Genetic Markers of Atopic Dermatitis Risk for Screening Aviation Applicants

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INTRODUCTION: Atopic dermatitis (AD) is a skin condition with many genetic risk factors. In this review, we summarize the different genetic variants for AD from the perspective of screening purposes within the U.S. Air Force aviation community. Using a PRISMA-informed systematic review approach, we found 13 papers reporting genetic associations with AD. We report 98 genetic associations with AD, of which 4 had a greater than twofold increased odds of developing the condition when present. These 98 variants were found in 45 associated genes, including LRRC32, OVOL1, and IL13, which were each replicated in 3 studies; as well as RTEL1 and ZNF365, which were each replicated in 2 studies. A polygenic risk model created based upon these variants or genes could contribute to a risk screening protocol for military aviation candidates, potentially helping minimize risk for candidates at increased genetic risk for AD or other atopic diseases (e.g., asthma, allergic rhinitis).

KEYWORDS: eczema, genetic variants, aviation risk assessments, flight physicals, medical evaluations.

Gregory ID, Collie J, Chapleau RR. *Genetic markers of atopic dermatitis risk for screening aviation applicants*. Aerosp Med Hum Perform. 2022; 93(11):806–810.

Atopic dermatitis is an inflammatory, chronic, recurrent, and relapsing skin disorder. It falls under the eczematous family of skin presentations, with multiple underlying causes, including environmental factors, a disrupted skin barrier, and a significant genetic predisposition.[4] Atopic dermatitis is a part of the "atopic triad," which also includes asthma and allergic rhinitis, which are different presentations of conditions with related underlying causes (IgE mediated response to environmental conditions). When atopic dermatitis flares up, lesions can cause disruptive irritation, pruritis, cracks in the skin, and even secondary infections. While most of the time proper skin hydration and topical anti-inflammatory medications can prevent and treat the condition, uncontrolled atopic dermatitis can cause a significant disruption to quality of life for patients, and even distract from mission completion for aviators. It is estimated that about 15% of people within industrialized nations have atopic dermatitis;[20] therefore, it is highly likely that a small but not insignificant portion of the aviation community also suffers from the condition. According to the Air Force Medical Standards Directory, which outlines those conditions which are not compatible with special duties (such as aviation), "atopic dermatitis that requires chronic topical steroids for control" does not meet aviation standards and would require a waiver for continued flying duties.[1] Multiple studies, including a twins study,[16] have shown that the genetic component of atopic dermatitis is significant.[3]

Ongoing research attempts to isolate the specific variations within the genome that are associated with increased risk of developing atopic dermatitis. Reviewing different studies from Genome Wide Association Studies (GWAS), researchers look through cases of atopic dermatitis and analyze whether any specific genetic variations (specifically single-nucleotide polymorphisms – SNPs) stand out as leading to an increased risk of the condition.[11] Several larger GWAS studies have specifically looked at which possible genetic variations lead to atopic dermatitis.[8,10,19]

Eczema in and of itself is a concern for the U.S. Air Force (USAF) aviation community, but it is generally a minimally

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This manuscript was received for review in May 2022. It was accepted for publication in August 2022.

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DOI: https://doi.org/10.3357/AMHP.6128.2022

problematic condition. A recent look into the Aeromedical Information Management Waiver Tracking System showed that in the last 20 yr (dating back to 2001), there were 202 applications for aviation waivers for atopic dermatitis in the USAF. Of those applications, 178 were granted. Of the 24 that were disqualified for the condition, all of them were for initial applicants. All trained aviators who developed the condition and had adequate control received a waiver. While atopic dermatitis is not a widespread problem within the USAF aviation community, asthma is definitely a significant concern (along with allergic rhinitis to a lesser degree). Both of these diagnoses can prevent mission completion while flying, which is a problem for the safety of the member and the mission. Atopic march has been described as a common progression of the "atopic triad," where patients diagnosed with atopic dermatitis go on to develop asthma and allergic rhinitis.[7,17] Understanding the genetic predisposition for one condition of relatively minimal aeromedical significance can help understand and anticipate the risk for other conditions of greater aeromedical significance. One study has already specifically used a GWAS to identify specific genetic variations which lead to the "atopic march," where members with eczema who then developed asthma had their genomes analyzed to look for common anomalies.[14] The genetic connection among the diseases is already known and a genetic link to the progression within the disease has now been verified.

Since atopic dermatitis is a condition for which genetic variants have already been analyzed and identified, this condition is a candidate for the creation of a screening protocol for aviation applicants. Once established, this protocol could be used as a model for development of screening protocols for other conditions.

METHODS

The same methods were used here as in a recent review of the genetic markers associated with obstructive sleep apnea and the possible role of genetic health screening in aerospace medicine.[6] In order to make it easier for the reader, the methods section was reproduced here. No human subjects or human subjects data were used in this literature review and assessment, therefore no IRB review was obtained. The concepts outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement were followed while developing the study[15] and the Begg's and Egger's test for characterization bias was not performed.

Publication Search

The authors identified eligible studies from two GWAS databases (the NHGRI-EBI GWAS Catalog[5] and the Atlas of GWAS Summary Statistics[21]) and from keyword searches using PubMed and Google Scholar. Keywords used for searching were "eczema" and ("SNP" or "allele" or "variant" or "polymorphism" or "gene") and ("GWAS" or "genomics" or "genetic" or "gene" or "meta-analysis" or "review"). These GWAS and publication database searches were supplemented with citations contained within identified studies reporting additional genetic associations with atopic dermatitis.

Inclusion and Exclusion Criteria

Studies were included that met the following conditions: 1) published in peer-reviewed journals; 2) reported data about genetic associations with atopic dermatitis or eczema risk; and 3) were case-control or cohort design studies. Reviews were included in this study for background knowledge, as a meta-analysis was not performed. Additional genetic markers from reviews that included meta-analyses that met statistical significance were included as a part of the research. Studies with sufficient sample sizes to identify associations yet still reporting null results (lack of an association) were included. Studies were excluded for the following reasons: 1) lacked participants in the cohort with dermatitis; 2) did not report data; or 3) associations were contradictory within the study. Studies reporting results contradictory to prior literature reports were included. For articles not published in English, the English language abstract was used for identifying genetic associations. English abstracts of non-English papers that did not include *P*-values for associations were excluded.

RESULTS

Search Results

In total, 16 studies were identified using the established search criteria. After screening for inclusion and exclusion criteria and duplicate removal, 12 remained for review.

Study Characteristics

The earliest study was published in 2009 and the most recent, at the time of the search in the summer of 2021, was published in 2019. The geographic sources of the studies included Europe, Asia, North America, and Australia/Oceana. The populations studied included children and adults, a range of bodyweights including healthy weight and overweight participants, and multiple ethnicities. All of the papers reported effect sizes using odds ratios.

Variant and Gene Characteristics

There were 90 variant associations reported with the risk of developing atopic dermatitis from 12 published genome-wide association studies found. There were no duplicated variants, however, several variants were in close proximity to each other and are in linkage disequilibrium (LD). LD is a measure of how often two variants are associated with each other in a nonrandom manner.[18] This is in contrast to conventional Mendelian genetics, where the assumption of inheritance relies upon every genetic location being independently assorted. Therefore, LD can only occur when two genetic locations are on the same chromosome and, the closer they are to each other, the more likely it is that they will be coinherited. For the purposes of our discussion, since the ability to sequence every base on the

genome has only recently come about, we use LD blocks to suggest that the specific genetic mutation increasing eczema risk exists in a localized region of the genome (termed an "LD block"). To that end, variant associations with eczema risk were identified on 13 chromosomes, 6 of which did not have LD blocks.[13] Of the seven chromosomes with LD blocks, chromosomes 5 and 11 had three LD blocks each; chromosomes 1 and 6 had two LD blocks each; and chromosomes 2, 19, and 20 each had one LD block (**Table I**). These LD blocks account for 61% (N = 43) of the variants on chromosomes with LD blocks (N = 70) and 48% of the cumulative variant associations.

The 90 variants identified were found in 45 genes and the remainder were within intergenic regions. Similar to the variant associations, the majority (37, 79%) of genes were only represented once. Of the nine genes with at least one association, four genes had two associations, one gene had three associations, two genes had four associations, and a single gene had five variant associations (**Table II**).

Association strength effect size was compared by using the reported odds ratios that represent a doubling of the odds of decreased (OR ≤ 0.5) or increased risk (OR ≥ 2.0).[6] The observations identified four variants associated with significant increased risk (rs13403179, OR = 2.95, $P = 8.1 \times 10^{-8}$; rs9540294, OR = 2.66, $P = 1.0 \times 10^{-8}$; rs675531, OR = 2.19, $P = 6.8 \times 10^{-7}$; and rs3099143, OR = 2.13, $P = 3.0 \times 10^{-7}$) and none associated with decreased risk of developing eczema.

Table I. Linkage Disequilibrium Analysis of Variants Associated with Eczema Risk.

CHROMOSOME	VARIANTS IN LD BLOCKS	VARIANTS NOT IN LD BLOCKS
1	9	5
2	2	3
5	13	2
6	6	13
11	9	2
19	2	1
20	2	1
Total	43 (61%)	27 (39%)

LD = linkage disequilibrium.

Table II. Genes with More Than One Association.

GENE NAME	NUMBER OF ASSOCIATIONS	ASSOCIATED VARIANTS
FLG	2	rs11204971 rs3126085
IL13	2	rs1295686 rs20541
OVOL1	2	rs10791824 rs479844
ZNF365	2	rs2393903 rs2944542
TNXB	3	rs12198173 rs12211410 rs13199524
LRRC32	4	rs7130588 rs2155219 rs2155219 rs2212434
TMEM232/ SLC25A46	4	rs10067777 rs13360927 rs13361382 rs7701890
RAD50	5	rs2897443 rs6871536 rs3091307 rs12188917 rs2158177

DISCUSSION

Within the 13 articles that were reviewed (and the 12 that were used in the study), 90 genetic variants were found to be associated with atopic dermatitis. All of the studies reviewed were case controls of some sort, except one (a cross-sectional study of an ongoing prospective cohort study). Of the articles, 5 conducted straight case control studies, while 4 articles were meta-analyses of multiple other case control studies, ranging from 3 to 30 in number. Two articles were considered cohort case control studies. Ages of the cases within the studies ranged from infants (less than 3 yr old) up to adults, with a majority of the cases being children since eczema frequently presents during childhood and sometimes resolves before adulthood. The study sizes ranged from 797 cases and controls in one of the single case control studies up to 459,000 in the large meta-analysis study. An average of 82,868 and a median of 6163 cases/controls were included in the articles. Study participants came from different countries, with European countries, Germany in particular, being the most numerous. Other countries involved in the studies included Ireland, Scotland, The United Kingdom, China, Japan, Czech Republic, Poland, Sweden, and unspecified African countries.

There is still much to learn about polygenic risk scores (PRS), including their usefulness in the aerospace medicine environment. The full utility is still to be determined, but genetic testing in the medical field in general is still in its infancy. As scientists and clinicians learn more about the use of genetic testing to evaluate risk, determine the most effective medications and other treatments, the efficient use of PRS in the aerospace medicine setting will naturally evolve. Currently, genetic testing is most frequently used for diagnosis, screening, prognosis, and treatment of conditions with known underlying genetic causes, and no fewer than 16 organizations have resources or practice guidelines for genetic testing.[2,9] However, none of these organizations currently have clinical practice guidelines incorporating PRS.

In aerospace medicine, the main advantage of incorporating PRS is recognizing the risk of developing a condition and taking steps to minimize that risk or instituting early interventions. Every single pilot applicant in the USAF comes to one of two places for their medical evaluation and/or certification (U.S. Air Force Academy, Colorado Springs, CO, USA; or U.S. Air Force School of Aerospace Medicine, Wright-Patterson Air Force Base, OH, USA). During this medical evaluation to clear the pilot applicant for flying duties, saliva samples could be taken to obtain genetic information. Through the PRS described above, the genetic material could be evaluated for any one of the variants outlined in this article. If the member were to have any of the variants, measures could be taken to minimize the impact of those variants. To prevent clinically significant atopic dermatitis, members could be counseled on the need to ensure proper skin hydration. Education could be provided on what to look for with the early stages of atopic dermatitis eruption so care and treatment of the condition could be obtained before it disrupts quality of life or job performance.

Additionally, as noted, atopic dermatitis is often an early precursor to asthma, which is very disruptive in the aviation environment, especially in a high-G environment. With increases in altitude, a decrease in atmospheric pressure of oxygen in the ambient air can lead to decreased oxygen delivery to tissue. Any disease that inhibits efficient oxygen exchange from the air into the blood stream will be exacerbated by the decrease in available oxygen molecules in the air. Asthma, where inflammation around airways is combined with muscular constriction of airways, inherently decreases efficient oxygen exchange. Asthma can be a chronic condition with insidious onset where an aviator may not recognize a decrease in oxygen delivery and, therefore, a decrease in performance, or it may present as an acute attack leading to sudden incapacitation. In the high altitude and high-g environments of military fighter aircraft, conditions such as asthma which exacerbate ventilation-perfusion mismatches have a higher impact on performance compared to at the terrestrial level. Aviation is an occupational environment that is susceptible to hypoxia that people without asthma or other respiratory diseases can cope with, but when an aviator has asthma, then the ability to overcome subtle decreases in oxygen levels may not present.

Pilot applicants with the noted genetic variants can undergo more frequent pulmonary evaluations to monitor for early lung function changes that are indicative of asthma. Counseling on environmental precautions could be given to minimize the atopic reactions which may lead to asthma as well. If indicated, medical treatment could be instituted as well. A waiver would be needed to continue flying duties if a member is diagnosed with asthma, but they are frequently granted in the trained aviator if the condition is well controlled on appropriate medication. In fiscal year 2021 within the U.S. Air Force, there were 148 total requests for an initial waiver to start training as an aviator because of a history of asthma. Of those, 92 members received the waiver, 50 were disqualified from flying, 4 were qualified (found to not actually have the diagnosis of asthma), and 2 requests were incomplete (did not follow through on waiver request).

More generally, asthma poses an additional problem for military recruits and presents management challenges to military medical staff for service members in any career field, especially considering the Department of Defense's recent policy requiring the separation of any soldier, sailor, or airman who has not been able to deploy for 12 consecutive months.[12] With this in mind, asthma relapse and deployment waivers can pose significant roadblocks to mission readiness and directly conflict with this newer deployment policy by the Department of Defense. Given the impact on mission readiness, as well as the career ramifications for military personnel, further studies on genetic predictors of relapse and/or pharmacogenetic predictors of response are worthwhile endeavors. Such information could help optimize asthma management for personnel, as well as provide additional parameters for waiver considerations during military medical evaluations.

For this information to be useful when screening USAF pilot applicants and other service members, an algorithm will need to be developed which can help predict who might be affected by atopic dermatitis within the population if they have the genetic variants of concern. Creating this algorithm will be the next step in the process and will be accomplished by analyzing the genetic material of USAF aviators who were found to have atopic dermatitis and comparing those genes to the genetic material of controls without atopic dermatitis. The algorithm could then be applied to applicants who provide their genetic material for analysis.

In conclusion, while atopic dermatitis is not seen as a significant risk to aviation safety, in some instances severe cases can interfere with mission completion and aviator quality of life. Additionally, since atopic dermatitis is a part of the atopic triad, development of this condition can be a part of progression to the more concerning condition of asthma. Screening for atopic dermatitis can be a part of a greater program of screening within the aviator medical evaluation process. Development of a polygenic risk score using the information already obtained from prior research is an efficient way to determine risk for multiple diseases, including atopic conditions. The identification of specific genetic variants associated with atopic dermatitis allows for improved awareness and monitoring of aviation applicants who are at higher risk for developing atopic dermatitis or other atopic diseases. When these individuals are identified, efforts to minimize development of these conditions can be implemented, thereby decreasing risk for aviation mishaps and medical disqualifications.

ACKNOWLEDGMENTS

This work was produced by government employees of the U.S. Air Force in the course of their official duties. The views, opinions, and/or findings contained in this document are those of the authors and should not be interpreted as representing the official views or policies, either expressed or implied, of the Air Force Research Laboratory, the U.S. Air Force, or the Department of Defense.

Financial Disclosure Statement: Funding provided to R. R. Chapleau from the U.S. Air Force with intramural research funds. R. R. Chapleau was an employee of the U.S. government at the time the work was performed but is now employed by a private company. The authors have no conflicts to disclose.

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