Longitudinal and Exploratory Genome-Wide Analysis in Alopecia AreaTA (LEGAATA): A Study of FinnGen Participants

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BACKGROUND

- Alopecia areata (AA) is an autoimmune disease characterized by nonscarring hair loss on the scalp, with or without loss of facial and/or body hair[1]
- Development of AA appears to be influenced by genetic, environmental, and immunological factors[2]
- The FinnGen database is a comprehensive biorepository used to analyze genetic and phenotypic data, aiding in the understanding of various diseases, including AA[3]
- This study used the FinnGen database to characterize AA-associated genetic variants, comorbidity burden, and healthcare utilization among patients diagnosed with AA in a large Finnish population

METHODS

Patients

- Participants in the FinnGen database aged 12 years or older were selected based on their diagnosis of AA (*International Classification of Diseases [ICD]-8, -9, or -10* codes) and who had data quality marked as "acceptable" in the database
- Quality control was performed using a SQL query and the FinnGen LifeTrack GUI tool to review the entire AA cohort and ensure it was truly representative of patients with AA

Analyses

- A **genome-wide association study (GWAS)** was conducted to identify genetic variants associated with AA. The analysis focused on single nucleotide polymorphisms across the genome. Participants were compared with unmatched controls from the FinnGen database
- The association between patients with AA compared with all FinnGen participants and the **polygenic risk scores** (**PRSs**; an estimate of the relative risk of developing a disease) of AA comorbidities was quantified using PRSs derived from the Polygenic Score (PGS) Catalog (https://www.pgscatalog.org/), an open database of published PGSs[4]
- **Phenotypic analyses** were performed to explore:
  - The relationship between AA and ICD codes for various comorbid conditions of interest with previously reported associations in AA (**Table 1**)
  - The use of specific treatments among patients with AA. Prescriptions of topical corticosteroids and topical calcineurin inhibitors were analyzed to provide insights into treatment patterns and their potential implications for patient care
- For the phenotypic analyses, participants were compared with age- and sex-matched controls (1:10)
- To examine the risk of developing the prespecified comorbidities in AA cases and matched controls, excess comorbidities were compared with the entire FinnGen biorepository using a binomial logistic regression model

Table 1. Comorbid conditions of interest

Group	Included Conditions
Atopic	Atopic dermatitis, allergic rhinitis, asthma
Cardiovascular and metabolic	Hypertension, obesity, diabetes mellitus, myocardial infarction, stroke
Gastrointestinal	Inflammatory bowel disease, irritable bowel syndrome
Connective tissue and dermatologic	Vitiligo, psoriasis, systemic lupus erythematosus, rheumatoid arthritis
Hematologic	Anemia, iron-deficiency anemia
Malignancies	Malignant neoplasms
Psychiatric	Anxiety, depression, obsessive-compulsive disorder, schizophrenia
Thyroid	Thyroid disorders, autoimmune thyroiditis, autoimmune hypothyroidism, Graves' disease

RESULTS

- A total of 1633 patients with AA and 374,073 controls were included in the GWAS analysis; 1302 (79.7%) patients with AA were female, and mean age at diagnosis was 46.5 years (SD, 17.0 years) (**Table 2**)

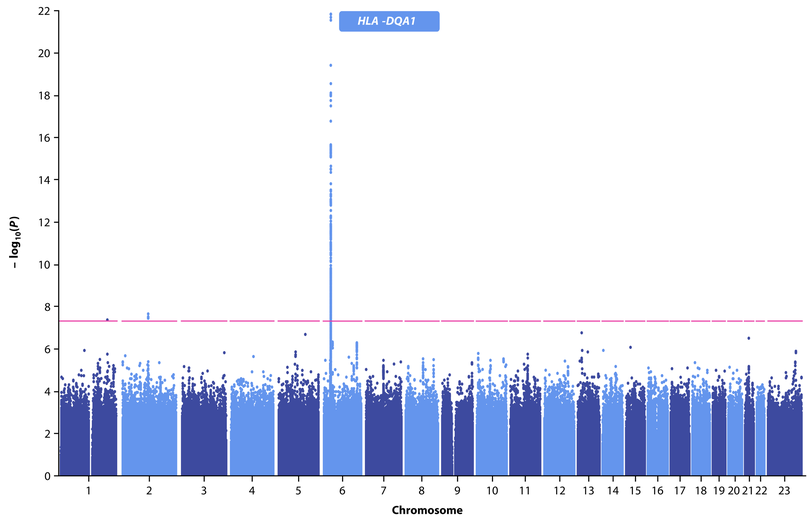
Table 2. Demographics of AA cases

	AA (n=1633)
Female, n (%)	1302 (79.7)
Age, mean (SD), years*	46.5 (17.0)
Time between cohort start and end, mean (SD), years	9.01 (8.11)

AA, alopecia areata.
*Age is defined as age at diagnosis of AA through ICD code assignment.

- The GWAS replicated previously identified genetic associations with AA located in the HLA region of chromosome 6, with the most significant signal observed for *HLA-DQA1* (P=1.54×10^{-22}) (**Figure 1**)[5,6]
- For the non-HLA variants identified in the GWAS, only the RAET1L (ULBP6) variants demonstrated significant associations with protein quantitative trait locus (pQTL) or expression quantitative trait locus (eQTL). RAET1L variants have shown previous significant GWAS associations with AA and are known to be involved in hair follicle immune privilege collapse[5-7]

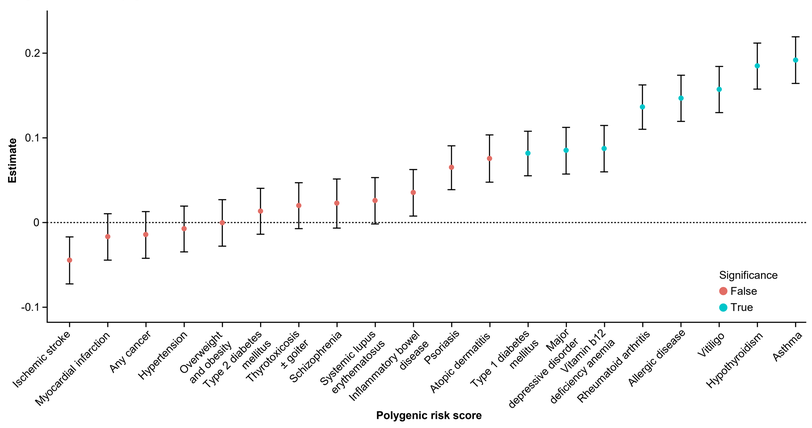
Figure 1. Manhattan plot of the GWAS of AA from the FinnGen dataset



GWAS, genome-wide association study.
Red line: genome-wide significance threshold (P<5×10^{-8}).

- Patients with AA had a significantly higher risk, as quantified by PRS analysis, of allergic diseases, asthma, hypothyroidism, major depressive disorder, rheumatoid arthritis, type 1 diabetes, vitamin B12 deficiency anemia, and vitiligo compared with all other FinnGen patients (**Figure 2**)

Figure 2. Polygenic risk* of other comorbidities in patients with AA (N = 1633)



AA, alopecia areata.
*Defined as being in the top 20% of the polygenic risk score distribution for each comorbidity.
Of the comorbid conditions examined in the phenotypic analyses, polygenic risk scores were not available for irritable bowel syndrome, iron deficiency anemia, anxiety, obsessive-compulsive disorder, and thyroid disorders.

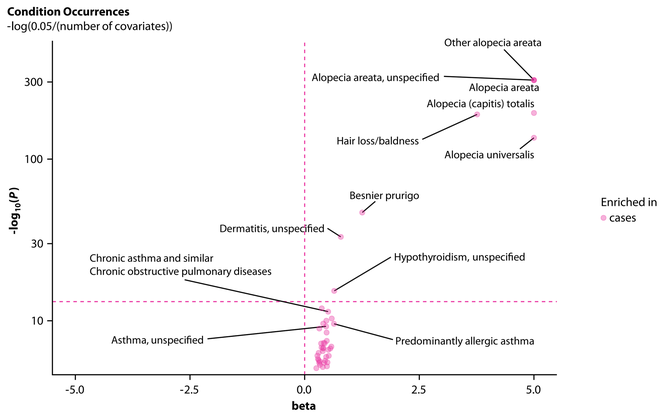
- For the phenotypic analyses, 15,689 matched controls were included (**Table 3**)
  - *ICD* codes for atopic dermatitis, allergic rhinitis, asthma, irritable bowel syndrome, vitiligo, psoriasis, anemia, anxiety, depression, thyroid disorders, autoimmune thyroiditis, and autoimmune hypothyroidism were significantly increased (P<0.05) in patients with AA vs matched controls
  - Association with AA was further confirmed by analysis of predefined endpoints; see https://risteys.finngen.fi/ for medical code definitions[8]
- **Figure 3** shows the comorbidities that were enriched in the AA group

Table 3. Prevalence of comorbidities of interest in the AA and matched control groups

Condition*	AA Cases (n=1633)	Matched Controls (n=15,689)†	OR	-log10(P)	P Value‡
Atopic					
Atopic dermatitis	278	887	3.42	51.15	7.31×10^{-68}**
Allergic rhinitis	103	476	2.15	9.74	4.16×10^{-12}**
Asthma	250	1476	1.74	12.09	4.92×10^{-14}**
Cardiovascular and metabolic		1352	5.15	141.9	9.48×10^{-194}**
Hypertension	385	3551	1.05	0.41	4.04×10^{-1}
Obesity	109	1018	1.03	0.12	8.12×10^{-1}
Diabetes mellitus	247	2228	1.08	0.50	3.28×10^{-1}
Myocardial infarction	46	459	0.96	0.06	8.64×10^{-1}
Stroke	117	1074	1.05	0.22	6.64×10^{-1}
Gastrointestinal					
Inflammatory bowel disease	50	359	1.35	1.23	6.09×10^{-2}
Irritable bowel syndrome	80	458	1.71	4.34	1.60×10^{-5}**
Connective tissue and dermatologic					
Vitiligo	16	10	15.51	10.11	1.88×10^{-18}**
Psoriasis	65	361	1.76	4.00	4.38×10^{-5}**
Systemic lupus erythematosus	10	50	1.93	1.15	8.89×10^{-2}
Rheumatoid arthritis	67	509	1.28	1.16	7.69×10^{-2}
Hematologic					
Anemia	123	964	1.24	1.50	3.18×10^{-2}**
Iron deficiency anemia	65	560	1.12	0.40	4.37×10^{-1}
Malignancies					
Malignant neoplasms	284	3005	0.89	1.07	9.01×10^{-2}
Psychiatric					
Anxiety	272	1885	1.46	6.73	8.00×10^{-8}**
Depression	266	1928	1.39	5.1	4.51×10^{-6}**
Obsessive-compulsive disorder	10	81	1.19	0.23	7.40×10^{-1}
Schizophrenia or delusion	55	458	1.16	0.5	3.46×10^{-1}
Thyroid					
Thyroid disorders	433	2722	1.72	17.62	9.07×10^{-20}**
Autoimmune thyroiditis	9	16	5.43	3.54	2.58×10^{-5}**
Autoimmune hypothyroidism	319	1919	1.74	14.62	7.76×10^{-17}**
Graves' disease	25	155	1.56	1.28	5.35×10^{-2}

AA, alopecia areata.
*Predefined Risteys endpoints for each condition are: L12_ATOPIC, ALLERG_RHINITIS, J10_ASTHMACOPDKELA, I9_HYPTENS, E4_OBESITY, E4_DIABETES, I9_MI_STRICT, C_STROKE, K11_IBD_STRICT, K11_IBS, L12_VITILIGO, L12_PSORIASIS, M13_SLE, M13_RHEUMA, D3_ANAEMIA, D3_ANAEMIA_IRONDEF, C3_CANCER, EXALLC, KRA_PSY_ANXIETY, EXMORE, F5_DEPRESSIO, F5_OCD, KRA_PSY_SCHIZODEL, EXMORE, E4_THYROID, E4_THYROIDITAUTOIM, E4_HYTHY_AI_STRICT, E4_GRAVES_STRICT. †1:10 matched controls n=15,699, from which 15,689 patients were included in the analysis. ‡P value represents difference in proportion between cases vs controls. **Statistically significant at P<0.05.

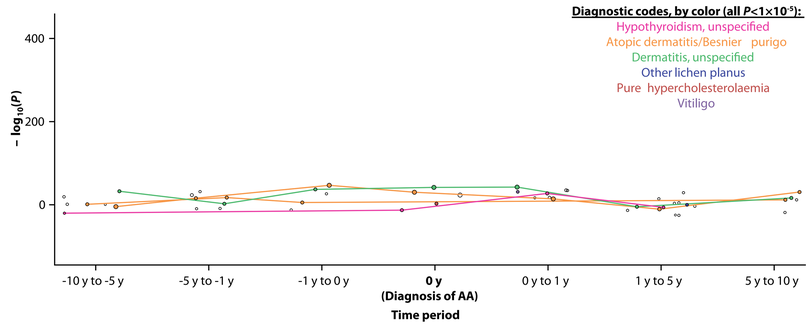
Figure 3. Comorbidities enriched in the AA group



AA, alopecia areata.
Only codes with P<1×10^{-5} and minimum 100 total cases were included.
Vertical line: right-hand side = increased expression in cases compared with controls; left-hand side = increased expression in controls compared with cases. Horizontal line: above = statistically significant; below = not statistically significant.

- Phenome-wide significant diagnoses of atopic dermatitis and hypothyroidism were observed over 10 years before AA diagnosis and persisted over time, while phenome-wide significant diagnoses of hypercholesterolemia, lichen planus, and vitiligo were new comorbidities observed after AA diagnosis (**Figure 4**)

Figure 4. Enriched diagnostic codes (*ICD*-8, -9, -10) in AA cases (N=1633) over time relative to diagnosis of AA



AA, alopecia areata.
The data point size is directly proportional to the number of codes. Points connected by solid lines represent codes with phenome-wide significance over the denoted time span. Conditions (*ICD*-10 codes): Hypothyroidism, unspecified (E03.9); Atopic dermatitis/Besnier prurigo (L20.0); Dermatitis, unspecified (L30.9); Other lichen planus (L43.8). Conditions (SNOMED codes): Pure hypercholesterolaemia (267432004); Vitiligo (56727007). Filters: Phenome-wide significant (P<1×10^{-5}) non-AA diagnostic codes and a minimum of 150 cases.

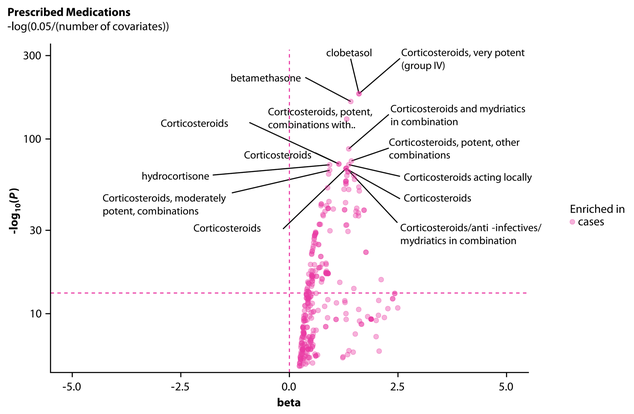
- In patients with AA, there was a significantly higher (P<0.05) number of prescriptions for topical corticosteroids and topical calcineurin inhibitors vs matched controls (**Table 4** and **Figure 5**)

Table 4. Medication usage in the AA and matched control groups

Drug	AA Cases (n=1633)	Matched Controls (n=15,689)*	OR	-log10(P)	P Value†
Corticosteroids, dermatological preparations‡					
Betamethasone, topical	915	3392	4.62	176.91	1.74×10^{-205}**
Mometasone, topical	704	2812	3.47	107.80	8.16×10^{-128}**
Hydrocortisone butyrate, topical	580	2744	2.60	59.69	3.97×10^{-69}**
Clobetasol, topical	534	1352	5.15	141.9	9.48×10^{-194}**
Hydrocortisone, topical	302	1043	3.19	49.92	1.27×10^{-64}**
Topical calcineurin inhibitors					
Tacrolimus, topical	34	38	8.76	15.96	3.60×10^{-27}**
Pimecrolimus, topical	21	15	13.61	12.45	1.56×10^{-22}**

AA, alopecia areata.
Listed ATC 5th codes are parenthesized: Betamethasone, topical (D07AC01); Mometasone, topical (D07AC13); Hydrocortisone butyrate, topical (D07AB02); Clobetasol, topical (D07AD01); Hydrocortisone, topical (D07AA02); Tacrolimus, topical (D11AH01); Pimecrolimus, topical (D11AH02).
*1:10 matched controls n=15,699, of which 15,689 patients were included in the analysis. †P value represents difference in proportion between cases vs controls; **, statistically significant at P<0.05. ‡Only the top 5 codes (based on highest number of counts in AA cases and controls) are presented for corticosteroids.

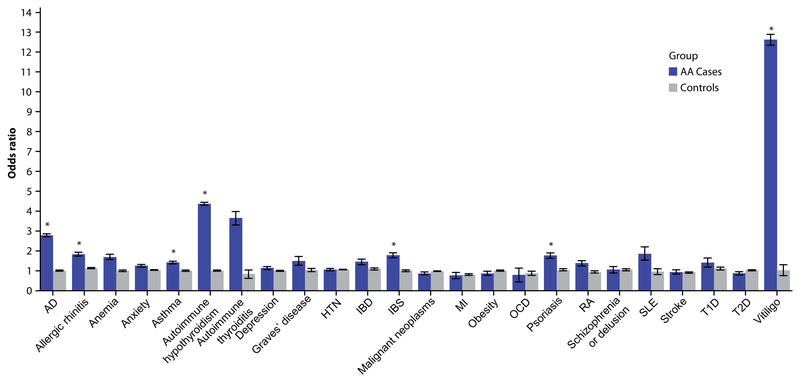
Figure 5. Prescribed medications enriched in the AA group vs matched controls



AA, alopecia areata.
Only codes with P<1×10^{-5} and minimum 100 total cases were included.
Vertical line: right-hand side = increased expression in cases compared with controls; left-hand side = increased expression in controls compared with cases. Horizontal line: above = statistically significant; below = not statistically significant.

- For the excess comorbidities analysis, AA cases demonstrated phenome-wide significant (P<1×10^{-5}) risk of developing atopic dermatitis, allergic rhinitis, asthma, autoimmune hypothyroidism, irritable bowel syndrome, psoriasis, and vitiligo compared with all patients in the FinnGen biorepository (**Figure 6**)

Figure 6. Excess comorbidities between AA cases and matched controls and other diseases in the FinnGen biorepository



AA, alopecia areata; AD, atopic dermatitis; HTN, hypertension; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; MI, myocardial infarction; OCD, obsessive-compulsive disorder; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; T2D, type 2 diabetes.
*Phenome-wide significance (P<1×10^{-5})

CONCLUSIONS

- This study is the first to use the FinnGen biorepository to characterize a large AA population in Finland
- Strong associations with HLA and RAET1L variants provide further supportive evidence for the autoimmune basis of AA and validate previous GWAS in different geographical populations[5,6]
- Patients had significantly higher risk of comorbidities, as quantified by PRS, highlighting the overall burden of disease of AA
- Phenotypic analysis of comorbidities validated previously implicated comorbidities in AA, while treatment usage phenotypic analysis contextualized available treatment options in Finnish patients with AA
- Prescriptions of topical corticosteroids and topical calcineurin inhibitors demonstrated phenome-wide significance (P<1×10^{-5}) in patients with AA vs controls. As new AA treatments emerge, replication of this analysis across different data sets would be of interest
- An inherent limitation of registry data is that data are collected from the time of *ICD* code assignment, which may not reflect when patients first developed AA
- The analysis did not capture the use of recently approved medications in Finland, such as baricitinib and ritlecitinib[9,10]
- Future combined meta-analyses exploring genotypic and phenotypic associations in detail could improve AA therapeutic strategies and guide personalized treatment approaches

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DISCLOSURES
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