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Known genetic susceptibility factors for chronic pancreatitis in patients of European ancestry are rare in patients of African ancestry☆

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ABSTRACT

Background: Multiple pathogenic genetic variants are associated with pancreatitis in patients of European (EA) and Asian ancestries, but studies on patients of African ancestry (AA) are lacking. We evaluated the prevalence of known genetic variations in African-American subjects in the US.
Methods: We studied prospectively enrolled controls (n = 238) and patients with chronic (CP) (n = 232) or recurrent acute pancreatitis (RAP) (n = 45) in the NAPS2 studies from 2000-2014 of self-identified AA. Demographic and phenotypic information was obtained from structured questionnaires. Ancestry and admixture were evaluated by principal component analysis (PCA). Genotyping was performed for pathogenic genetic variants in *PRSS1*, *SPINK1*, *CFTR* and *CTRC*. Prevalence of disease-associated variants in NAPS2 subjects of AA and EA was compared.

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Results: When compared with CP subjects of EA (n = 862), prevalence of established pathogenic genetic variants was infrequent in AA patients with CP, overall (29 vs. 8.19%, OR 4.60, 95% CI 2.74–7.74, p < 0.001), and after stratification by alcohol etiology (p < 0.001). On PCA, AA cases were more heterogeneous but distinct from EA subjects; no difference was observed between AA subjects with and without CP-associated variants. Of 19 A A patients with CP who had pathogenic genetic variants, 2 had variants in *PRSS1* (*R122H*, *R122C*), 4 in *SPINK1* (all N34S heterozygotes), 12 in *CFTR* (2 $CFTR^{sev}$, 9 $CFTR^{BD}$, 1 compound heterozygote with $CFTR^{sev}$ and $CFTR^{BD}$), and 1 in *CTRC* (*R254W*).
Conclusion: Pathogenic genetic variants reported in EA patients are significantly less common in AA patients. Further studies are needed to determine the complex risk factors for AA subjects with pancreatitis.

1. Introduction

Chronic pancreatitis (CP) is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress that eventually results in pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia [1]. Clinically, most patients with CP report a history of acute pancreatitis (AP) or recurrent AP (RAP) [2,3], indicating a complex, multifactorial, progressive disease scenario. CP results in multiple complications with a significant reduction in quality of life (QOL) when compared with non-pancreatitis controls [4], as well as overall survival when compared with age- and sex-matched general population [5]. Pancreatitis represents a significant burden to the health care system, and accounts for an annual health care expenditure of over $2.8 billion in the US [6].

Since the discovery in 1996 of a germline mutation in *PRSS1* as the cause of hereditary pancreatitis [7], disease-associated variations in several other pancreatitis susceptibility genes, including cystic fibrosis transmembrane conductance regulator [*CFTR*], serine peptidase inhibitor, Kazal type 1 [*SPINK1*], and chymotrypsin C [*CTRC*] have been identified and replicated in multiple cohorts from North America, Europe and Asia [8–17]. Testing for pathogenic variants in these genes is now performed routinely in clinical practice, especially when the cause of RAP or CP is unknown.

In epidemiologic studies, the risk of pancreatitis is noted to be 2–3 folds greater in patients of African ancestry (AA) including African-Americans, when compared with Caucasians [18–21]. AA patients also have a greater risk of readmission after an episode of pancreatitis [22]. The precise causes underlying these differences are unknown. Few studies have examined the effect of environmental and/or behavioral risk factors as potential mediators of racial differences in pancreatitis. For instance, racial differences in pancreatitis have been partially attributed to a higher prevalence of alcohol and tobacco exposure in AA patients [18–20]. In the North American Pancreatitis Study 2 (NAPS2), we found in AA patients with CP that the odds of self-reported *heavy* or *very heavy* drinking were 2.62 folds greater and odds of ever smoking were 2.97 folds greater than patients of European ancestry (EA). Similarly, the odds of physician-defined alcohol etiology and smoking as a risk factor were 4.31 and 2.54 times greater in AA patients with CP when compared to EA patients with CP [23].

Ancestral germ line genetic differences could also affect differences in disease risk and prevalence between Americans of European ancestry and African Americans [24,25]. Pathogenic genetic variants in *PRSS1, SPINK1, CFTR* and *CTRC* are clearly associated with pancreatitis in populations of EA and Asian ancestry (7–16). The effects and burden of these pathogenic genetic variants for RAP or CP in AA patients has not been reported.

We tested the hypothesis that the prevalence of pathogenic variations linked to the four most common RAP and CP susceptibility genes in patients of self-reported AA in the United States is similar to those of EA in the NAPS2 cohort. We further tested for the amounts of ancestral admixture, since previous studies have demonstrated the importance of genetics on disease risks and outcomes based on difference in the minor allele frequency [25,26]. Here, we report that RAP/CP-associated variants that are common in patients of EA are rare in patients of AA. These findings suggest that genetic testing of RAP/CP susceptibility variants that are frequent in cases of EC will likely be of lower yield in patients of AA. Further studies are needed to understand genetic and environmental risk factors for pancreatitis in subjects of AA.

2. Methods

2.1. Study population

The North American Pancreatitis Study Group has prospectively recruited carefully phenotyped controls and patients with RAP or CP from 27 US centers from 2000-2014 in a series of 3 studies: North American Pancreatitis Study 2 (NAPS2 Original), North American Pancreatitis Study 2 Continuation and Validation (NAPS2-CV), and North American Pancreatitis Study 2 Ancillary Study (NAPS2-AS) [23,27,28]. Although previous genetic studies focused on subjects of EA, this cohort also contains one of the largest number of RAP/CP patients of AA ascertained in the US [23]. RAP was defined by two or more documented episodes of AP (typical abdominal pain with elevation of serum pancreatic enzymes to more than 3 times the upper limit of normal or imaging evidence of AP), and CP was defined using definitive evidence on imaging or histology [27]. The NAPS2 studies were approved by the Institutional Review Board of each participating center, and all subjects provided informed consent prior to study enrollment. We have previously reported the prevalence of genetic variations in cases and controls of EA from the NAPS2 cohort [9,17,29–31].

2.2. Data collection

Study procedures and information collected in the NAPS2 studies have been described earlier [23,27,28]. Two detailed sets of questionnaires were used to obtain information from the study subjects and the enrolling physician. Questionnaires were completed by patients and controls with assistance of a trained research coordinator. Information was collected on demographics, personal and family history, exposure to environmental risk factors (alcohol, smoking), pain experience (presence, pattern), hospitalizations, emergency room visits, disability related to pain and pancreatitis, medication use, and quality of life. Race was self-

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