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

Victoria Basey,[1] Lynn Petukhova,[2] Regina C. Betz,[3] Christos Tziotzios,[4] Michael Simpson,[5] Buket Basmanav,[3] Laura Huilaja,[6] Mary Pat Reeve,[7] Alexandre Lejeune,[8] Gulraj Matharu,[1] Emmi Tikkanen,[9] Simon Chen[10]

[1]Pfizer Ltd., Surrey, UK; [2]Columbia University, NY, USA; [3]Institute of Human Genetics, Medical Faculty and University Hospital Bonn, Bonn, Germany; [4]St John's Institute of Dermatology, King's College London, London, UK; [5]Department of Medical and Molecular Genetics, King's College London, London, UK; [6]Research Unit of Clinical Medicine, University of Oulu, Oulu, Finland; [7]Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, Helsinki, Finland; [8]Pfizer Inc., Paris, France; [9]Pfizer, Helsinki, Finland; [10]Pfizer Inc., NY, USA

BACKGROUND

- Alopecia areata (AA) is an autoimmune disorder characterized by nonscarring hair loss on the scalp, face, and/or body[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 utilized the FinnGen database to characterize AA-associated genetic variants, and to explore comorbidities and currently available treatment options for 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), whose data quality was flagged 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 to unmatched controls from the FinnGen database
- **Phenome-wide association studies (PheWAS)** 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 AA patients. 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 PheWAS, participants were compared to age- and sex-matched controls (1:10)

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 1,633 patients with AA and 374,073 controls were included; 1,302 (79.7%) patients with AA were female, and the mean age at diagnosis was 46.5 years (SD, 17.0 years) (**Table 2**)

Table 2. Demographics

	AA (n=1,633)
Female, n (%)	1,302 (79.7)
Age (years), mean (SD)*	46.5 (17.0)
Time (years) between cohort start and end, mean (SD)	9.01 (8.11)

*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=1.54x10^{-22}) (**Figures 1** and **2**)[4,5]
- Nominal significance (P<0.05) was also met for *IL2RA* (P<1.80x10^{-6}) and *ACOXL* (P<5.31x10^{-5}) (**Figure 2**)

Figure 1. Comparison of FinnGen GWAS with a previous meta-analysis

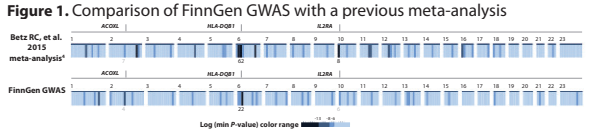
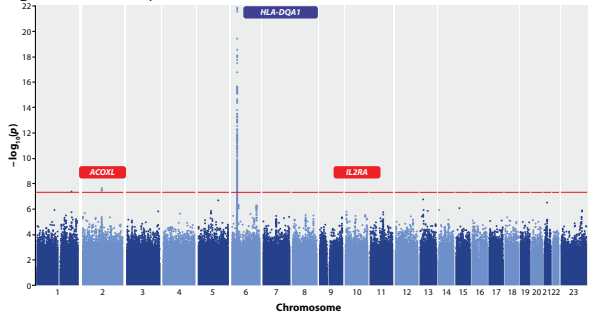


Figure 2. Manhattan plot of the GWAS of AA from the FinnGen dataset



Red line: genome-wide significance threshold (P<5x10^{-8}).

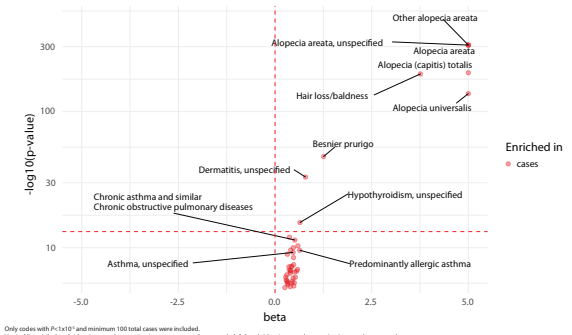
- For the PheWAS, 15,689 matched controls were included (**Table 3**)
  - ICD codes for atopic dermatitis, allergic rhinitis, asthma, vitiligo, anxiety, thyroid disorders, and autoimmune hypothyroidism were significantly increased (P<1x10^{-5}) in patients with AA vs controls
  - Association with AA was further confirmed by analysis of predefined endpoints; see https://risteys.finngen.fi/ for medical code definitions[6]
- **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=1,633)	AA controls (n=15,689)†	OR	-log10(p)
Atopic				
Atopic dermatitis	278	887	3.42	51.15
Allergic rhinitis	103	476	2.15	9.74
Asthma	250	1,476	1.74	12.09
Cardiovascular and metabolic				
Hypertension	385	3,551	1.05	0.41
Obesity	109	1,018	1.03	0.12
Diabetes mellitus	247	2,228	1.08	0.50
Myocardial infarction	46	459	0.96	0.06
Stroke	117	1,074	1.05	0.22
Gastrointestinal				
Inflammatory bowel disease	50	359	1.35	1.23
Irritable bowel syndrome	80	458	1.71	4.34
Connective tissue and dermatologic				
Vitiligo	16	10	15.51	10.11
Psoriasis	65	361	1.76	4.00
Systemic lupus erythematosus	10	50	1.93	1.15
Rheumatoid arthritis	67	509	1.28	1.16
Hematologic				
Anemia	123	964	1.24	1.50
Iron deficiency anemia	65	560	1.12	0.40
Malignancies				
Malignant neoplasms	284	3,005	0.89	1.07
Psychiatric				
Anxiety	272	1,885	1.46	6.73
Depression	266	1,928	1.39	5.1
Obsessive-compulsive disorder	10	81	1.19	0.23
Schizophrenia or delusion	55	458	1.16	0.5
Thyroid				
Thyroid disorders	433	2,722	1.72	17.62
Autoimmune thyroiditis	9	16	5.43	3.54
Autoimmune hypothyroidism	319	1,919	1.74	14.62
Graves' disease	25	155	1.56	1.28

*Predefined finngen 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_DY, ANAEMIA_DY, ANAEMIA_IRONDEF, C3_CANCER_EXALL, 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=15,689, from which 15,689 patients were included in the analysis.

Figure 3. Comorbidities enriched in the AA group



Only codes with P<1x10^{-3} and minimum 100 total cases were included.
Vertical line: right-hand side = increased expression in cases compared to controls; left-hand side = increased expression in controls compared to cases.
Horizontal line: above = statistically significant; below = not statistically significant.

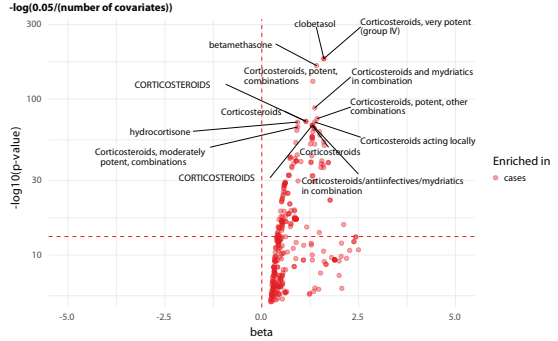
- Prescriptions of topical corticosteroids and topical calcineurin inhibitors demonstrated phenome-wide significance (P<1x10^{-5}) in patients with AA vs controls (**Table 4** and **Figure 4**)

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

Drug	AA cases (n=1,633)	AA controls (n=15,689)*	OR	-log10(p)
Corticosteroids, dermatological preparations†				
Betamethasone, topical	915	3,392	4.62	176.91
Mometasone, topical	704	2,812	3.47	107.80
Hydrocortisone butyrate, topical	580	2,744	2.60	59.69
Clobetasol, topical	534	1,352	5.15	141.9
Hydrocortisone, topical	302	1,043	3.19	49.92
Topical calcineurin inhibitors				
Tacrolimus, topical	34	38	8.76	15.96
Pimecrolimus, topical	21	15	13.61	12.45

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, from which 15,689 patients were included in the analysis.
†Only the top five codes (based on highest number of counts in AA cases and controls) are presented for corticosteroids.

Figure 4. Medication prescriptions enriched in the AA group



Only codes with P<1x10^{-3} and minimum 100 total cases were included.
Vertical line: right-hand side = increased expression in cases compared to controls; left-hand side = increased expression in controls compared to cases.
Horizontal line: above = statistically significant; below = not statistically significant.

CONCLUSIONS

- This study is the first to use the FinnGen biorepository to characterize a large AA population in Finland
- Strong replication of the HLA locus on chromosome 6 provides further supportive evidence for the autoimmune basis of AA and validates previous GWAS in different geographical populations[4,5]
- 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<1x10^{-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
- Future combined meta-analyses exploring genotypic and phenotypic associations in detail will strengthen these findings and further clinical understanding of AA

Presented at Winter Clinical - Hawaii 2025 Congress; February 14-19 2025; Waikoloa Village, HI, USA

REFERENCES

1. Gilhar A, et al. *N Engl J Med*. 2012;366:1515-1525.
2. Cheng Zhou, et al. *Clin Rev Allergy Immunol*. 2021;61:403-423.
3. Kurki MI, et al. *Nature*. 2023;613:508-518.
4. Betz RC, et al. *Nat Commun*. 2015;22:6:5966.
5. Petukhova L, et al. *Nature*. 2010;466:113-117.
6. Reeve MP, et al. *Am J Hum Genet*. 2024;111:1047-1060.

DISCLOSURES

This study was funded by Pfizer Inc. V Basey, A Lejeune, G Matharu, E Tikkanen, and S Chen report employment with and stock ownership in Pfizer Inc. C Tziotzios is a speaker for LEO Pharma; principal and chief investigator for Pfizer Inc; and consultant for Pfizer Inc.

https://scientificpubs.congressposter.com/p/im20wtf0g09u0du7