Surveying the Genomic Landscape Supporting the Development of Precision Military Aerospace Medicine

Richard R. Chapleau; Dara D. Regn; Mauricio J. de Castro

INTRODUCTION: Precision medicine is an approach to healthcare that is modifying clinical management by leveraging technological advances in genomics that assess a patient's genetic information to identify unique predispositions. While the civilian sector is integrating genomics widely to personalize diagnosis and treatment, the military medical environment has reacted more slowly. The operational requirements of military service encourage a tailored approach for focusing military precision medicine on occupation-specific conditions. Here, we present a survey of the genomic landscape related to military aerospace medicine.

METHODS: We collated observations from genome-wide association studies (GWAS) relating genetic markers to conditions that may negatively influence flight operations and for which the U.S. Air Force School of Aerospace Medicine's Aeromedical Consult Service (ACS) provides aeromedical waiver guidance. Our sources for identifying relevant literature were the GWAS Catalog, the Atlas of GWAS Summary Statistics, and PubMed/Google Scholar searches.

RESULTS: Using the ACS guidance as a starting point, we found 1572 papers describing 84 clinical conditions with genetic associations. The earliest aeromedical GWAS publication was in 2006, increasing to 225 publications in 2019. We identified 42,020 polymorphisms from more than 84 million participants across the studies.

CONCLUSION: Our study revealed areas where deeper investigations into how genetic markers manifest in clinical diagnosis, prevention, or risk management could lead to increased medical readiness. Additionally, our results show those clinical areas for which guidance could include genetic risk considerations.

KEYWORDS: genetics, precision medicine, aeromedical waivers, literature survey.

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Defined by the National Research Council as the "tailoring of medical treatment,"[11] precision medicine is best conceptualized by the extrapolation that it "describes a model for health care delivery that relies heavily on data, analytics, and information"[7] primarily obtained from genomics, molecular technologies, and patient histories combined with digital health, data science, and data sharing. While the scientific fields underlying precision medicine are rapidly advancing, best practices for implementing genetic information into the standard of care are still emerging. For example, recent review articles highlight challenges and strategies to leverage precision medicine in clinical trial designs[5,8] and in medical education and clinical research.[6] Widely used in oncology and mental health, recent work suggests a role for precision medicine in other fields such as public health and preventive medicine.[2]

As with the civilian sector, precision medicine has found a niche in the military healthcare system. Two examples are pharmacogenomics and the potential screening of highly penetrant, common genetic disorders. Recent studies have shown that using genetic testing to guide pharmacological treatment of depression is more effective than the traditional "trial and error" way of prescribing antidepressives.[4,14] For career fields with critical manning requirements or high ops-tempo, this could have tangible implications by returning service members

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to duty earlier. A second example is the potential to screen the force for highly penetrant, relatively common genetic disorders with clear evidence for improved outcomes with early intervention. Conditions such as familial hypercholesterolemia (prevalence of about 1 in 500), which can have devastating consequences in young, asymptomatic individuals, can be screened for with relative ease and low costs within the DoD. Early identification and intervention (statins) have life-changing implications.[13]

Here we focus on aerospace medicine as a unique, military-relevant application of preventive medicine. Aerospace medicine requires the clinician to consider the unique exposures of military members in the aerospace and deployed environments. Military service, deployed operations, and specialized operational career fields each present unique but overlapping sets of exposures that can affect health. Such exposures include but are not limited to altitude, g exposure, radiation, jet fumes, toxic and industrial chemicals, and dust, in addition to air pollution that may be encountered in the deployed environment. Individual service members are evaluated for medical clearance before they work in specialized career fields such as aircrew and special operations duty. An aeromedical waiver is a medical clearance for an individual to work in a specialized career field despite the presence of an otherwise disqualifying condition. A thorough medical evaluation and aeromedical risk assessment is necessary for medical clearance to occupy specialized operational careers such as pilots, air traffic controllers, or special warfare operators. The core requirements that must be met in order to be considered for an aeromedical waiver includes: 1) no risk of sudden incapacitation; 2) minimal potential for performance decrement, particularly with regard to the higher senses; 3) be resolved, or stable, and be expected to remain so in flight; 4) if the possibility of progression or recurrence exists, the first signs must be benign and easily detectable; 5) cannot require exotic tests, regular procedures, or frequent absences; and 6) be compatible with sustained flying operations.

The advances in integrating precision medicine within the civilian healthcare system and the unique possible applications of precision medicine within the military led us to ask: what is the current state-of-the-art regarding genetic risk predictors for aerospace medicine concerns? Currently, aeromedical waiver guidance uses population norms in the medical literature for recommending assessments, treatments, and prognostication of medically disqualifying conditions. We hypothesized that there is strong enough evidence in the literature to demonstrate clinical utility of precision aerospace medicine, with the corresponding null hypothesis that there are no genetic risk predictors significantly associated with aeromedical conditions. To test our hypothesis, we performed a systematic review of the genomic research literature using the aeromedical waiver guide of the U.S. Air Force's School of Aerospace Medicine (USAFSAM) as defining many of the conditions encountered in military aerospace medicine. We employed two genome-wide association studies (GWAS) databases[3,15] as our primary sources for literature searches and supplemented those sources with literature searches performed in PubMed[12] and Google Scholar.

METHODS

Study Selection

Studies were selected from two GWAS databases (the NHGRI-EBI GWAS Catalog[3] and the Atlas of GWAS Summary Statistics[15]) and from keyword searches using PubMed[12] and Google Scholar. Keywords used for PubMed and Google Scholar included the condition with "GWAS", "genomics", "SNP" (single nucleotide polymorphism), "genetics", and "meta-analysis." An example search was "asthma AND genomics OR SNP OR genetics OR meta-analysis OR GWAS."

Condition Selection

Medical conditions were identified using the USAFSAM Waiver Guide employed by the USAFSAM Aeromedical Consult Service during medical evaluations for airmen requiring waivers for flight rating. We maintained the USAFSAM Waiver Guide nomenclature for broad categories of conditions. For example, we combined references for obstructive sleep apnea, insomnia, and hypersomnia into "sleep disorders."

Since the focus of this paper is to review the landscape of conditions directly impacting aeromedical operational readiness, we down-selected the initial list of conditions by excluding transient conditions (infectious diseases, pregnancy/birth control, acute injuries), surgeries, and elective medical procedures. We also excluded cancers as an individual who manifests a cancerous tumor is evaluated for a fitness for continued military service regardless of career field.

Data Management

We categorized conditions first by the nomenclature in the USAFSAM Waiver Guide and then by ICD-10 code.[16] We stored citations for all references for the study in a single Microsoft Access database, which is available from the authors upon reasonable request. Included in the database are links to the PubMed page for each article, both categorizations, summary statistics regarding number of genetic associations identified, and publication parameters (first author, publication year, journal, article title, and sample size).

RESULTS

Our GWAS survey identified 1572 papers in the peer-reviewed literature related to 84 conditions of aeromedical importance with aircrew-qualification waiver guidance. These papers included in excess of 84.8 million participants and resulted in 42,020 genetic variants associated with the aerospace medicine conditions we evaluated (online **Table AI**, http://doi.org/10.3357/AMHP.5929sd.2022). The earliest studies were from 2006, with the most recent being published in 2020, and the number of papers increased from 1 in 2006 to 225 in 2019 (**Fig. 1**). We found strong correlations between the number of papers on a condition and the cumulative sample size for that condition (r = 0.861), the number of papers and associations identified (r = 0.731), and between sample size and number of

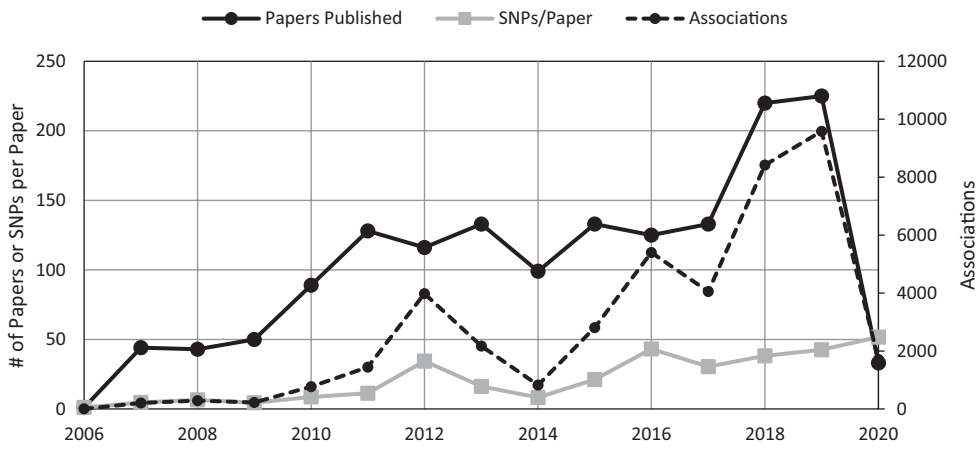

Fig. 1. Overview of annual growth in the aeromedical GWAS landscape. Publications (black circles) and associations (black dashed line) increased steadily from 2006 to 2019. Similarly, the average number of associations identified per study also increased steadily (gray squares).

SNP associations (r = 0.789). Of the 22 distinct ICD-10 code categories, 16 were represented by GWAS papers, with mental health disorders (F01–F99) accounting for the greatest number of papers and variants identified (**Fig. 2**). The second most represented ICD-10 category (nervous system diseases) had less than half the papers (180 vs. 382), but nearly the same number variants (10,267 for mental health vs. 9623 for nervous system diseases). The clinical condition with the largest number of papers was diabetes (150) and 11 conditions had only a single GWAS paper published. Of those 11, 3 (otosclerosis, pneumothorax, and ventricular tachycardia) had a single associated polymorphism.

We characterized the depth of the genomic landscapes for each condition by the number of papers published, number of associated SNPs, and the total sample size. To that end, the eight most well represented conditions by publications (top 10%) comprised nearly half of all papers at 736 combined papers (online **Table AII**, http://doi.org/10.3357/AMHP.5929sd.2022). The top eight conditions by associated variants accounted for 56% of the total associations at 23,511. When measured by sample size, the top 10% of conditions again represented well more than half of the total participants, with almost 48 million participants. Five conditions were very well represented in the database, occurring in the top 10% by all three metrics: asthma, diabetes, mood disorders, psychotic disorders, and sleep disorders.

As mentioned earlier, 11 conditions had a single paper, comprising the bottom 13% of conditions by publications (online **Table AIII**, http://doi.org/10.3357/AMHP.5929sd.2022). The bottom 10% of conditions as measured by associated polymorphisms included eight total conditions, of which three were also

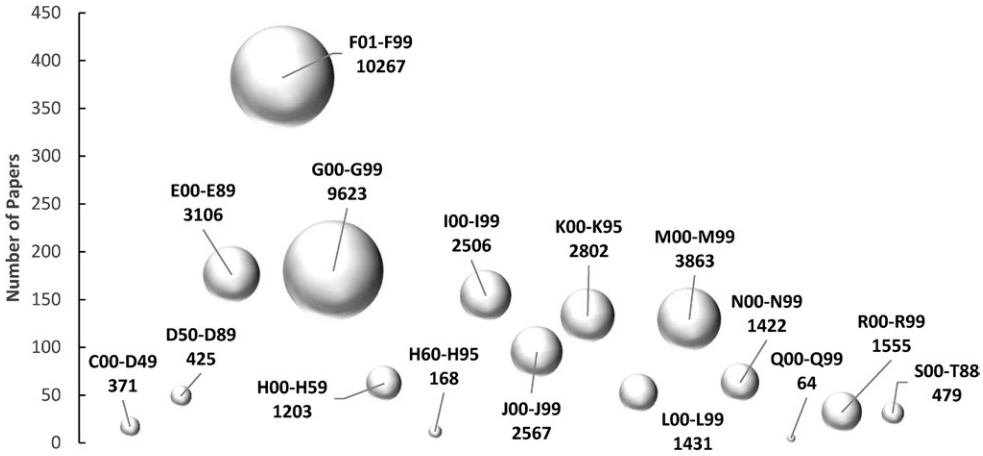

Fig. 2. Number of papers and associations by ICD-10-CM code. Spheres are sized based upon number of associated SNPs (listed below specialty name) and are positioned vertically by total number of publications found. C00–D49 = Neoplasms; D40–D89 = Diseases of the Blood and Blood-forming Organs and Certain Disorders involving the Immune Mechanism; E00–E89 = Endocrine, Nutritional and Metabolic Diseases; F01–F99 = Mental, Behavioral and Neurodevelopmental Disorders; G00–G99 = Diseases of the Nervous System; H00–H59 = Diseases of the Eye and Adnexa; H60–H95 = Diseases of the Ear and Mastoid Process; I00–I99 = Diseases of the Circulatory System; J00–J99 = Diseases of the Respiratory System; K00–K95 = Diseases of the Digestive System; L00–L99 = Diseases of the Skin and Subcutaneous Tissue; M00–M99 = Diseases of the Musculoskeletal System and Connective Tissue; N00–N99 = Diseases of the Genitourinary System; Q00–Q99 = Congenital Malformations, Deformations and Chromosomal Abnormalities; R00–R99 = Symptoms, Signs and Abnormal Clinical and Laboratory Findings; S00–T88 = Injury, Poisoning and Certain Other Consequences of External Causes.

in the bottom 11 conditions by publications. Finally, the eight conditions with the smallest sample sizes represented a combined 5883 participants, or 0.007% of the complete study size. Six conditions were found in the bottom 10% by all three measurements: hemochromatosis, otosclerosis, pneumothorax, salivary gland disorders, thalassemia, and ventricular tachycardia.

DISCUSSION

Our survey of the genomic landscape of aerospace medicine identified areas with large amounts of published evidence for pursuing clinical utilization, as well as areas with gaps in the knowledge base. The general fields of psychiatry and internal medicine have a wealth of information about the genetic determinants of health. Many precision medicine tools available in the civilian market are also in these areas of medicine, including predictions for treatment[1] and diagnosis.[9]

While our approach attempts to describe objectively the genomic research landscape related to military aerospace medicine, one limitation of our method is that we did not consider effect sizes (as reported by odds ratios or regression coefficients from primary authors). We elected not to perform such an analysis for a few reasons. First, the goal of this survey was to broadly characterize the field and identify those aeromedical conditions with a large amount of research and those conditions where there is a lack of research. This goal is best accomplished by quantifying the number of studies and reported associations. Second, by identifying the varying levels of research for aeromedical conditions, our goal was to bring these conditions to the attention of physicians and researchers so that condition-specific literature reviews can dive deep into a single topic and present the associations in context alongside clinical practice considerations. Finally, the concept of the "winner's curse" in genetics may apply to some of the associations reported in the literature.[17] The "winner's curse" results in overestimating the effect of some associations in initial reports and follow-up studies find lower or no effect in different populations or studies with smaller sample sizes. Rather than adding to the scope of this study and diluting the primary goal, we left resolving the issue of the winner's curse for associations reported for individual conditions up to future topic-focused studies.

Precision medicine has the potential to reduce the time to accomplish aeromedical waivers and decrease so called 'down time' in which operators cannot perform their duties. It can enable providers to more easily identify which treatments are most likely to benefit patients based upon on their genetics. Traditionally in treatment of diseases, there is titration and trials of medications followed by labs or additional tests to objectively assess clinical response. With precision medicine, the most effective medications and even dosages can be targeted, reducing time to optimization of treatment management with personalized therapy. Precision medicine can also be used in prognostication and aeromedical risk assessment. A classic example is asthma, which is the most common chronic lung disease worldwide, with global prevalence steadily increasing and presenting with a spectrum of phenotypes. Numerous epidemiological studies of deployed personnel have demonstrated an association between respiratory symptoms and environmental exposures encountered during deployment with 1.7-fold increase in respiratory symptoms. Genetic testing during asthma evaluations could identify the optimal medications for those service members diagnosed with asthma, thereby improving the individual's health management and operational fitness. The U.S. Navy and U.S. Army are investigating retaining mild asthmatics as such individuals have similar attrition and healthcare usage as nonasthmatic controls[10] and precision medicine could help with clinical management throughout a sailor or soldier's career.

Ultimately, our research has demonstrated that there is indeed a body of evidence suggesting genetic information could be useful in delivering care in the aeromedical enterprise. Our research resulted in a database of peer-reviewed publications spanning 14 yr that can be used by medical professionals and those enrolled in graduate medical education programs to tailor and update guidance for evaluating aeromedical conditions. We intend for the genomic landscape we presented here to identify areas of research need as well as areas ready for establishing clinical utility for the aerospace medicine research and operational communities.

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