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

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Introduction & Objectives: 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. While the exact cause of AA remains unknown, genetic predisposition and environmental factors appear to play a role in disease development. The FinnGen database offers a unique opportunity to explore genetic and phenotypic characteristics of patients with AA in a large population. This study aimed to characterize AA-associated genetic variants, comorbidity burden, and healthcare utilization in the AA population in Finland (FinnGen study participants).

Materials & Methods: Adults and adolescents (aged ≥12 years) in the FinnGen biorepository with a diagnosis of AA (ICD-8, -9, or -10 codes) were identified. A genome-wide association study (GWAS) was carried out to identify genetic variants associated with AA. The association between patients with AA 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. Phenome-wide association studies (PheWAS) comparing patients with AA with age- and sex-matched healthy controls without AA (1:10 matching ratio) were used to examine the association between AA and (1) comorbid conditions of interest previously implicated in AA and (2) treatments used for AA.

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 (defined as age at ICD code assignment) was 46.5 years (SD, 17.0 years). 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; OR=0.70). Nominal significance (P<0.05) for loci previously published was also met for *IL2RA* (P<1.80x10-6) and *ACOXL* (P<5.31x10-5). Patients with AA had a significantly higher risk, as quantified by PRS, of hypothyroidism, vitiligo, allergic disease, and major depressive disorder. PheWAS revealed that 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 15,689 matched controls (see https://risteys.finngen.fi/ for medical code definitions). In patients with AA there were significantly higher (P<0.05) number of prescriptions for topical corticosteroids and topical calcineurin inhibitors vs controls.

Conclusion: This study is the first to use the FinnGen biorepository to characterize a large AA patient population in Finland. Strong replication of the HLA locus on chromosome 6 validates previous GWAS in different geographical populations. Phenotypic analysis of comorbidities validated previously implicated comorbidities in AA, while treatment usage phenotypic analysis highlighted available treatment options in Finnish patients with AA. Future combined meta-analyses of patients with AA from multiple geographies exploring genotypic and phenotypic associations in detail will corroborate these findings and enhance clinical understanding of AA.