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Evidence for excess familial clustering of Post Traumatic Stress Disorder in the US Veterans Genealogy resource

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ABSTRACT

A genealogy of the United States has been record-linked to National Veteran's Health Administration (**VHA**) patient data to allow non-identifiable analysis of familial clustering. This genealogy, including over 70 million individuals linked to over 1 million VHA patients, is the largest such combined resource reported. Analysis of familial clustering among VHA patients diagnosed with Post Traumatic Stress Disorder (**PTSD**) allowed a test of the hypothesis of an inherited contribution to PTSD. PTSD is associated strongly with military service and extended familial clustering data have not previously been presented. PTSD-affected VHA patients with genealogy data were identified by presence of an ICD diagnosis code in the VHA medical record in at least 2 different years. The Genealogical Index of Familiality (**GIF**) method was used to compare the average relatedness of VHA patients diagnosed with PTSD with their expected average relatedness, estimated from randomly selected sets of matched linked VHA patient controls. Relative risks for PTSD were estimated in first-, second-, and third-degree relatives of PTSD patients who were also VHA patients, using sex and age-matched rates for PTSD estimated from all linked VHA patients. Significant excess pairwise relatedness, and significantly elevated risk for PTSD in first-, second-, and third-degree relatives was observed; multiple high-risk extended PTSD pedigrees were identified. The analysis provides evidence for excess familial clustering of PTSD and identified high-risk PTSD pedigrees. These results support an inherited contribution to PTSD predisposition and identify a powerful resource of high-risk PTSD pedigrees for predisposition gene identification.

1. Introduction

The US Veterans Genealogy Project links a genealogy of the United States with medical data for Veterans who use the VHA system. At a current size of over 70 million individuals with genealogy data linked to 1 million VHA patients with diagnosis and procedure data, it is already the largest resource of its kind, and sufficiently large for the investigation of familial clustering for health-related conditions (Cannon-Albright et al., 2013, 2018). This genealogic resource, with identification of individuals diagnosed with Post Traumatic Stress Disorder (PTSD), provides a unique opportunity to explore evidence for familial clustering of PTSD (Cannon-Albright, 2008).

The hypothesis of a genetic contribution to predisposition to PTSD is not new. In one of the earliest explorations of the causes of war-associated neuroses, a study of psycho-neurosis in the immediate family history of 100 WWI Veterans diagnosed with psycho-neurosis compared to the family history of controls with somatic combat-related injuries found a family history in 75% of cases, but in no controls (Wolfsohn, 1918). More recently, a family psychiatric history was among the most uniform predictors of PTSD in a meta-analysis of 77 studies (Brewin et al., 2000); and Breslau (Breslau et al., 1991) reported that a history of familial psychopathology was associated with increased risk of developing PTSD. Twin studies (Lyons et al., 1993; True et al., 1993; Xian et al., 2000a; Xian et al., 2000b; Stein et al., 2002; Koenen et al., 2002; Afifi et al., 2010; Sartor et al., 2011; Sartor et al., 2012; Wolf et al., 2014; Wolf et al., 2018), and other genetic analyses of unrelated

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PTSD patients (Almli et al., 2014; Voisey et al., 2014; Ashley-Koch et al., 2015) have shown evidence for a genetic contribution to PTSD.

Using a unique VHA resource, we present analysis of close and distant genetic relationships among individuals diagnosed with PTSD. This analysis of familial clustering of PTSD in a population of US Veterans showed excess pairwise relatedness of PTSD cases, observed significantly elevated risks for PTSD in relatives, and identified multiple extended high-risk pedigrees; these findings suggest an inherited component to predisposition to PTSD.

2. Materials and methods

2.1. US Veterans Genealogy

Genealogical data for over 70 million individuals gathered from public sources have been linked into an initial genealogy that represents 20–25% of the population of the United States (Cannon-Albright et al., 2013, 2018). The demographic data for 13 million Veterans registered by the Veterans Health Administration (VHA) System was evaluated to record-link to this current US genealogy data using specific software tools included in GenMergeDB (http://www.pleiades-software.com), which has been used to create, and link records to, multiple genealogic resources for decades (Cannon-Albright et al., 2018). Approximately 1 million of the VHA patients were linked to a unique individual in the genealogy. After this initial record linking, no individual identifying data was used; informed consent was waived. A total of 284,382 of these linked VHA patients have extensive genealogy data, including at least 6 of their 14 immediate ancestors (both parents, and all 4 grandparents); many have much more genealogy data. This study analyzed these 284,382 VHA patients and their over 3 million ancestors, providing sufficient numbers of both close and distant relatives for appropriate genetic analysis. Access to over 300 million coded diagnoses or medical procedures linked to the 1 million VHA patients with linked genealogy (who remained unidentified) was approved by the Institutional Review Board and an oversight committee for the VHA resource.

The US Veterans Genealogy Resource currently includes VHA patients born in every state of the US. Among the ~1 million VHA patients with any linked genealogy data, 67,926 (6.5%) were female. We observed a similar percentage of among those 284,382 Veterans who link to an individual with at least 6 ancestors in the US Veterans Genealogy (4.5%). There are patients with genealogy identified in all 23 VHA Veterans Integrated Service Networks in 2017 (VISNs or local VHA health care providers) across the U.S. Approximately 81% of the linked VHA patients have VISN data, and among those, the largest numbers of linked VHA patients were in VISN 8 (Florida, Puerto Rico, US Virgin Islands; n = 71,238), VISN 23 (Illinois, Iowa, Minnesota, Nebraska, North and South Dakota; n = 64,763), and VISN 16 (Arkansas, Louisiana, Mississippi, Oklahoma, Texas; n = 59,142). The birth years for VHA patients linked to genealogy data ranged from the 1890s to the 1990s. There was a large peak of births for the 972,306 linked males for the birth years 1921–1930 (24% of all linked males born in this range) and a peak for the 67,926 linked females for birth years 1951–1960 (20% of all linked females born in this range).

2.2. Identification of VHA patients diagnosed with PTSD

The VHA has an electronic medical record system at most VHA medical centers for both inpatient and outpatient care that has been used since 1994; these data were used to assign health-related phenotypes to the linked Veterans who use, or have used, the VHA system for care. For this analysis, the presence of International Classification of Disease (ICD) Revision 9 (309.81) or Revision 10 (F43.1) diagnostic coding for PTSD recorded in at least 2 different years was used to identify affected Veterans. To increase the homogeneity of the PTSD phenotype, patients with an additional diagnosis of schizophrenia (ICD9 295 or ICD 10 F20) or bipolar disorder (ICD 9296.0–296.1, 296.4–296.8 or ICD10 F31) in at least 2 different years were excluded from this study of PTSD.

2.3. Genealogical index of familiality test for excess relatedness

The Genealogical Index of Familiality (GIF) method tests for excess relatedness, or excess familial clustering among individuals. It was originally created and used with the Utah Population Database (UPDB), the first US genealogical resource used in research (Cannon-Albright, 2008; Skolnick, 1980), and has previously been used to establish evidence for many disease phenotypes, including cancer (Cannon et al., 1982; Cannon-Albright et al., 1994; Albright et al., 2012; Teerlink et al., 2012); heart disease (Horne et al., 2004, 2006); orthopedic disorders (Tashjian et al., 2009; Patel et al., 2011, 2012); and chronic fatigue syndrome (Albright et al., 2011), among many others. The GIF has also been used to analyze some phenotypes in earlier, smaller versions of the US Veterans Genealogy Resource analyzed here (Cannon-Albright et al., 2013, 2018).

The GIF statistic measures the average pairwise relatedness for a set of individuals. The pairwise relatedness is measured using the Malécot coefficient of kinship (Malecot, 1948), which is computed from pedigree information and estimates genetic relatedness. The coefficient of kinship estimates the probability that two alleles at a locus are identical by descent (inherited from a common ancestor) in a pair of individuals. All possible paths of relatedness are considered in the calculation of the kinship; most pairwise relationships between individuals in a large population-based genealogy are genetic distance = 0 (unrelated). The GIF statistic is the mean pairwise coefficient of kinship for all possible pairs of cases and is multiplied by 10^5.

The GIF test allows comparison of the average pairwise relatedness of a group of individuals (e.g. PTSD cases) to the average relatedness of a group of similar individuals in the same population (representing the *expected* pairwise relatedness of the cases). To estimate the mean *expected* pairwise relatedness for the VHA PTSD cases in the population, 1000 sets of matched VHA controls were randomly selected and analyzed; with 1 matched control selected for each case in each of the 1000 sets. Each set of matched controls was randomly selected from the population of all VHA patients with linked genealogy; controls were matched to cases for sex and 10-year-birth year ranges. The empirical significance of the GIF test was obtained by comparison of the case GIF statistic to the distribution of the 1000 mean control GIF statistics. This comparison of average pairwise relatedness allows a test for excess relatedness or familial clustering; that is, whether the VHA patients diagnosed with PTSD have significantly higher pairwise relatedness than expected in the VHA population, as measured in similar groups of sex- and birth year-matched VHA patients selected randomly from all VHA patients with genealogy data. The GIF test does not, however, allow determination of whether the familial clustering observed is due to environmental factors, genetic factors, or some combination of both. In order to consider whether familial clustering is primarily due to shared exposures, or behavior, among close relatives, the GIF method includes a distant relatedness test, termed dGIF. The dGIF test is performed as the GIF test, but all relationships that are closer than third-degree (e.g. first cousins) are ignored. The dGIF ignores relationships most affected by shared environment or behavior, and tests for the presence of excess distant relatedness only; significant evidence for excess distant relatedness is strongly suggestive of a genetic contribution.

2.4. Relative Risks in Relatives

The estimation of relative risk (RR) in relatives provides the more traditional test for evidence of inherited effects. Evidence for an inherited contribution to a phenotype is supported when both close and distant relatives show evidence of elevated risk for the phenotype. RRs for PTSD were estimated among first-, second- and third-degree relatives to test for familial clustering as follows. All 284,382 patients in the US

Veterans Genealogy with genealogy data including at least both parents and all 4 grandparents were assigned to one of 35 cohorts based on birth year (in 10-year groups) and recorded sex. To estimate the cohort-specific rates of PTSD, the total number of linked VHA patients in each cohort was counted, and the total number of these linked VHA patients diagnosed with PTSD was counted. The cohort-specific rate of PTSD was estimated as the number of PTSD cases among the linked VHA patients in each cohort, divided by the total number of linked VHA patients in the cohort. Expected numbers of first-degree relatives with PTSD, for example, were estimated by counting the number of first-degree relatives who were VHA patients with genealogy data by cohort (without duplication), and summing the cohort-specific rate for each first-degree relative. Observed numbers of PTSD cases among relatives were counted without duplication. RRs were estimated similarly for each degree of relationship as the observed/expected number of PTSD patients; 95% confidence intervals for the RR were calculated using the method of Agresti (1990). First-degree relatives include parents, siblings and offspring; second-degree relatives are the first-degree relatives of the first-degree relatives (e.g. uncle, grandmother); third-degree relatives are the first-degree relatives of the second-degree relatives (e.g. first cousin, great grandfather).

2.5. Identification of high-risk PTSD pedigrees

To identify high-risk pedigrees, all relationships among all VHA patients diagnosed with PTSD were considered. Definition of all ancestors for each case allowed the identification of all clusters of related PTSD cases; the nearest common ancestor or pair of ancestors was identified for each independent cluster of related cases. No completely overlapping clusters were considered, but some cases could appear in more than 1 such cluster (or pedigree). For a given founder of a set of related PTSD patients, the observed PTSD cases among VHA patients who were descendants of the founder were counted. The expected number of PTSD patients among the members of a pedigree was estimated by summing the cohort-specific rate of PTSD for all descendants who were linked VHA patients. A comparison of the number of observed to expected linked VHA cases among the descendants in each pedigree was made; a pedigree was considered high-risk for PTSD if a statistically significant excess of PTSD patients was observed ($p < 0.05$).

3. Results

In the US Veterans Genealogy resource, 22,071 patients had genealogy data for at least 6 immediate ancestors (both parents, and all 4 grandparents) and had an ICD9 or ICD10 code indicating a diagnosis of PTSD in at least two different diagnosis years. Of these VHA patients diagnosed with PTSD, 2369 who also had a diagnosis of schizophrenia or bipolar disorder were excluded, for a total of 19,702 VHA PTSD patients with genealogy data analyzed. 1168 (6%) were female and 18,534 male. The birth year distribution for the VHA patients diagnosed with PTSD ranged from 1900 to the early 1990s.

3.1. Genealogical index of familiality test for excess relatedness

Table 1 summarizes the results for the GIF analysis of PTSD. The GIF test summary includes the sample size (n), the GIF statistic for the cases (case GIF), the mean of the 1000 sets of matched VHA controls (mean control GIF), the empirical significance for the comparison of the overall GIF (empirical GIF p), the distant GIF statistic for the cases (case dGIF), the mean dGIF of the 1000 sets of matched VHA controls (mean control dGIF), and the empirical significance for the comparison of the dGIF (empirical dGIF p). The average pairwise relatedness for the 19,702 PTSD patients was significantly higher than expected for the VHA patient population ($p < 0.023$); however, when relationships closer than third degree (first cousins) were ignored, the average pairwise relatedness of the PTSD patients was not elevated over expected relatedness in the linked VHA population ($p = 0.909$).

3.2. Relative risks in relatives

Estimated RRs for PTSD among the relatives of PTSD patients (who are also VHA patients) are shown in Table 2, which includes the type of relative, the total number of relatives of that type who were linked VHA patients (n), the number of PTSD patients observed in the relatives (obs), the expected number of relatives with PTSD (exp), the estimated RR, the 1-tailed significance of the RR test (p value), and the 95% confidence interval for the RR (95% CI). RRs for PTSD were significantly elevated among first-to third-degree relatives of PTSD patients. RRs in second-degree relatives in this resource are problematic because there are fewer observations that cross generations given the narrow window of view to diagnosis in the current resource (data from the early 1990s). Many first- (siblings) and third-degree (cousins) relatives belong to the same generation, but few second-degree relatives do (except half-siblings). As seen in Table 2, the number of second-degree relatives is smaller than the number of first- and third-degree relatives.

3.3. High-risk pedigrees

11,840 clusters of related PTSD cases were identified, including from 2 to 44 related cases; 1004 of these exhibited a significant excess of PTSD among the descendants who were VHA patients ($p < 0.05$) and included from 2 to 17 related cases. Fig. 1 shows an example high-risk PTSD pedigree identified in the US Veterans Genealogy Resource. The pedigree includes 9 related VHA PTSD patients, only 4 cases were expected ($p = 0.009$). The pedigree founder was born in the early 1700s and has 1177 total descendants in the genealogy, and 37 VHA linked patients among those descendants.

4. Discussion

PTSD is a mental disorder that can develop after exposure to a traumatic event; such events might include a violent assault, a natural disaster, an accident, or combat, among other forms of violence. Exposure to such events is not particularly uncommon; over 50% of US adults experience a traumatic event at least once in their life, but most do not

Table 2
Estimated RRs for PTSD among first-, second- and third-degree relatives of 19,702 VHA patents diagnosed with PTSD.

Relative	n	obs	exp	RR	p value	95% CI
First	5608	621	435.8	1.42	<0.0001	1.31, 1.54
Second	4907	421	325.0	1.30	<0.0001	1.17, 1.43
Third	6124	515	382.3	1.35	<0.0001	1.23, 1.47

Table 1
Genealogical Index of Familiality (GIF) analysis of 19,702 VHA patients diagnosed with PTSD.

Cases	n	Mean			Mean		
		Case GIF	control GIF	empirical p	case dGIF	control dGIF	empirical p
PTSD	19,702	.101	.095	0.023	.044	.046	0.909

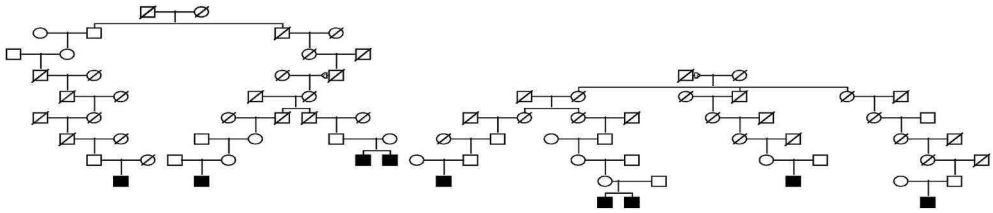

Fig. 1. Example VHA high-risk PTSD pedigree. Males are squares; females are circles. The second male descendent shown in the 4th generation had two marriages, indicated by an arrow on the marriage lines to his 2 spouses.

go on to develop PTSD. It has been estimated that approximately 7–8 percent of all adults in the US will develop PTSD during their lifetime (Kessler et al., 1995, 2008), suggesting some variability in predisposition to response to trauma.

US combat veterans are potentially exposed to many more such traumatic events, and they have been estimated to demonstrate a 2 to 4-fold increase in prevalence of PTSD compared to US civilians (Richardson et al., 2010). The U.S. Department of Veterans Affairs estimates that PTSD afflicts almost 31% of Vietnam veterans, up to 12% of Gulf War veterans, and between 11 and 20% of veterans of Operation Iraqi Freedom and Operation Enduring Freedom (the Afghan theater) (www.ptsd.va.gov). PTSD is recognized as a "signature injury" of individuals serving in the Iraq and Afghanistan conflict (Hoge et al., 2004; Yaffe et al., 2010). It is a significant and costly illness to veterans, their families, and to society. Better understanding of the causes of PTSD could allow improvements in prevention, diagnosis, and treatment.

Although twin studies based mostly on combat Veterans have indicated that PTSD symptoms and symptom clusters are moderately heritable, more distant genetic relationships and families have not typically been studied. A study examining risk and clustering of PTSD in both close and distant relatives has not been possible previously. This study of genetic relationships among VHA patients diagnosed with PTSD has allowed examination of the hypothesis of a heritable contribution to PTSD predisposition by comparing the familial clustering of PTSD with the expected clustering in the VHA population. Using this partial US genealogy of over 70 million individuals linked to diagnosis records for VHA patients, significant evidence for excess familial clustering of PTSD has already been observed; significantly elevated risks to first-, second-, and third-degree relatives were observed, and multiple high-risk PTSD pedigrees were identified; these results provide strong evidence that there is some heritable contribution underlying PTSD predisposition.

Some genetic relationships, and therefore some familial clustering, might be expected among Veterans. Service in the Armed Forces does cluster in families, likely for social rather than genetic reasons. The power of this resource is that comparisons of familial clustering extend to distant relationships among individuals, and that observed familial clustering can be compared to "expected" familial clustering as observed in the resource, allowing control for "Military families". This unique resource has allowed the identification of extended pedigrees with multiple related PTSD cases that exhibit a statistically significant excess of PTSD and are unlikely to represent chance clusters or clusters based on shared environment.

In a previous analysis of a smaller version of this resource we replicated published evidence for excess familial relatedness for Alzheimer's Disease, Parkinson's Disease and Prostate cancer, thus validating this US Veterans Genealogy Resource in terms of data quality and power for genetic analysis (Cannon-Albright et al., 2018). Here we analyze an even more complete version of the resource for a phenotype more associated with military service.

There are limitations to analysis of the US Veterans Genealogy Resource. It would be optimal to match controls based on all characteristics that might affect record linking; we know that birth year, sex, and birth state (Utah or not) affect relatedness in the similar UPDB genealogical resource that represents the Utah population (Cannon-Albright, 2008). We have only matched on birth year and sex for this VHA analysis, due to lack of sufficient sample sizes for matching on birth state. Similarly, we did not have sufficient sample size for matching on VISN. Matching for factors affecting risk of PTSD is also critical; higher rates of PTSD in African Americans have been demonstrated (Alegria et al., 2013), and it is estimated that more than 10% of the VHA population is African American. Historically race data has not been stored for the majority of demographic medical records in the VHA system; it was not available for these analyses. In future we propose to access and use additional VHA data, which might include, for example, race, birth state, VISN, occupational exposures, rank, and socio-economic status when available, for purposes of matching.

Data censoring could also cause limitations in analysis of this resource. VHA cases without genealogy data, or who fail to link to genealogy data, were censored (or remain unidentified as cases), as were individuals with PTSD who were diagnosed outside the VHA system or diagnosed before 1994, or who remained undiagnosed. In addition, genealogy data may not always represent biological relationships. An additional limitation is that the data represents primarily males, Veterans, and individuals with public genealogy data available (primarily those of Northern European ancestry); conclusions may not be appropriately extrapolated beyond this population. Richardson (Richardson et al., 2010) has additionally noted that the VHA serves only about one third of all Veterans nationally, and that this patient population may have a lower income and higher illness burden than the general population of veterans.

The use of ICD coding to identify PTSD cases is a potential limitation that has been investigated. McCarron (McCarron et al., 2014) showed that for 90% of the medical records of Veterans containing at least one ICD9 code for PTSD the diagnosis was confirmed by VA mental health care providers; for 6% of such patients the diagnosis was refuted by the provider (false positives). Gravely (Gravely et al., 2011) showed a positive predictive value of 75% for PTSD using a classification rule of at least 1 PTSD diagnosis. To provide stringent classification of PTSD affection in this analysis, a diagnosis of PTSD present in at least one diagnosis-coded encounter in at least two different years was required. Additionally, VHA patients diagnosed with PTSD who also had either a schizophrenia or a bipolar disorder diagnosis in at least 2 different years were excluded.

The US Veterans Genealogy Resource also has several strengths. The familial clustering methods presented are robust to the types of data censoring expected. Controls are VHA patients who are matched for sex and birth year and are required to have linkage to genealogy data of similar quality and quantity as cases (at least 6 of 14 immediate ancestors representing both maternal and paternal lines). It is difficult to conceive of a mechanism by which significant excess relatedness would exhibit itself in the resource in the absence of any true heritable component. The methods presented are also robust to misclassification of cases. False negatives (missing identification of true PTSD cases) could result in failing to observe evidence for excess relatedness. False positives, even at a very high rate, could only affect this clustering analysis if the assignment of a false diagnosis of PTSD in a VHA patient occurred much more often among close and distant relatives of PTSD cases than among all VHA patients. This is unlikely given the distance of

the genetic relationships that provide the evidence of excess clustering. The relationships represented were identified from many VHA facilities across the US, with diagnoses assigned by many different health care providers.

This US Veterans Genealogy Resource represents what may be the largest existing genealogy linked to medical phenotype data; this is based on its current size of over 70 million individuals and its linkage to medical data for over 1 million VHA patients. This resource needs to be completed with additional genealogy data which will link to additional VHA patients. The eventual size of this US genealogy, upon completion, could be 300–400 million individuals, including 40–60% of the 13 million VHA patients with demographic data expected to link to genealogy data. The analysis of the clustering of PTSD presented here is an example of the utility of the resource for genetic studies. Evidence for a genetic contribution to predisposition to health-related phenotypes can be demonstrated, and high-risk pedigrees informative for predisposition gene identification can be identified. This resource may be uniquely powerful for analysis of phenotypes like PTSD that are highly associated with military service.

This VHA resource could continue to grow and improve. More PTSD cases will be identified and the PTSD phenotype can be further refined with additional medical data. Combining the US Veterans Genealogy data with the VHA Million Veterans Program (MVP), which is collecting and storing DNA and demographic and risk data for 1 million VHA patients, would provide opportunities for powerful genetic analyses. Combining the US Veterans Genealogy data with genotypes, exposure data, and demographic data would allow informative genetic studies that include relationship data on an extremely large scale, unique gene x environment combinations, and analysis of other service-related medical conditions. PTSD has been linked to an increased risk of Alzheimer's and other dementias (Greenberg et al., 2014), and other associations are possible. Stein (Stein et al., 2021) recently reported a GWAS of PTSD and symptom subdomains in the VHA MVP data using more specific qualitative and quantitative symptom phenotypes extracted from the medical record. If MVP genotype data were available for some of the PTSD cases in some of the high-risk PTSD pedigrees described here, it is likely that rare, shared predisposition genetic variants could be identified.

This VHA genealogy resource with linked medical data may be especially powerful for analysis of phenotypes that are rarely observed and that are strongly associated with military service; it can powerfully address the potential genetic contribution to conditions prevalent in Veterans and of interest to the VHA. This analysis of familial clustering for VHA patients diagnosed with PTSD appears to be the first such analysis of PTSD familial clustering. The analyses presented support a genetic contribution to PTSD predisposition, but do not exclude the additional contribution of environmental risk factors. Nor do the analyses shed any light on the basis of the genetic contribution, but such a predisposition might, for example, be related to the ability to build or store strong memories (De Quervain et al., 2012), or to resilience (Vyas et al., 2016), among other characteristics.

Author statement

Lisa A Cannon-Albright: Conceptualization; Formal analysis; Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jennifer Romesser:** Validation, Writing – review & editing. **Craig C Teerlink:** Data curation, Methodology, Validation, Writing – review & editing. **Alun Thomas:** Methodology, Validation, Writing – review & editing. **Lawrence J. Meyer:** Funding acquisition, Investigation, Resources, Writing – review & editing.

Declaration of competing interest

All authors have no conflicts to declare.

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References

Afifi, T.O., Asmundson, G.J.G., Taylor, S., Jang, K.L., 2010. The role of genes and environment on trauma exposure and posttraumatic stress disorder symptoms: a review of twin Studies. Clin. Psychol. Rev. 30, 101–112.
Agresti, A., 1990. Categorical Data Analysis. Wiley, New York.
Albright, F., Light, K., Light, A., Bateman, L., Cannon-Albright, L.A., 2011. Evidence for a heritable predisposition to chronic fatigue syndrome. BMC Neurol. 11 (1), 62.
Albright, F., Teerlink, C., Werner, T.L., Cannon-Albright, L.A., 2012. Significant evidence for a heritable contribution to cancer predisposition: a review of cancer familiality by site. BMC Cancer 12, 138.
Alegria, M., Fortuna, L.R., Lin, J.Y., Norris, L.F., Gao, S., Takeuchi, D.T., Jackson, J.S., Shrout, P.E., Valentine, A., 2013 Dec. Prevalence, risk and correlates of posttraumatic stress disorder across ethnic and racial minority groups in the. U.S. Med Care. 51 (12), 1114–1123.
Almli, L.M., Fani, N., Smith, A.K., Ressler, K.J., 2014 Feb. Genetic approaches to understanding post-traumatic stress disorder. Int. J. Neuropsychopharmacol. 17 (2), 355–370.
Ashley-Koch, A.E., Garrett, M.E., Gibson, J., Liu, Y., Dennis, M.F., Kimbrel, N.A., 2015. Veterans Affairs mid-Atlantic mental illness research, education and clinical center workgroup, Beckham JC, Hauser MA. Genome-wide association study of posttraumatic stress disorder in a cohort of Iraq-Afghanistan era veterans. J. Affect. Disord. 184, 225–234.
Breslau, N., David, G.C., Andreski, P., Peterson, E., 1991 Mar. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch. Gen. Psychiatr. 48 (3), 216–222.
Brewin, C.R., Andrews, B., Valentine, J.D., Oct 2000. Meta-analysis of risk factors for posttraumatic stress disorder in trauma-exposed adults. J. Consult. Clin. Psychol. 68 (5), 748–766.
Cannon, L., Bishop, D.T., Skolnick, M.H., Hunt, S., Lyon, J.L., Smart, C., 1982. Genetic epidemiology of prostate cancer in the Utah Mormon genealogy. Cancer Surv. 1 (1), 48–69.
Cannon-Albright, L.A., Thomas, A., Goldgar, D.E., Gholami, K., Rowe, K., Jacobsen, M., McWhorter, W., Skolnick, M.H., 1994. Familiality of cancer in Utah. Cancer Res. 54 (9), 2378–2385.
Cannon-Albright, L.A., 2008. Utah family-based analysis: past, present and future. Hum. Hered. 65 (4), 209–220.
Cannon-Albright, L.A., Dintelman, S., Maness, T., Backus, S., Thomas, A., Meyer, L.J., 2013. Creation of a national resource with linked genealogy and phenotypic data: the Veterans Genealogy Project. Genet. Med. 15 (7), 541–547.
Cannon-Albright, L.A., Dintelman, S., Maness, T., Cerny, J., Thomas, A., Backus, S., Farnham, J.M., Teerlink, C.C., Contreras, J., Kauwe, J.K., Meyer, L.J., 2018; Aug 1. A Population Genealogy Resource shows evidence of familial clustering for Alzheimer's Disease. Neurol Genet (4), 4.
De Quervain, D.J.F., Kolassa, I.-T., Ackermann, S., Aerni, A., Boesiger, P., Demougin, P., Elbert, T., Ertl, V., Gschwind, L., Hadziselimovic, N., Hanswer, E., Heck, A., Hieber, P., Uuynh, K.-D., Klarhofer, M., Luechinger, R., Raxch, B., Scheffler, K., Spalek, K., Stippich, C., Vogler, C., Vukojevic, V., Stetak, A., Papassotiropoulos, A., 2012. PKCα is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors. Proc. Natl. Acad. Sci. Unit. States Am. 109 (22), 8746–8751.
Gravely, A.A., Cutting, A., Nugent, S., Grill, J., Carlson, K., Spoont, M., 2011. Validity of PTSD diagnoses in VA administrative data: comparison of VA administrative PTSD diagnoses to self-reported PTSD checklist scores. JRRD Vol 48 (Number 1), p21–30.
Greenberg, M.S., Tanev, K., Marin, M.-F., Pitman, R.K., 2014. Stress, PTSD, and dementia. Alzheimer's Dementia 10, S155–S165.
Hoge, E.W., Castro, C.A., Messer, S.C., McGurk, D., Cotting, D.I., Koffman, R.L., 2004. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. N E J M 35 (1), 13–22.
Horne, B.D., Camp, N.J., Muhlestein, J.B., Cannon-Albright, L.A., 2004. Evidence for a heritable component in death resulting from aortic and mitral valve diseases. Circulation 110 (19), 3143–3148.
Horne, B.D., Camp, N.J., Muhlestein, J.B., Cannon-Albright, L.A., 2006. Identification of excess clustering of coronary heart diseases among extended pedigrees in a genealogical population database. Am. Heart J. 152 (2), 305–311.
Kessler, R.C., Wang, P.S., 2008. The descriptive epidemiology of commonly occurring mental disorders in the U.S. Annu. Rev. Publ. Health 29, 115–129.
Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B., 1995. Posttraumatic stress disorder in the national comorbidity survey. Arch. Gen. Psychiatr. 52, 1048–1060.
Koenen, K.C., Harley, R., Lyons, M.J., Wolfe, J., Simpson, J.C., Goldberg, J., Eisen, S.A., Tsuang, M., 2002. A twin registry study of familial and individual risk factors for trauma exposure and posttraumatic stress disorder. J. Nerv. Ment. Dis. 190, 209–218.

Lyons, M.J., Goldberg, J., Eisen, S.A., True, W., Tsuang, M.T., Meyer, J., Henderson, W. G., 1993. Do genes influence exposure to trauma: a twin study of combat. Am. J. Med. Genet. 48, 22–27.

Malecot, G., 1948. Les Mathematiques de l'heredite. Masson & Cie, Paris, France.

McCarron, K.K., Reinhard, M.J., Bloeser, K.J., Mahan, C.M., Kang, H.K., 2014 Oct. PTSD diagnoses among Iraq and Afghanistan veterans: comparison of administrative data to chart review. J. Trauma Stress 27 (5), 626–629.

Patel, A.A., Spiker, W.R., Daubs, M., Brodke, D., Cannon-Albright, L.A., 2011. Evidence for an inherited predisposition to lumbar disc disease. J Bone Joint Surg Am 93 (3), 225–229.

Patel, A.A., Spiker, W.R., Daubs, M., Brodke, D.S., Cannon-Albright, L.A., 2012. Evidence of an inherited predisposition for cervical spondylotic myelopathy. Spine 37 (1), 26–29.

Richardson, L.K., Frueh, B.C., Acierno, R., 2010 Jan. Prevalence estimates of combat-related PTSD: a critical review. Aust NZ J Psychiatry 44 (1), 4–19.

Sartor, C.E., McCutcheon, V.V., Pommer, N.E., Nelson, E.C., Grant, J.D., Duncan, A.E., Waldron, M., Bucholz, K.K., Madden, P.A., Heath, A.C., 2011 Jul. Common genetic and environmental contributions to post-traumatic stress disorder and alcohol dependence in young women. Psychol. Med. 41 (7), 1497–1505.

Sartor, C.E., Grant, J.D., Lynskey, M.T., McCutcheon, V.V., Waldron, M., Statham, D.J., Bucholz, K.K., Madden, P.A., Heath, A.C., Martin, N.G., Nelson, E.C., 2012; Mar. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. Arch. Gen. Psychiatr. 69 (3), 293–299.

Skolnick, M., 1980. The Utah Geneological Database: a resourse for genetic epidemiology. In: Banbury Report No 4: Cancer Incidence in Defined Populations. Cold Spring Harbor. Cold Spring Harbor Laboratories, New York.

Stein, M.B., Jang, K.L., Taylor, S., Vernon, P.A., Livesley, W.J., 2002 Oct. Genetic and environmental influences on trauma exposure and posttraumatic stress disorder symptoms: a twin study. Am. J. Psychiatr. 159 (10), 1675–1681.

Stein, M.B., Levey, D.F., Cheng, Z., Wendt, F.R., Harrington, K., Pathak, G.A., Cho, K., Quaden, R., Radhakrishnan, K., Girgenti, M.J., Ho, Y.-L.A., Posner, D., Aslan, M., Duman, R.S., Zhao, H., Feb 2021. Department of veterans Affairs cooperative studies Program (no.575B), VA million veteran Program, polimanti R< concato J, Gelernter J. Genome-wide association analyses of post-traumatic stress disorder and its symptom subdomains in the million veteran Program. Nat. Genet. 53, 174–184.

Tashjian, R.Z., Farnham, J.M., Albright, F.S., Teerlink, C.C., Cannon-Albright, L.A., 2009. Evidence for an inherited predisposition contributing to the risk for rotator cuff disease. J Bone Joint Surg Am 91 (5), 1136–1142.

Teerlink, C.C., Albright, F.S., Lins, L., Cannon-Albright, L.A., 2012. A comprehensive survey of cancer risks in extended families. Genet. Med. 14 (1), 107–114.

True, W.R., Rice, J., Eisen, S.A., Heath, A.C., Goldberg, J., Lyons, M.J., Nowak, J., 1993. A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch. Gen. Psychiatr. 50, 257–264.

Voisey, J., Young, R.M., Lawford, B.R., Morris, C.P., 2014. Progress towards understanding the genetics of posttraumatic stress disorder. J. Anxiety Disord. 28, 873–883.

Vyas, K.J., Fesperman, S.F., Nebeker, B.J., Gerard, S.K., Boyd, N.D., Delaney, E.M., Webb-Murphy, J.A., Johnston, S.L., 2016. Preventing PTSD and Depression and reducing health care costs in the military: a call for building resilience among service members. Mil. Med. 181 (10), 1240.

Wolf, E.J., Mitchell, K.S., Koenen, K.C., Miller, M.W., 2014 May. Combat exposure severity as a moderator of genetic and environmental liability to posttraumatic stress disorder. Psychol. Med. 44 (7), 1499–1509.

Wolf, E.J., Miller, M.W., Sullivan, D.R., Amstadter, A.B., Mitchell, K.S., Goldberg, J., Magruder, K.M., 2018. A classical twin study of PTSD symptoms and resilience: evidence for a single spectrum of vulnerability to traumatic stress. Depress. Anxiety 35, 132–139.

Wolfsohn, J.M., 1918. The predisposing factors of war psycho-neuroses. Lancet 191, 177–181.

Xian H, Scherrer JF, Eisen SA, True WR, Heath AC, Goldberg J, Lyons MJ, Tsuang MT. Self-reported zygosity and the equal-environments assumption for psychiatric disorders in the Vietnam Era Twin Registry. Behav. Genet. 2000a Jul; 30(4):303-310.

Xian, H., Chantarujikapong, S.I., Scherrer, J.F., Eisen, S.A., Lyons, M.J., Goldberg, J., Tsuang, M., True, W.R., 2000b. Genetic and environmental influences on posttraumatic stress disorder, alcohol and drug dependence in twin pairs. Drug Alcohol Depend. 61, 95–102.

Yaffe, K., Vittinghoff, E., Lindquist, K., Barnes, D., Covinsky, K.E., Meylan, T., Kluse, M., Marmar, C., 2010. Posttraumatic stress disorder and risk of dementia among US veterans. Arch. Gen. Psychiatr. 67 (6), 608–613.