Original article

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

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ABSTRACT

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.

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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 feature 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; Aytekin et al., 2015). Based on ethnicity, typical AA affects 0.1–0.2 % of the global population, showing no age and sex preference (Safavi et al., 1995; Miao et al., 2014; Pratt et al., 2017; Strazzulla et al., 2018;).

Although the exact etiology of AA is not fully elucidated, AA is considered to be a multifactorial disorder (Moravvej 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; Moravvej 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 different 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; Lucafò 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; Mosallaei et al., 2019; Ruyssen-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 (70.4 %) 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-untraslated 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 SNPStat 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 (χ^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 % (2 3 8) in the patients compared to 91 % (2 2 8) 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[a]	MAF[b]	HWE P-value	MA[a]	MAF[b]	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

[a] MA: Minor Allele.
[b] 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	
		CC	93, 63	96, 63	0.85
		CT	42, 28	46, 30	
		TT	13, 9	10, 7	
	rs2229151	G	293, 100	303, 100	1.0
		A	1, 0	1, 0	
		GA	1, 1	1, 1	1.0
		GG	146, 99	151, 99	
	rs4819554	A	256, 86	268, 88	0.67
		G	40, 14	36, 12	
		AA	11, 75	118, 78	0.79
		AG	34, 23	32, 21	
		GG	3, 2	2, 1	
IL2RA	rs3118470	A	236, 80	227, 75	0.40
		C	60, 20	77, 25	
		AA	6, 4	9, 6	0.41
		AC	48, 32	59, 39	
		CC	94, 64	84, 55	
IL23R	rs10889677	C	177, 61	185, 61	1.0
		A	115. 39	117, 39	
		AA	24, 16	25, 17	0.96
		CA	67, 46	67, 44	
		CC	55, 38	59, 39	
IL31RA	rs161704	G	222, 76	210, 69	0.27
		A	70, 24	94, 31	
		AA	8, 5	19, 13	0.14
		GA	54, 37	56, 37	
		GG	84, 58	77, 51	

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 ± 12.57). 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 than10 years) compared to females. Female patients are often have 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; Kyriakis 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 AU, 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.

CRediT authorship contribution statement

Mansour A. Alghamdi: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Laith 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.

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