid disease (Lundin et al., 2014; Darwin et al., 2018). Although there is evidence of clinical and epidemiology heterogeneity of AA between genders, many reports found no differences based on sex or ethnicity (Goh et al., 2006; Mirzoyev et al., 2014; Miao et al., 2014; Moravvej et al., 2018). Consistent with this report where no differences of age and gender reflects in the incidence of AA. On the other hand, different worldwide studies reported either a female predominance (Barahmani et al., 2009; Kyrilakis et al., 2008; Lundin et al., 2014) or a male predominance (Ebling and Rook, 1972; Yang et al., 2004; Kavak et al., 2008). These differences in gender incidence might be due to recruiting bias, which mainly a result of cultural background and the psychological state of patients associated with the disease.

Compatible with the findings of this study and according to AA studies conducted on different ethnicities, the patchy subtype was the most common form presenting in more than 60 % of the patients, while AT, AU, and AT/AU subtypes showed in less than 20 % of the cases (Lew et al., 2012; Miao et al., 2014; Aytekin et al., 2015; Hamed et al., 2018; Seleit et al., 2021). Although AA can be found anywhere on the body, scalp is being the most often affected site in more than half of the reported cases. The other hair-bearing sites such as the eyebrows, eyelashes, beard, axillary, and pubic hair account for less than third of the patients (Finner, 2011; Lew et al., 2012; Aytekin et al., 2015; Seleit et al., 2021). Additionally, AA can involve nail changes where abnormalities occur in 10–66 % of the patients (Finner, 2011). Typical abnormalities might include shallow pits up to trachyonychia (Finner, 2011; Villasante Fricke and Miteva, 2015). However, nail involvement is unusual prognostic factor since it correlated with the more severe forms of AA (Villasante Fricke and Miteva, 2015; Pratt et al., 2017). This observation might explain that only 9.8 % of our patients having one of the severe forms of alopecia (AT and AU) and nail involvement reported in less than 10 % of the cases.

The molecular mechanisms underlying the pathogenesis of AA are not completely understood. Nevertheless, based on various studies, genetic variants play a key role in the disease development and progression. Particularly, genes that mediated immunological responses of T cells that target hair follicle autoantigens (Ito and Tokura, 2014). IL2RA, which binds IL-2 and regulates Tregs immune responses (Cheng et al., 2011), has been well investigated for its genetic association with the pathogenesis of AA in different populations. IL2RA rs3118470 has been reported as a prognostic marker for AA susceptibility based on GWAS analysis of North American patients (Petukhova et al., 2010) and cases from the United State and Central Europe (Betz et al., 2015). Also, case-control evidence suggested the involvement of rs3118470 with AA among Chinese (Miao et al., 2014), Iranian (Moravvej et al., 2018), German and Belgium populations (Redler et al., 2012). For the Jordanian population, rs3118470 has never been studied for its potential association with AA, however, the current results contradict these findings, where IL2RA rs3118470 lacks any significant linkage. Similarly, the IL23R rs10889677 variant was associated with the amenability to generate AA in Iranian population (Tabatabaei-Panah et al., 2020), but not in the Jordanian patients. Another vital receptor is IL17RA that has been studied for its association with AA susceptibility for the first time in the Korean population (Lew et al., 2012). The association of IL17RA variants rs879575, rs2229151, and rs4819554 with AA lack any significant differences of expression in patients’ group, clinical subtype, nail and body hair involvement, and age of onset, except for the rs4819554, where it showed a significant difference with AA onset (Lew et al., 2012). These observations are in agreement with our findings in which rs2229151, rs4819554 and rs879575 variants also lack any relation with the AA incidence. The genetic association of IL31RA rs161704 is a rarely investigated variant according to the literature search in the database (https://www.ncbi.nlm.nih.gov/snp/rs161704). In a whole-exome sequencing (WES) study of some immune-related genes, rs161704 has emerged as a unique marker associated with AA, having A allele as a risk factor in the dominant model (Lee et al., 2013). Herein, this variant appears to be a candidate locus associated with the recessive model of AA where A allele had a significantly higher distribution in the patients considering it a risk factor for increasing AA susceptibility in Jordanians.

5. Conclusion

Our findings showed that IL17RA rs879575 and IL31RA rs161704 variants are not associated with AA susceptibility among Jordanian patients. These observations support the multifactorial/ polygenetic nature of AA where the genetic factors of the disease vary from one ethnicity to another. However, the involvement of larger sample sizes is highly recommended in future studies in addition to further investigation of AA risk alleles among patients of Arab descent, which will provide better insights into AA pathogenesis in the region and globally as well.

Funding

The authors extend their appreciation to the Deanship of Scientific Research at King Khalid University for funding this work through Small Groups Project (Grant No: RGP. 1/66/43).

CRediT authorship contribution statement

Mansour A. Alghamdi: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. Lath N. Al-Eitan: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. Hanan A. Aljamal: Data curation, Methodology, Software, Writing – original draft, Writing – review & editing. Ayed A. Shati: Conceptualization, Investigation, Project administration, Visualization. Mohammed A. Alshehri: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Visualization.
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study received DNA samples for patients and control individuals from Al-Eitan et al., group working on genetic association of AA project in Jordanian patients that funded by the Deanship of Research at Jordan University of Science and Technology (JUST). Jordan (RN: 104/2017). The authors would also thanks King Khalid University (KKU), Saudi Arabia, for providing administrative and technical support.

References

Al-eitan, L.N., Al-Eitan, H.A., Aljamar, M.A., Alghamdi, M.A., Muhanna, A.M., Al-Qarqaz, F.A., 2019. Candidate Gene Analysis Of Alopecia Areata In Jordanian Population Of Arab Descent: A Case-Control Study. Appl. Clin. Genet. 12, 221–228. https://doi.org/10.2147/ACCG.S26664.

Alkilahif, A., Alsantali, A., Wang, E., McElwee, K.J., Shapiro, J., 2010. Alopecia areata: New approaches, new findings, new treatments. J. Investig. Dermatol. Symp. Proc. 8, 164–167. https://doi.org/10.1038/ncomms6966.

Betiz, R.C., Petukhova, L., Riplek, S., Huang, H., Menelaou, A., Redler, S., Becker, T., Heilmann, S., Yamany, T., Duvin, M., Hordinsky, M., Norris, D., Price, V.H., 2014. Genome-wide meta-analysis in alopecia areata resolves HLA associations and reveals two new susceptibility loci. Nat. Genet. 46, 1034–1040. https://doi.org/10.1038/ng.2984.

Biran, R., Zlotogorski, A., Ramot, Y., 2015. The genetics of alopecia areata: New approaches, new findings, new treatments. J. Investig. Dermatol. 135, 213–217. https://doi.org/10.1016/j.jid.2013.464.

Bojko, A., Ostasz, R., Białecka, M., Klimowicz, A., Malinowski, D., Budawski, R., Bojko, P., Drozdzik, M., Kurzawa, M., 2018. IL18R, IL23A and HLA-C06 genetic variants in psoriasis susceptibility and response to treatment. Hum. Immunol. 79, 213–217. https://doi.org/10.1016/j.humimm.2018.02.003.

Catanoso, M.G., Boiardi, L., Macchioni, P., Garagnani, P., Sazzini, M., De Fanti, S., Forstbauer, L.M., Brockschmidt, F.F., Moskvina, V., Herold, C., Redler, S., Göke, B., Forstbauer, L.M., Brockschmidt, F.F., Moskvina, V., Herold, C., Redler, S., Göke, B., 2012. Genome-wide pooling approach identifies SPATA5 as a new susceptibility locus for alopecia areata. Eur. J. Hum. Genet. 20, 326–332. https://doi.org/10.1038/ejhg.2011.285.

Courtois, M., Loussouarn, G., Hourseau, S., Grollier, J.F., 1996. Periodicity in the growth and shedding of hair. Br. J. Dermatol. 134, 47–54. https://doi.org/10.1111/j.1365-2131.1996.00748.x.

Darwin, E., Hirt, P.A., Fertiç, R., Delcanto, G., Jimenez, J.J., 2018. Pharmacogenetics of treatments for inflammatory bowel disease. Expert Opin. Drug Metab. Toxicol. 12, 1049–1055. https://doi.org/10.1080/08820139.2018.1480032.

Dey, S., Singh, Y., Do Han, K., Park, Y.M., Lee, J.Y., Park, Y.G., Lee, Y.B., 2018. Cancer risk by subtype of the alopecia. Sci. Rep. 8, 1–7. https://doi.org/10.1038/s41598-018-28142-1.

Lew, B.L., Cho, H.R., Haw, S., Kim, H.J., Chung, J.H., Sim, W.Y., 2012. Association between IL17A/IL17RA gene polymorphisms and susceptibility to alopecia areata in the Korean population. Ann. Dermatol. 24, 61–65. https://doi.org/10.5021/ad.2012.24.1.61.

Lin, M.W., Lee, D.D., Liu, T.T., Lin, Y.F., Chen, S.Y., Huang, C.C., Weng, H.Y., Liu, Y.F., Tang, X., Ling, Y., 2010. Novel IL18R gene mutation and ancestral OSMR mutant allele in familial primary cutaneous amyloidosis. Eur. J. Hum. Genet. 18, 26–32. https://doi.org/10.1038/ejhg.2009.135.

Lundin, M., Chawa, S., Schadev, A., Bhanusali, D., Seiffert-Sinha, K., Sinha, A., 2014. Gender differences in alopecia areata. J. Drugs Dermatol. 13, 409–413.

McGovern, D.P.B., Rotter, J.I., Mei, L., Haritunians, T., Landers, C., Derkowski, C., Malek, T.R., Castro, I., 2010. Interleukin-2 Receptor Signaling: At the Interface Between Tolerogenic Cells and Autoimmunity. Immunity 31, 1523–1533. https://doi.org/10.1016/j.immuni.2009.11.004.

Mehmet, A.M., Meesters, C., Heilmann, S., Hallman, S., Hennies, H.C., Goebeler, M., Jung, A., Petsch, W.K., Kortüm, A.K., Moll, I., Kruse, R., Lutz, G., Wolff, H., Blauemier, B., Böhm, M., Krov, G., Becker, T., Nöthen, M. M., Betz, R.C., 2012. Genome-wide pooling approach identifies SPATA5 as a new susceptibility locus for alopecia areata. Eur. J. Hum. Genet. 20, 326–332. https://doi.org/10.1038/ejhg.2011.185.

Moravvej, H., Tabatabaei-Panah, P.S., Abgoon, R., Khorasani, L., Sokhandan, M., Torgerson, R.R., 2014. Lifetime incidence of alopecia areata in a randomly sampled Iranian population. Dermatol. Venereol. 22, 977–981. https://doi.org/10.1111/exd.12480.

Nahed, F.N., McDonagh, A.J.G., Almaghrabi, S., Bakri, Y., Messenger, A.G., Malek, T.R., Castro, I., 2010. Alopecia areata: Review of Epidemiology, Clinical Features, Pathogenesis, and New Treatment Options. Int. J. Trichol. 10, 51–60. https://doi.org/10.4103/0974-9755.6978.

Oliveira, J.B., Silva, S.P., Martini, M., Véries, J., Andrade, I.G., 2013. Alopecia areata prevalence by gender and age. J. Eur. Acad. Dermatol. Venereol. 29, 572–573. https://doi.org/10.1111/j.1468-3083.2008.02956.x.

Peytavi, U., Wolff, H., Lutz, G., Kruse, R., Bian, L., Amos, C.I., Lee, A., Gregersen, P.K., 2000. Interleukin-17 receptor A expression is associated with poor survival in gastric cancer patients. J. Clin. Exp. Pathol. 8, 7002–7008.

Sørli, D.M., Mathisen, H., Trefjell, F., Skjerven, C., Hauge, O.J., 2014. IL17RA rs4819554 and receptor IL-17RA expression is associated with poor survival in gastric cancer patients. J. Clin. Exp. Pathol. 8, 7002–7008.

Yilmaz, A., Özgüc, G., Kılıç, M., Betz, R.C., 2012. Genome-wide pooling approach identifies SPATA5 as a new susceptibility locus for alopecia areata. Eur. J. Hum. Genet. 20, 326–332. https://doi.org/10.1038/ejhg.2011.285.
M.A. Alghamdi, I.N. Al-Eitan, H.A. Aljamal et al. Saudi Journal of Biological Sciences 29 (2022) 103460

Mosallaei, M., Simonian, M., Esmaeilzadeh, E., Bagheri, H., Miraghabajani, M., Salehi, A.R., Mehrzad, V., Salehi, R., 2019. Single nucleotide polymorphism rs10889677 in miRNAs Let-7e and Let-7f binding site of IL23R gene is a strong colorectal cancer determinant: Report and meta-analysis. Cancer Genet. 239, 46–53. https://doi.org/10.1016/j.cancergen.2019.09.003.

Moseley, T.A., Haudenschild, D.R., Rose, L., Reddi, A.H., 2003. Interleukin-17 family and IL-17 receptors. Cytokine Growth Factor Rev. 14, 155–174. https://doi.org/10.1016/S1359-6101(03)00002-9.

Olayinka, J. (Jadé) T., Richmond, J.M., 2021. Immunopathogenesis of alopecia areata. Curr. Res. Immunol. 2, 7–11. https://doi.org/10.1016/j.crimu.2021.02.001.

Olsen, E.A., Hordinsky, M.X., Price, V.H., Roberts, J.L., Shapiro, J., Canfield, D., Duciv, M., King, L.E., McMichael, A.J., Randall, V.A., Turner, M.L., Sperring, L., Whiting, D.A., Norris, D., 2004. Alopecia areata investigational assessment guidelines—Part II. J. Am. Acad. Dermatol. 51 (3), 440–447.

Petukhova, L., Duciv, M., Hordinsky, M., Norris, D., Price, V., Shimomura, Y., Kim, H., Singh, P., Lee, A., Chen, W.V., Meyer, K.C., Paus, R., Jehovah, C.A.B., Amos, C.L., Gregersen, P.K., Christiano, A.M., 2010. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature 466, 113–117. https://doi.org/10.1038/nature09114.

Pratt, C.H., King, L.E., Messenger, A.G., Christiano, A.M., Sundberg, J.P., 2017. Alopecia areata. Nat. Rev. Dis. Prim. 3, 1–17. https://doi.org/10.1038/nrdp.2017.11.

Redler, S., Albert, F., Brockschmidt, F.F., Herold, C., Hanneken, S., Eigelshoven, S., Giehl, K.A., Kruse, R., Lutz, G., Wolff, H., Blume-Peetavi, U., 2012. Investigation of selected cytokine genes suggests that IL2RA and the TNF/LTA locus are risk factors for severe alopecia areata. Br. J. Dermatol. 167, 1360–1365. https://doi.org/10.1111/j.1365-2133.2012.09331.x.

Safavi, K.H., Muller, S.A., Fiume, N.J., Moshell, A.N., Melton, L.J., 1995. Incidence of Alopecia Areata in Olmsted County, Minnesota, 1975 Through 1989. Mayo Clin. Proc. 70 (7), 628–633.

Saito, S., Aoki, A., Arai, I., Takaishi, S., Ito, H., Akiyama, N., Kiyonari, H., 2017. Regulation of Th2 responses by different cell types expressing the interleukin-31 receptor. Allergy. Asthma Clin. Immunol. 13, 1–11. https://doi.org/10.1186/s11722-017-0194-9.

Seleit, I.A., Mohamed, O.A.B., El-Hefnawy, S.M., Azooz, S.M., 2021. Interleukin 17A gene polymorphism in alopecia areata. MMJ 34, 23–28. https://doi.org/10.4103/ mmj.mmj.

Strazzulla, L.C., Wang, E.H.C., Avila, L., Lo Sicco, K., Brinster, N., Christiano, A.M., Shapiro, J., 2018. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. J. Am. Acad. Dermatol. 78, 1–12. https://doi.org/10.1016/j.jaad.2017.04.1141.

Tabatabaei-Panah, P.S., Moravej, H., Delpasand, S., Jafari, M., Sephehri, S., Abgoon, R., Ludwig, R.J., Akbarzadeh, R., 2020. IL12B and IL23R polymorphisms are associated with alopecia areata. Genes Immun. 21, 203–210. https://doi.org/10.1038/s41435-020-0100-1.

Tan, E., Tay, Y., Goh, C., Giam, Y.C., 2002. The pattern and profile of alopecia areata in Singapore – a study of 219 Asians Eileen Tan, MD, Yong-Kwang Tay, MD, Chee-Leok Goh, MD, and Yoke Ching Giam, MD. Int. J. Dermatol. 41, 748–753.

Villasante Frickie, A.C., Miteva, M., 2015. Epidemiology and burden of alopecia areata: A systematic review. Clin. Cosmet. Investig. Dermatol. 8, 397–403. https://doi.org/10.2147/CCID.S53995.

Wasserman, D., Guzman-Sanchez, D.A., Scott, K., McMichael, A., 2007. Alopecia areata. Int. J. Dermatol. 46, 121–131. https://doi.org/10.1111/j.1365-4632.2007.03193.x.

Wolff, H., Fischer, T.W., Blume-Peetavi, U., 2016. Diagnostik und Therapie von Haar- und Kopfhauterkrankungen. Dtsch. Arztebl. Int. 113, 377–386. https://doi.org/10.3238/arztebl.2016.0377.

Yang, S., Yang, J., Liu, B.B., Wang, H.Y., Yang, Q., Gao, M., Liang, Y.H., Lin, G.S., Lin, D., Hu, X.L., Fan, L., Zhang, X.J., 2004. The genetic epidemiology of alopecia areata in China. Br. J. Dermatol. 151, 16–23. https://doi.org/10.1111/j.1365-2133.2004.05915.x.

Zhang, Q., Putheti, P., Zhou, Q., Liu, Q., Gao, W., 2008. Structures and biological functions of IL-31 and IL-31 receptors. Cytokine Growth Factor Rev. 19, 347–356. https://doi.org/10.1016/j.cytogfr.2008.08.003.

Zhu, Y., Jiang, H.G., Chen, Z.H., Lu, B.H., Li, J., Shen, X.N., 2020. Genetic association between IL23R rs11209026 and rs10889677 polymorphisms and risk of Crohn’s disease and ulcerative colitis: evidence from 41 studies. Inflamm. Res. 69, 87–103. https://doi.org/10.1007/s00011-019-01296-y.