

# An Imperative Need for Further Genetic Studies of Alopecia Areata



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Human genetic studies of diseases that are multifactorial and prevalent have generated a wealth of knowledge about the genetic architecture of chronic diseases. Generalizable attributes are shaping the development of models to explain how the human genome influences our health and can be leveraged to improve it. Importantly, both rare and common genetic variants contribute to disease risk and provide complementary information. Although initial genetic studies of alopecia areata have yielded insight with high clinical impact, there remains a number of important unanswered questions pertaining to disease biology and patient care that could be addressed by further genetic investigations.

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## INTRODUCTION

Alopecia areata (AA) is a prevalent autoimmune disease that is caused by an aberrant interaction between the immune system and hair follicle resulting in the infiltration and expansion of immune cell populations and destruction of the hair follicle. A genetic basis for the disease was first suggested by studies in families and twin pairs that demonstrated an increased risk of disease among family members (Blaumeiser et al., 2006; Jackow et al., 1998; Rodriguez et al., 2010). Genetic linkage studies in AA families provided definitive evidence for etiological contributions from rare variants, with the identification of several genomic regions with strong statistical evidence for disease cosegregation (Martinez-Mir et al., 2007). However, these linkage regions were too large to implicate specific genes, and causal genes have not yet been identified for AA.

More recently, GWASs identified common variants that are associated with AA across 14 genomic regions, much smaller than the linkage intervals, many of which implicated individual genes or small clusters of functionally related genes, thus providing new and clinically relevant insight (Betz et al., 2015; Petukhova and Christiano, 2016; Petukhova et al.,

2010). Immunological, pharmacological, and clinical studies conducted to validate the GWAS statistical evidence demonstrated that IFN $\gamma$ -producing CD8<sup>+</sup> NKG2D<sup>+</sup> cytotoxic T cells are necessary and sufficient to induce AA in a mouse model, and that targeting those cells with systemic or topical Jak inhibitors induces hair regrowth in AA patients (Dai et al., 2016; Jabbari et al., 2016; Kennedy Crispin et al., 2016; Mackay-Wiggan et al., 2016; Xing et al., 2014). Jak inhibitors are the first targeted therapy with success in treating AA, and these studies represent an unusual example of GWAS leading directly to new treatment approaches (Collins, 2011).

Despite this notable achievement, a need for additional therapeutic options for AA patients persists. Safety profile data for Jak inhibitors in the treatment of AA are still nascent, but trials for other indications demonstrate that the risk of serious adverse events restricts the use of Jak inhibitors for some patients. Of the AA patients who are able to tolerate Jak inhibition and who demonstrate at least a partial response to treatment (~70%), most will experience relapse within three months of treatment cessation (Phan and Sebaratnam, 2019). Interestingly, the need for maintenance therapy could suggest that the hair follicle itself may be provoking relapse. Furthermore, the lack of response in ~30% of patients indicates that other disease mechanisms are operating independently of Jak signaling, which could involve either the hair follicle and/or as yet uncharacterized immune cell populations.

Here we provide a rationale for further investment in large-scale genetic studies of AA. We draw upon lessons learned from more than 30 years of human genetic studies of chronic diseases to argue that etiologically important variants remain uncharacterized, limiting our knowledge of the biology that underlies AA, and ultimately impacting patient care.

## THE GENETIC ARCHITECTURE OF CHRONIC DISEASE

Human genetic studies of chronic diseases have implicated both rare (i.e., mutations) and common (i.e., single nucleotide polymorphisms; SNPs) genetic variation (Table 1). Mutations underlie monogenic forms of chronic diseases. Risk SNPs contribute to polygenic forms.

### Rare variant contributions to chronic disease

Monogenic forms of chronic diseases were first discovered by linkage studies that identified causal mutations cosegregating with disease in families, including breast cancer (Hall et al., 1990; Wooster et al., 1995), Crohn's disease (Hugot et al., 2001; Ogura et al., 2001) and atopic dermatitis (AD) (Palmer et al., 2006), among others. It is now widely recognized that monogenic forms exist for many chronic diseases and causal mutations have been implicated by several experimental approaches (Blair

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Abbreviations: AA, alopecia areata; AD, atopic dermatitis; LD, linkage disequilibrium; IBD, inflammatory bowel disease; LDL, low-density lipoprotein; PRS, polygenic risk score

**Table 1. The genetic architecture of chronic diseases includes rare and common variants**

Disease	Monogenic etiologies (mutations)		Polygenic risk (SNPs)	
	Linkage Mapping	Additional monogenic genes	Case count	Loci
Low-density lipoprotein	<i>PCSK9</i>	<i>LDLR, APOB, LDLRAP1</i>	297,626	220
Breast cancer	<i>BRCA1, BRCA2</i>	<i>TP53, CHEK2, PALB2, ATM, CDH1, RECQL, FANCM</i>	122,977	167
Inflammatory bowel disease	<i>NOD2</i>	<i>ADAM17, AICDA, BTK, CYBA, CYBB, DCLRE1C, DOCK8, G6PC3, GUCY2C, HPS1, HPS4, HPS6, ICOS, IKBKG, IL10, IL10RA, IL10RB, IL21, IPEX, ITGB2, LRBA, MEFV, MVK, NCF1, NCF2, NCF4, PIK3R1, PLCG2, SLC37A4, STXPB2, TTC37, TTC7A, WAS, XIAP, PRDM1, NDP52</i>	25,042	215
Atopic dermatitis	<i>FLG</i>	<i>ADA, ADGRE2, ARPC1B, CARD11, CARMIL2, CDSN, CHD7, DCLRE1C, DOCK8, DSG1, DSP, ERBB2IP, FOXP3, IFNGR1, IL2RA, IL2RG, IL4RA, IL7RA, JAK1, KIT, LIG4, MALT1, PGM3, PLCG2, RAG1, RAG2, SPINK5, STAT1, STAT3, STAT5, STAT5B, TGFB1, TGFB2, TPSAB1, WAS, WIPF1, ZAP70</i>	18,900	31
Alopecia areata			3,000	14

Chronic diseases have monogenic forms that are caused by mutations in genes that sometimes implicate therapeutic targets (e.g., *PCSK9*). Strategies that have identified monogenic etiologies have not yet been widely implemented for alopecia areata. GWASs for chronic diseases show that as cohort sizes increase, so does the yield of polygenic risk loci. Low-density lipoprotein was analyzed as a quantitative trait.

et al., 2013; Chong et al., 2015; Lupski et al., 2011). Linkage studies proved to be successful for chronic diseases when etiological heterogeneity was reduced by selecting families with strong family history, early disease onset, and/or the presence of distinct comorbidities, thus defining a phenotypic subtype of disease. Additional monogenic causes have been identified by the selection and screening of candidate genes that cause phenotypically-linked monogenic disorders (Brown, 2017; Skol et al., 2016; Uhlig, 2013). For example, genes causing syndromes with a high incidence of breast cancer (e.g., Li–Fraumeni syndrome, Fanconi anemia) have been implicated in nonsyndromic breast cancer (Skol et al., 2016). Similarly, genes that cause primary immunodeficiency disorders with clinical manifestations reminiscent of inflammatory bowel disease (IBD; an umbrella diagnosis that includes Crohn's disease) or AD have been found to have risk variants in patients without severe congenital immunodeficiency (de Lange et al., 2017; Paternoster et al., 2015). Although the use of exome sequence data for mutational burden testing has yielded some success, very large cohorts are needed for adequate power.

The effects of causal mutations that underlie monogenic forms of chronic diseases are often easy to interpret because they tend to change protein structure and/or function, providing knowledge about disease biology that sometimes proves to be of high clinical relevance. For example, genes identified in these studies cause conspicuous phenotypic changes when altered and thus provide insight into the biological and clinical effects of therapeutic targeting (Plenge et al., 2013). These genes also tend to be the most responsive to drug-induced alterations and account for higher success rates in clinical development than targets without causal mutations (Nelson et al., 2015; Plenge et al., 2013; Shih et al., 2018). Monogenic causes of chronic diseases also provide efficient screening and diagnostic tools, and it is becoming increasingly apparent that the cumulative effect of such rare causal mutations impacts disease burden. For

example, monogenic causes of breast cancer account for up to 20% of all cases (Skol et al., 2016), and a recent study of severe hypercholesterolemia found that ~50% of patients carried a causal mutation (Wang et al., 2016).

Genes that underlie monogenic forms of chronic diseases have proven to be relevant to common polygenic forms by informing on biology (Blair et al., 2013; Freund et al., 2018) and revealing new therapeutic strategies (Lupski et al., 2011; Plenge et al., 2013; Timpson et al., 2018). A limitation of mutation studies of chronic diseases is that each identified gene provides one causal explanation, but complex diseases involve multiple pathways. Thus, the population relevance of identified disease mechanisms remains to be established with other approaches.

#### Common variant contributions to chronic disease

The use of GWAS to identify risk SNPs have illuminated polygenic contributions to chronic diseases, greatly expanding the number of disease loci and providing a more comprehensive view of the pathways involved in pathogenesis (Klarin et al., 2018; de Lange et al., 2017; Michailidou et al., 2017; Paternoster et al., 2015). One unexpected revelation of GWAS is the vast extent of polygenicity. To date, more than 10,000 independent loci have been significantly associated ( $P < 5 \times 10^{-8}$ ) with chronic diseases by GWAS (Visscher et al., 2017). For individual diseases, as cohort sizes increase, providing more power to detect associations, new loci continue to be discovered (Table 1). The biological effects of these variants tend to be less severe than those of the mutations that cause monogenic disease. The majority of GWAS SNPs reside in noncoding regions and influence gene transcription, for example, by changing the binding of transcriptional machinery or altering chromatin structure (GTEx Consortium et al., 2017). Because many disease-associated SNPs fall within cell-specific enhancers (Maurano et al., 2012), analytic methods have been developed to identify disease-relevant cell types from GWAS SNPs (Backenroth et al., 2018; Farh et al., 2015; Maurano et al., 2012). This is especially important for immune cell populations, which

can dramatically change in response to environmental cues, obscuring the causal order of changes in frequency distributions.

Identifying disease-relevant cells is crucial for designing functional experiments to determine how a risk variant influences disease. SNPs that mediate transcriptional regulation have been shown to operate in context-dependent manners. For example, some SNPs only exert transcriptional effects within particular cell types (Kasela et al., 2017; Naranbhai et al., 2015; Raj et al., 2014) or only in response to specific changes in the cell micro-environment (Fairfax et al., 2014; Kim et al., 2014; Lee et al., 2014). Functional testing of GWAS SNPs in the wrong cellular context will obscure effects and create a barrier to translating genetic evidence into disease mechanism (Dimas et al., 2009; Farh et al., 2015; Heinzen et al., 2008; Jonkers and Wijmenga, 2017; Ye et al., 2014).

The diagnostic utility of GWAS risk variants has been investigated with the use of polygenic risk scores (PRSs), which are calculated as a weighted sum of SNP risk alleles that a person carries for a particular disease. The predictive performance of a PRS instrument improves as the number of identified GWAS loci increases. A recent study using robust PRS instruments identified patients with greater than 3-fold risk for several chronic diseases, which is on scale with carrying a causal mutation, and thus suggests that PRS will have utility for clinical care (Khera et al., 2018).

#### **An integrative approach improves the translational potential of human genetic studies**

Monogenic and polygenic loci provide complementary information about the genetic architecture of a disease. Results from mutational studies are easiest to interpret biologically, providing mechanistic insight, and can improve clinical care when they identify genes that can be therapeutically targeted or screened for risk assessment or diagnosis. Polygenic variation characterizes disease-relevant cell types, which improves our ability to understand the biological consequences of disease variants, provides a more comprehensive view of etiologically important pathways, and helps to establish population relevance for therapeutic strategies. Each variant type provides unique and complementary information. Thus, an integrative approach to genetic research improves our translational capacity.

A major challenge to the biological translation of GWAS evidence resides in determining which genes underlie the associations, given that associated linkage disequilibrium (LD) blocks may contain multiple genes, and regulatory SNPs can be located hundreds of kilobases away from the genes whose expression they influence (Mifsud et al., 2015). The discovery that GWAS loci are enriched for monogenic genes offers a strategy for prioritizing genes and variants from GWAS loci for functional studies (Blair et al., 2013; Chong et al., 2015; Freund et al., 2018; Lupski et al., 2011). The discovery that polygenic variation can modulate biological and clinical effects of mutations in monogenic genes suggests that GWAS results will improve our ability to determine the consequences of mutations identified in exome data (Badano and Katsanis, 2002; Moss et al., 2017; Riordan and Nadeau,

2017; Weiner et al., 2017) and further underscores the necessity of pursuing monogenic and polygenic studies in parallel.

Integrating knowledge gained from both rare and common variants also enhances drug discovery efforts. Although drug targets supported by any genetic evidence are more likely to pass through drug development pipelines (Nelson et al., 2015; Shih et al., 2018), the number of successful drug targets with both rare and common disease variants suggests that one of the characteristics of a good drug target is natural variation in function (Timpson et al., 2018). The presence of both causal mutations and risk SNPs in a gene also provides insight into its candidacy for development as a drug target. Monogenic variants supply strong and easy to interpret biological evidence of disease mechanism, whereas polygenic variants provide well-defined clinical endpoints and commercial markets. Integrated evidence also has the potential to reduce the high failure rates of drug development by providing information about the effects of target modulation in humans (Plenge et al., 2013). Most failures occur at Phase II when in vitro testing and preclinical models fail to accurately predict the effects of target modulation in humans. Human genetic studies provide a natural experiment to determine the effects of target modulation. Each disease variant links a specific alteration in protein function or expression level with a discrete outcome. Having a set of disease variants associated with a target allows us to describe the relationship between gene function and phenotype, constructing a genetic equivalent to a drug dose-response curve. Ideally, potential drug targets will have both rare and common disease variants. The effects of mutations identified in exome data provide information about severe protein perturbation, whereas polygenic effects identified by GWAS inform about more subtle modulation (Plenge et al., 2013).

#### **Emerging genetic models of human disease**

Acknowledgment that both rare and common variants contribute to the genetic architecture of chronic diseases, and that both are needed to fully leverage the human genome for biological knowledge and clinical insight, has inspired the development of theoretical models to explain how the interplay of rare and common genetic variants generates disease risk in a population and influences a patient's health.

The clan genomics model posits that a person's disease risk arises from the total collection of variants a person has inherited from both distant ancestors (SNPs, variants that rose to frequency in the population over long periods of time and have small effects) and more recent ancestors (mutations, which appeared more recently and have potentially larger effects), as well as de novo mutations (Lupski et al., 2011). Evidence to support this model is derived from the observation that biological perturbations of disease-relevant pathways can arise from variants along the entire spectrum of allele frequencies and is supported by large-scale investigations into the relationships between monogenic and polygenic diseases (Blair et al., 2013; Freund et al., 2018).

The omnigenic model of human disease was similarly derived from a set of analyses and observations of genes regulated by risk SNPs and genes that harbor causal mutations (Boyle et al., 2017). It posits that disease variants

operate in highly interconnected, cell-specific regulatory networks to affect disease risk. Thus, all genes operating within a disease-relevant cell type define a given network, and network genes are characterized as either peripheral or core genes. Peripheral genes are identified by the presence of GWAS SNPs and core genes are identified by the presence of causal mutations. While peripheral genes greatly outnumber core genes, core genes tend to have biologically interpretable roles in disease and stronger effects on disease risk. The net effect of peripheral genes can perturb core gene function, even if a patient lacks functional mutations in core genes. Multiple cell types are likely to contribute to each chronic disease. Importantly, this model suggests that the translation of genetic evidence will be enhanced by the identification of disease-relevant cell types. Knowledge about both polygenic and monogenic variation will inform on how specific cell types are mediating disease.

These models were derived from experimental evidence indicating roles for rare and common variants in chronic diseases, and together, they underscore that both need to be characterized in order to understand sources of risk in the population and to evaluate genetic contributions to disease within individual patients.

#### IMPLICATIONS FOR ALOPECIA AREATA: A ROADMAP FOR FUTURE STUDIES

It is evident from this large body of empirical and theoretical evidence that there is much more work to be done to characterize the genetic architecture of AA. In stark contrast to most other chronic diseases, no monogenic causes of AA have been identified (Table 1). The polygenic contributions that have been identified represent only a few “tip-of-the-iceberg” loci (those with the greatest visibility due to stronger effect sizes and greater allele frequencies). It is clear from GWAS conducted for other chronic diseases that many more polygenic loci await discovery with an expansion of cohort size (Table 1).

The clinical consequences of these gaps in our knowledge can be distilled into a single question: what can we do for AA patients who don't respond to Jak inhibition, who only partially respond, who relapse off-treatment, who are intolerant to Jak inhibition, or who are unable to afford expensive long-term therapy? Alternative effective treatments are needed. Continued investment in genetic studies of AA will help to discover other etiologically important pathways that can be therapeutically targeted.

Knowledge about genes that cause monogenic (i.e., familial) forms of chronic diseases has been used to facilitate drug discovery with the identification of new disease mechanisms and therapeutic targets. Several strategies have been used successfully to identify causal genes in other chronic diseases, including linkage analysis, screening candidate genes identified through phenotypic overlap with other monogenic disorders, and analysis of whole exome data. Linkage analysis has identified several genomic regions that cosegregate with AA in families (Martinez-Mir et al., 2007). Linkage evidence provides a robust scaffold for the interpretation of mutations found in exome data. Our group is developing new methods to integrate linkage evidence with

mutation data and deploying these methods in a cohort of unrelated AA patients that has been exome-sequenced.

The use of phenotypic overlap with other monogenic disorders as a means to identify candidate genes for follow-up high throughput sequencing has proven to be successful for other chronic diseases. This strategy has not yet been rigorously pursued for AA. The Union of Immunological Societies has categorized at least 354 genes that cause inborn errors of immunity, some of which include hair phenotypes that overlap with AA symptoms (Picard et al., 2018). Our group recently compiled a list of 684 monogenic causes of hair disorders, a subset of which also includes symptoms of immune dysfunction (Severin et al., 2017). Importantly, a number of these monogenic causes of congenital immune or hair disorders reside at AA GWAS loci. A synthesis of these data would provide a discrete list of candidate genes that could be investigated with exome or whole sequence data. Given that this strategy dramatically reduces the amount of testing relative to an exome-wide strategy, burdens for multiple-testing are also reduced, increasing the power to detect genes with an excess burden of mutations.

The identification of monogenic causes of AA could help to identify the disease pathways that are operating independent of Jak signaling and could inform on new therapeutic strategies. It would also establish a foundation for precision medicine, providing tools for molecular diagnoses.

The size of the largest AA GWAS cohort analyzed to date, which was used in the meta-analysis and contained only 3,000 cases, has limited statistical power to detect risk SNPs. An expansion of cohort size would yield new loci. Identifying more AA GWAS loci would allow us to computationally define disease-relevant cell types with greater resolution and gain a more comprehensive overview of etiologically important pathways.

Although the main limitation in expanding cohorts is the expense of ascertaining patients, precision medicine initiatives have made available new methods and resources for constructing cohorts that are vastly more efficient than the traditional methods of ascertaining patients through clinical practices. Our group has been working to implement such methods.

Finally, cell-specific gene expression profiles and variant annotations that identify expression quantitative trait loci (eQTLs) and define genomic structure (e.g., chromosomal looping) for many cell types are publicly available. Integration of these data with genetic evidence has aided mechanism discovery for other chronic diseases. However, publicly available resources rarely if ever include cells from hair follicles, which limits our interpretation of genetic evidence in the case of AA. Thus, single cell sequencing experiments and chromatin conformation capture techniques performed on lesional tissue are also needed to facilitate translation.

#### CONCLUSION

AA GWAS had an immediate impact on patient care by implicating Jak-STAT signaling, which led directly to the first successful use of a targeted therapy to treat AA. Although this represents a notable achievement, a need for therapeutic alternatives persists. It is imperative to dispel the notion that

an investment in further AA genetic studies is an act of fiscal profligacy. Patients who are unresponsive to Jak inhibition or who relapse off-treatment provide testament to the existence of additional disease mechanisms that await detection. It remains undetermined if these mechanisms involve as yet undefined immune cell populations, aberrant physiology in the hair follicle, or a combination of both. Increasing the size of AA GWAS cohorts and generating whole genome sequence data will clearly yield new discoveries that will allow us to improve our understanding of disease biology and our ability to screen, diagnose, and treat patients.

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#### CONFLICT OF INTEREST

The author states no conflict of interest.

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