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A genome-wide association study suggests correlations of common genetic variants with peritoneal solute transfer rates in patients with kidney failure receiving peritoneal dialysis

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Abstract

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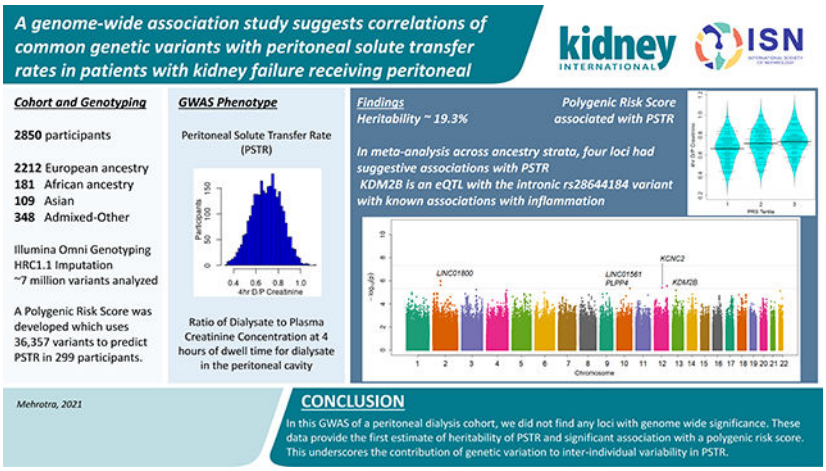
Data Sharing Statement

The investigators are working with the NIH to deposit the phenotype-genotype data from participants enrolled prospectively in Australia, Canada, and the United States to the database of Genotype and Phenotypes (dbGaP). The request has already been submitted, and an accession ID is currently pending.

The Institutional Review Board of the University of Washington and the Ethics Boards of participating institutions have determined that the data from participants in Belgium, Sweden, and the United Kingdom is not eligible for submission in a public data repository in either the United States or Europe. Since the participants did not sign a consent for their data to be deposited in a public repository, it has been deemed that doing so will serve no lawful purpose under the European Union General Data Protection Regulation (EU-GDPR).

Movement of solutes across the peritoneum allows for the use of peritoneal dialysis to treat kidney failure. However, there is a large inter-individual variability in the peritoneal solute transfer rate (PSTR). Here, we tested the hypothesis that common genetic variants are associated with variability in PSTR. Of the 3561 participants from 69 centers in six countries, 2850 with complete data were included in a genome-wide association study. PSTR was defined as the four-hour dialysate/plasma creatinine ratio from the first peritoneal equilibration test after starting PD. Heritability of PSTR was estimated using genomic-restricted maximum-likelihood analysis, and the association of PSTR with a genome-wide polygenic risk score was also tested. The mean four hour dialysate/plasma creatinine ratio in participants was 0.70. In 2212 participants of European ancestry, no signal reached genome-wide significance but 23 single nucleotide variants at four loci demonstrated suggestive associations with PSTR. Meta-analysis of the 2850 ancestry stratified regressions revealed five single nucleotide variants at four loci with suggestive correlations with PSTR. Association across ancestry strata was consistent for rs28644184 at the *KDM2B* locus. The estimated heritability of PSTR was 19% and a significant permuted model polygenic risk score was associated with PSTR. Thus, this genome-wide association study of patients receiving peritoneal dialysis bolsters evidence for a genetic contribution to inter-individual variability in PSTR.

Graphical Abstract



Keywords

kidney failure; peritoneal dialysis; peritoneal solute transfer rate; genetics; genome wide association study; epithelial mesenchymal transition

Introduction

In 2019, about 390,000 people with kidney failure were being treated with peritoneal dialysis (PD) comprising 11% of the dialysis patient population worldwide[1]. Since PD provides similar short- and long-term survival as in-center hemodialysis often at lower societal costs, the use of PD is anticipated to further expand in many parts of the world including the United States[2, 3]. This growing patient population underscores the need to

better understand the biology that allows the peritoneum to serve as a dialysis membrane. This, in turn, will facilitate the development of biomarkers to monitor peritoneal health and treatments to enhance solute or fluid removal or mitigate peritoneal damage associated with long-term PD.

PD utilizes the diffusive and convective movement of solutes across the peritoneum to manage uremia. The peritoneal solute transfer rate (PSTR) is routinely measured in clinical practice with a peritoneal equilibration test (PET) and it is highly reproducible. PSTR is described as the ratio of the concentration of creatinine in the dialysate at four hours of a dwell of dialysate solution to that in the plasma (4-h D/P creatinine)[4, 5]. Large cohort studies have consistently shown that there is an over 3-fold inter-individual variability in PSTR (4-h D/P creatinine, 0.3–1.0) and demographic and clinical factors explain less than 10% of this variability[6–10]. The variability is clinically meaningful as it influences PD prescription, and a faster PSTR is associated with a higher risk for death or hospitalization[5, 9, 11].

Experimental, clinical, and several candidate gene association studies suggest that some of this inter-individual variability in peritoneal function is heritable[12–21]. Thus far, human studies have had small sample sizes, they examined a limited range of genetic variability in few candidate genes, and have rarely been replicated. Genome-wide association studies (GWAS) provide an unbiased approach to identifying common genetic variants associated with a given phenotype and overcome many of the limitations of the candidate gene studies of peritoneal function to date[22]. However, no GWAS has been undertaken for any PD-related phenotype. To bridge this gap in knowledge, we undertook the Biological Determinants of PD (Bio-PD) study to perform a GWAS to test the hypothesis that common genetic variants explain some of the inter-individual variability in PSTR in people with kidney failure treated with PD.

Methods

Study Population

The study cohort comprised participants with kidney failure treated with PD from 69 centers in six countries (Australia, Belgium, Canada, Sweden, United Kingdom, and United States) enrolled either prospectively for Bio-PD study (NCT02694068; n=1677), or by procuring frozen DNA of participants in other studies (n=1884).

Participants in Bio-PD were prospectively enrolled from 54 centers in four countries (Australia, 2; Canada, 5; United Kingdom, 32; and United States, 15 centers) from September 2013 through November 2018. Ten of the 56 centers were also participating sites in the Peritoneal Dialysis Outcomes and Practice Patterns (PDOPPS) study; however, enrollment in PDOPPS was not required for enrollment in Bio-PD. All individuals treated with PD in participating facilities who had undergone a PET within six months of starting PD were eligible for enrollment, without regard to duration of PD treatment. There were no exclusion criteria. The overall plan for prospective enrollment was reviewed and approved by the Institutional Review Board (IRB) of the University of Washington, with additional approvals from IRBs or Ethics Boards of participating institutions as needed. All participants provided written informed consent for participation.

DNA samples and phenotype data were also procured for participants enrolled through three different sources: (1) Peritoneal Dialysis Competitive Risk Analysis for Long-Term Outcomes (PD-CRAFT) that enrolled participants from 42 centers in the United Kingdom from August 2012 through December 2014 (n=1355), 31 of which also participated in prospective enrollment in Bio-PD study; (2) participants enrolled in an ongoing cohort study of peritoneal function in Belgium from November 1994 through March 2018 (n=314); and (3) longitudinal cohort study of incident patients with kidney failure in Sweden from February 1993 through August 2014 (n=215)[23]. The consent forms from these studies were reviewed by the IRB at the University of Washington to ensure that they allowed for use of genomic and phenotypic data for this current study.

Phenotype, and Other Covariates

The phenotype was PSTR, as described by the 4-h D/P creatinine from the first PET performed for clinical care after initiating PD. Covariates included age (years), sex, self-reported race, cause of kidney failure (diabetes, hypertension, glomerular disease, cystic kidney disease, other, or unknown), diabetes mellitus (yes/no), body mass index, interval from start of PD to PET in days (PD start-PET interval), tonicity of dextrose used for PET (1.5%, 2.5%, or 4.25%), and country of enrollment.

Genome-wide genotyping and imputation

Of the 3561 study participants, blood samples were collected and available for 3470 individuals (Figure 1). DNA was purified using a non-enzymatic method from either whole blood collected and stored frozen in PAXgene blood DNA tubes, or from buffy coat[24]. The details of the method for DNA extraction are summarized in the Supplemental Methods. The amount of DNA was insufficient for 45 participants, and the sample failed quality control for an additional 414 participants (Figure 1 and Supplemental Table 1). Hence, genome-wide genotyping was completed and available for 3010 participants and performed in two batches at the Northwest Genomic Center at the University of Washington. The first batch (n=1957) was genotyped on the InfiniumOmni2–5-8v1–3_A1 array with 2,372,784 single nucleotide variants (SNVs). The second batch (n=1053) was genotyped on the InfiniumOmni2–5-8v1–4_A1 array with 2,382,209 SNVs. For quality control, we removed subjects with duplicated sample-subject IDs between batches that were genotype discordant and sex discordant upon comparison of the heterozygosity of the X chromosome to reported sex. Each batch was also filtered for missingness of genotype call rates using plink -geno 0.02 -mind 0.02 and prepared for imputation of SNVs using the Michigan Imputation Server and the HRC1.1 SNV reference panel[25–27]. The resulting imputed genotype files (VCFs) were merged using bcftools and converted to plink bfiles for analysis[28, 29]. The mean of the r^2 imputation quality information scores for each variant from the two batches were calculated and a threshold of $r^2 > 0.3$ was used as the minimum imputation quality for including SNV in the analyses.

Data from each autosomal chromosome was linkage-disequilibrium-pruned using the function (plink --maf 0.02 --geno 0.1 --mind 0.1 --indep-pairwise 1000 50 0.7) (plink v1.90b6.21) and we excluded the hg19 regions (chr5:44000000–51500000, chr6:25000000–33500000, chr8:8000000–12000000, chr11:45000000–57000000). These

linkage-disequilibrium pruned files were then merged and identity-by-descent (IBD) (plink --genome) and principal component analyses (PCA) (plink --pca) were performed genome wide (Supplemental Figures 1 and 2, respectively). A homogeneous subset of 2212 participants self-reported “White” race and with European ancestry identified by kmean clustering was used to calculate the Hardy-Weinberg equilibrium statistics.

The IBD plot was inspected to identify and remove (1) apparent duplicates/twins, parent-child, sibling, or lower degree related individuals; and (2) related individuals with IBD0 < 0.83 or IBD1 > 0.1 (Supplemental Figure 1). Sixty-two participants with relatedness on IBD analyses were removed prior to analyses (Figure 1 and Supplemental Table 1). The PC1 and PC2 was plotted with an overlay of self-reported race categories and a visual inspection of the plot showed good concordance between the expected ancestry clusters and reported race (Supplemental Figure 2).

Statistical Analyses

Participants with missing data on the phenotype, 4-h D/P creatinine (n=89), and those with physiologically improbable values of 4-h D/P creatinine < 0.3 (n=4) or > 1.15 (n=5) were excluded from analyses (Figure 1 and Supplemental Table 1). The missing data for age (n=7), diabetes mellitus (n=401), body mass index (n=114), and PD start-PET interval (n=6), by ancestry, are summarized in Supplemental Table 2. Missing data were handled using five multiple imputations with a regression model with age, sex, diabetes mellitus, body mass index, 4-h D/P creatinine, and country of enrollment as predictors (Supplemental Table 3)[30]. The reported interval between PD start and PET was between −45 and +365 in 2601 (89%) of 2912 participants; it was < −45 d in 35 participants and > 365 d in 276 participants. Prior to inclusion in the regression model, data on this variable was winsorized and placed in the tails of the distribution in an ordered manner so as not to create artificial peaks in the histogram (Supplemental Methods)[31]. Furthermore, as the log of PD start-PET intervals yielded a more normal distribution than the untransformed values, we used log ((PD start-PET interval) + 100) in regression analyses and then centered and scaled these values for the resulting transformation.

As a first step in the analysis, we built a regression model using clinical covariates, with 4-h D/P creatinine as an outcome. The model was inspected using transformed, untransformed and bounded (range −45 to 365) PD start-PET interval variable, as well as with and without imputation of the missing data. If a covariate was significant in unadjusted analyses, or in any other modelling, it was included in the final model. Cause of kidney failure was not included in the final regression model due to collinearity with the covariate diabetes mellitus, and because adding it to the model resulted in little gain in model r-square.

For GWAS analyses, the clinical covariates of age, sex, diabetes mellitus, body mass index, log transformed PD start-PET interval, dialysate tonicity for PET, country of enrollment, and genomic PCA (PCs 1–10) were adjusted for in regressions, performed using mixed model analysis with the Genome-wide Complex Trait Analysis (GCTA, version 1.93.2 beta) software with the –mlma-loco genotype relationship matrix computation[32–35]. SNVs with low imputation quality ($r^2 \leq 0.3$) or out of Hardy-Weinberg Equilibrium (p-value < 10^{-6}) in participants of European ancestry that also self-reported ‘White’ were removed from the

analysis. Common variants with minor allele frequency > 2% across all 2850 participants were included in additive (0/1/2) models. Ancestry-stratified analyses were undertaken in the sub-groups of participants with concordant self-reported and genetic ancestry (by k-means clustering): European (n=2212), African (n=181), Asian (n=109), and Admixed/Other (n=348). These analyses were adjusted for principal components of ancestry specific to the ancestral subset. The analyses were run five times, one with each set of imputed covariates and the resultant p-values were combined using the Median P-value Rule (MPR) to construct summary Manhattan and Quantile-Quantile (QQ) plots[36, 37]. Meta-analysis was performed to combine the resulting GWAS in four strata of ancestry using the METAL software (released on 2011–03-25)[38]. We excluded variants in strata for meta-analyses that had a minor allele count of ≤ 10 and where the effect allele, major allele, and minor allele did not harmonize using the EasyQC imputation preparation R package[39]. Variants with combined p-values $< 5 \times 10^{-8}$ were considered to have genome-wide significance and with combined p-values $< 5 \times 10^{-6}$ as suggestive[40, 41].

Heritability was calculated using the GREML method as implemented in the Genome-wide Complex Trait Analysis (GCTA) software[32–35]. This was done using the continuous variable outcome methods, with a linkage disequilibrium (LD) score region of 200kb and stratified variants by quartiles for making the four genetic relationship matrices representing high to low LD. The same covariates were used for calculating heritability as for the GWAS. The mean of the heritability estimates of each of the imputed covariate versions and median p-value rule was used to obtain a single heritability estimate.

A genome-wide polygenic risk score (PRS) was developed for 4-h D/P creatinine by randomly holding out a 10.5% (n=299) subset of participants and then fitting betas with GWAS of the remaining 89.5% of the data in all participants without regard to ancestry, using five iterations of covariate imputations. The combined betas from the fitted GWASs and the same demographic and clinical covariates (age, sex, diabetes, body mass index, log transformed PD start-PET interval, dialysate tonicity for PET, country of enrollment, and principal components (PC) 1–10 of ancestry) were used to predict 4-h D/P creatinine in the held-out subset (n=299) using the polygenic risk score (PRSice version 2.2.6) software package which implements a LD pruning and p-value thresholding method to select the model SNVs[42]. A permutation (n=10,000) empirical test of the held-out data was performed to control over-fitting. Both the unadjusted primary and permuted empirical models are reported.

Results

Characteristics of Study Participants

Of the 3561 participants enrolled in the study, 2850 (80%) unrelated individuals, with adequate genotyping quality control and complete phenotypic characterization, were included in the analyses (Figure 1 and Supplemental Table 1). The excluded participants were more likely to be enrolled in the UK and have “other/unknown” as the cause of their kidney failure, but had similar 4-h D/P creatinine as compared with included participants (Supplemental Table 4). The demographic and clinical characteristics of the 2850 participants by ancestry are summarized in Table 1. The largest proportion of study

participants (81%) were of European ancestry. Among the total study population across all ancestries, 55% were enrolled from the UK and 38% were women. The mean ± standard deviation 4-h D/P creatinine was 0.70 ± 0.13, it was obtained using a PET done at a median (interquartile range) of 63 (28, 120) days after PD start, and it was performed using 2.5% dextrose in 79% of participants.

The demographic and clinical variables explained 5.4% (95% confidence interval, 4.1%, 8.0%) of the variability in the 4-h D/P creatinine in participants with no missing data (n=2062) and 5.7% (95% confidence interval, 4.1%, 7.5%) using data with multiple imputation (n=2912).

GWAS by Ancestry

There were 7,066,544 SNVs which passed our quality parameters in participants of European ancestry with the lambda for genomic inflation of 0.991. The quantile-quantile (QQ) plots did not show any significant deviations from the expected p-values, implying there was no residual population stratification in the analyses (Supplemental Figure 3). No SNV reached genome-wide significance ($p < 5 \times 10^{-8}$) for association with 4-h D/P creatinine (Figure 2A and Table 2). The association of 23 SNVs at four loci reached the threshold for suggestive associations ($p < 5 \times 10^{-6}$) (Figure 2A and Table 2). The genomic inflation in analyses in individuals of African (n=181), Asian (n=109), and admixed/other ancestry (n=348) were 0.910, 0.773, and 0.854, respectively and the results of the GWAS by ancestry strata are summarized in Supplemental Table 5.

Meta-Analysis of Ancestry-Stratified GWAS

In the multi-ancestry meta-analyzed GWAS, 7,066,534 SNVs were included with a collective lambda of 0.963. Five SNVs at four loci reached the threshold for suggestive significance (Table 3); the coefficients for the estimates for the SNVs in the largest sub-groups by center (Belgium and Sweden) were similar to the entire study population (Supplemental Table 6). Two of the five SNVs (rs76108553 and rs111976243 at *LINC01800* locus) were among the 23 SNVs identified in the analyses limited to participants with European ancestry, and were supportive only with data from the sub-group of European ancestry in the meta-analysis (Table 3). The other three SNVs were identified only in the meta-analysis and not in analyses stratified by ancestry.

The SNVs had high imputation quality (all $r^2 \geq 0.87$); the r^2 for 23 of the 26 SNVs identified either in the analyses in participants of European ancestry or meta-analysis, was ≥ 0.98. Each SNV had a minor allele frequency > 2% and five SNVs identified in the meta-analyses had a minor allele frequency of > 18%.

Of the five SNVs with suggestive associations, one was intronic in the protein coding gene *KDM2B,* three were in or near two long intergenic non-coding (LINC) RNAs (*LINC01800, and LINC01561*), and one SNV was in a region adjacent to the *KCNC2* gene, (Tables 2 and 3). The rs28644184 SNV in the *KDMB2* intronic region had evidence of expression quantitative trait loci (eQTLs) in the genotype-tissue expression (GTEx) data – the gene variants have been associated with differential expression of the index gene *KDM2B*. Figure

3A depicts the regional association plot of the region with *KDMB2* on chromosome 12 and Figure 3B presents the box plots for PSTR by *KDMB2* genotype .

Supplemental Figure 4 includes the regional association plots for the other genomic regions with suggestive associations. Supplemental Figure 5 presents the box plots for PSTR by genotype for the genes with suggestive associations in either the meta-analysis or individuals of European ancestry. The other biologic effects of the gene loci known to date are summarized in Supplemental Table 7.

Mixed Model GWAS in the Entire Cohort adjusted for PCAs of ancestry

The results of the GWAS analyses in the entire cohort (n=2850), adjusted for principal components for ancestry, age, sex, diabetes, body mass index, dialysis tonicity used for the PET, PD start-PD interval, and country of enrollment are summarized in Supplemental Table 8 and Supplemental Figure 6. This analysis identified six SNVs in six genomic regions with suggestive associations and they included four of the five SNVs identified in the meta-analyses of ancestry-stratified data (rs76108553, rs2901257, rs117559199, and rs28644184). The lamda is 0.981.

Heritability of 4-h D/P creatinine and Association with Polygenic Risk Score

The REML heritability of the phenotype was estimated at 19.3% (SE 17.3, p-value = 0.07). The polygenic risk score (PRS) GWAS was fitted with 2551 participants and the prediction was tested in 299 participants. LD pruning and p-value thresholding selected 36,357 SNVs at the 0.049 p-value threshold to be included in the PRS model. The PRS model explained 4.2% of the variance in 4-h D/P creatinine (primary model p-value, 0.0004; p-value for permutation test of data, 0.008). Figure 4 illustrates the relationship between the tertiles of PRS and 4-h D/P creatinine (n=299; p=0.0002 for difference across tertiles).

Discussion

This first report of a GWAS in people with kidney failure treated with PD provides new insights into biological determinants of PSTR as described by 4-h D/P creatinine. While no association reached genome-wide significance, the SNVs at loci with suggestive associations highlight the potential significance of several mechanistic pathways in determining PSTR. This study also provides the first estimates on the heritability of the PSTR and its association D/P with a genome-wide PRS. These findings collectively bolster the evidence supporting the premise that a significant part of the inter-individual variability in PSTR is genetically determined.

This international collaborative effort is the largest cohort study with bio-samples to date of patients with kidney failure treated with PD. The number of participants enrolled in this study is equal to about 1% of the entire point-prevalent population of patients treated with PD globally. The greatest challenge for studies of this kind is that a modest-sized patient population is dispersed in a few thousand centers around the world. In the United States, about 60,000 PD patients are presently treated in over 2500 dialysis facilities. Hence, even though the sample size for this GWAS is modest relative to that for other continuous polygenic traits such as eGFR or albuminuria, it required collaboration of 69 centers in six

countries in three continents. Nevertheless, this first effort to undertake a GWAS to better understand peritoneal biology provides a strong foundation on which to build in the future.

Even though none of the associations reached genome-wide significance, suggestive associations with five SNVs at four loci in the meta-analyses and the 21 SNVs at three loci in analyses of European ancestry may help our understanding of peritoneal biology. The peritoneum is a complex membrane that comprises a mesothelial cell mono-layer, and sub-mesothelial matrix with numerous embedded capillaries that participate in dialysis with PD[43]. Biopsy studies have indicated that the peritoneum of humans with kidney failure is thicker and has a higher density of capillaries than in those with normal kidney function[44]. These processes are substantially amplified with treatment with PD[44]. There is evidence that several of the SNVs with suggestive association in our study influence some of the mechanistic pathways relevant for peritoneal fibrosis and neo-vascularization with uremia and/or treatment with PD[45].

Peritoneal fibrosis is the process that underlies the thickening of the peritoneum with uremia and following exposure to PD. Experimental evidence has suggested that epithelial-mesenchymal transition (EMT) of mesothelial cells is an important mechanistic pathway leading to peritoneal fibrosis[45]. There is laboratory evidence linking the *KDM2B* (meta-analyses) and *PCHD9* (European ancestry) genes with EMT. For example, upregulation of epigenetic factors such as *KDM2B* facilitates the metabolic switch from oxidative phosphorylation to glycolysis and EMT in mouse embryonic fibroblasts[46]. *PCDH9* has been shown to be an inhibitor of EMT in cancer and the down-regulation of *PCDH9* is a poor prognostic factor[47, 48]. Whether any of these variants influence EMT in peritoneal mesothelial cells and peritoneal fibrosis has not been studied and needs further study.

Our study also identified suggestive associations of PSTR with SNVs in loci for long non-coding RNAs (lncRNAs); two of the three SNVs had suggestive associations with PSTR in both the meta-analyses and analyses limited to participants of European ancestry. The lncRNAs are non-coding RNAs ranging in length from 200 nt to about 100 kb and are involved in multiple biologic processes, such as proliferation, differentiation, migration, and apoptosis[49]. There is also growing evidence that lncRNAs may play a role in PD-induced peritoneal fibrosis. For instance, in a microarray analysis of the peritoneum in a mouse model of PD-fluid induced peritoneal fibrosis, there was differential expression of 232 lncRNAs when compared with normal mouse peritoneum – 127 were upregulated and 105 were down-regulated[50]. Cell culture or animal studies have identified lncRNAs such as AV310809 as promoters or AK089579 and 6030408B1RIK as inhibitors of EMT of peritoneal mesothelial cells[51–53]. In conjunction with these prior studies, our findings underscore the potential importance of lncRNAs in peritoneal biology and pathobiology.

There is compelling evidence for the importance of intraperitoneal inflammation, particularly IL-6, in influencing the variability in PSTR[8, 12]. Recent evidence indicates that *KDM2B* is required for the induction of IL-6 in macrophages and dendritic cells, independent of its demethylase activity[54]. Whether this SNV influences intraperitoneal inflammation and PSTR is currently not known and requires further investigation. *KDM2B*

is also involved in angiogenesis, another potential mechanistic pathway that could influence PSTR[55].

In addition to these mechanistic insights, our study confirms our prior finding that demographic and clinical factors explain < 10% of the inter-individual variability in PSTR[9]. More importantly, our results indicate that genetic variation may explain 19% of the variability in PSTR. Furthermore, our findings show a genome-wide polygenic risk score that captured 4.2% of the variance in the phenotype, was associated with the 4-h D/P creatinine. Taken together, these data support the premise that genetic variation is an important determinant of inter-individual variability in PSTR and provides a a strong basis for further research.

Our study has several important strengths. This is the first GWAS for peritoneal function and the first report of an estimate of heritability of the trait. The study is an international collaborative effort that enrolled participants from 69 centers in six countries and hence, our findings have significant external validity. The external validity of our findings is further underscored by the observation that the distribution of 4-h D/P creatinine in our cohort is similar to what has been reported in previous large PD patient populations and was similar in participants from different parts of the world in the study. Even though the vast majority of participants were of European ancestry, a significant minority of the participants were racial/ethnic minorities and this further increase the validity of our findings.

Notwithstanding its strengths, our study has several weaknesses. The phenotype was measured in several individual laboratories around the world, with different tonicities of dialysate with varying intervals from the time of start of PD. This variability in ascertaining the phenotype may have led to some loss in precision of the phenotype. Furthermore, our study is focused on a transfer rate of a single solute and did not include associations with ultrafiltration capacity. The study was under-powered to identify SNVs with genome-wide significance and the SNVs with suggestive associations may be false positives. The cohort comprised people primarily of European descent and our findings may not extend to other populations. There was also no other cohort available for independent replication of our findings and this will need to be done in future studies.

In conclusion, this study provides several lines of evidence to support the premise that genetic variations underlie a significant component of the inter-individual variability in PSTR seen in people starting treatment with PD. Our analyses in participants of European ancestry and meta-analyses across ancestry strata identified several SNVs with suggestive associations with 4-h D/P creatinine. Experimental evidence suggests that several of these loci include genes that are linked to mechanistic processes, such as EMT, that leads to peritoneal fibrosis, or inflammation or angiogenesis that influences PSTR. Our findings suggest that genetic variation may explain 19% of the variability in the trait and provide evidence for significant association of a genome-wide polygenic risk score with the phenotype. These findings require replication, meta-analysis of findings from our study with those with other cohorts, and mechanistic work to link SNVs and biologic pathways identified herein to peritoneal pathobiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures

Rajnish Mehrotra has received honoraria from Baxter Healthcare.

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Gail Jarvik has nothing to disclose.

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Jonathan Himmelfarb is a founder and has equity interest in Kuleana Technology, Inc., a portable/wearable dialysis company.

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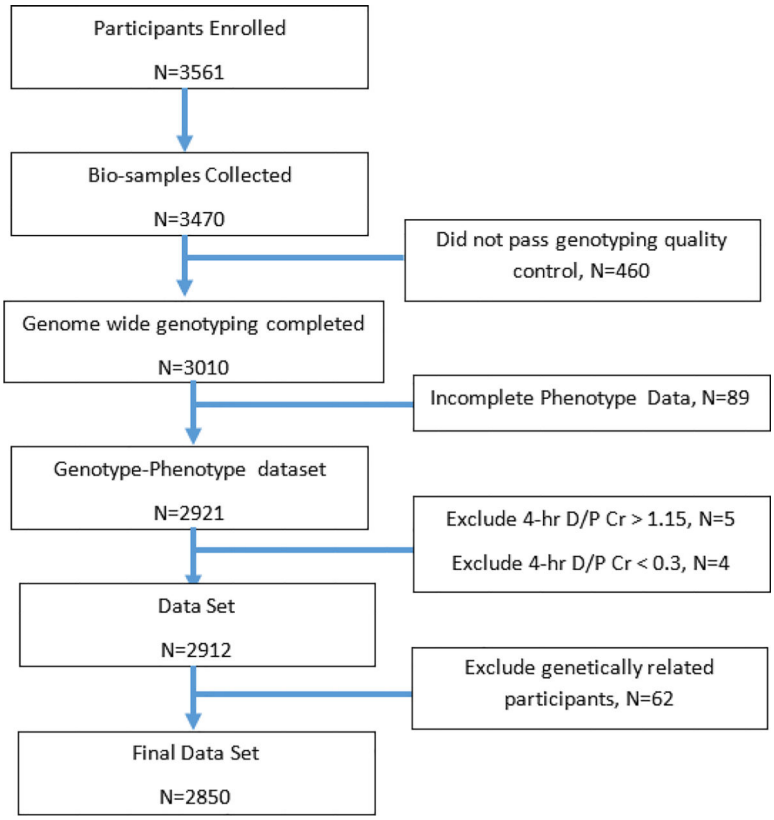

Figure 1: Flow diagram of building the study cohort.

Number of participants that were enrolled, that underwent genome wide genotyping, that were included in the final analytic cohort, and reasons for exclusion of participants at each step

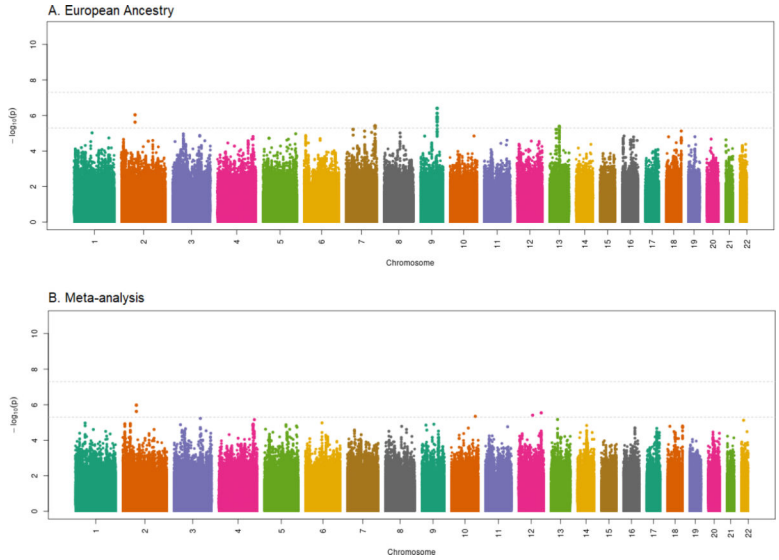

Figure 2: Results of genome wide association study (GWAS) as − log10 p plot (Manhattan plot).

Association of peritoneal solute transfer rate, as measured by 4-h D/P creatinine on peritoneal equilibration test, in: (A) 2212 individuals of European ancestry. The association of no single nucleotide variant reached genome-wide significance ($p < 5 \times 10^{-8}$). A total of 23 single nucleotide variants in four genomic regions demonstrated suggestive association ($p < 5 \times 10^{-6}$) with the phenotype of peritoneal solute transfer rate; (B) meta-analyses of GWAS in individuals of European, African, Asian, and admixed ancestry (n=2850). The association of no single nucleotide variant reached genome-wide significance ($p < 5 \times 10^{-8}$). A total of five single nucleotide variants at 4 loci demonstrated suggestive association ($p < 5 \times 10^{-6}$) with the phenotype of peritoneal solute transfer rate. All analyses are adjusted for age, sex, diabetes (yes/no), body mass index, dialysate tonicity used for the Peritoneal Equilibration Test, log transformed interval from start of PD to date of Peritoneal Equilibration Test in days, country of enrollment, and principal components (PC) 1–10 of ancestry, as covariates

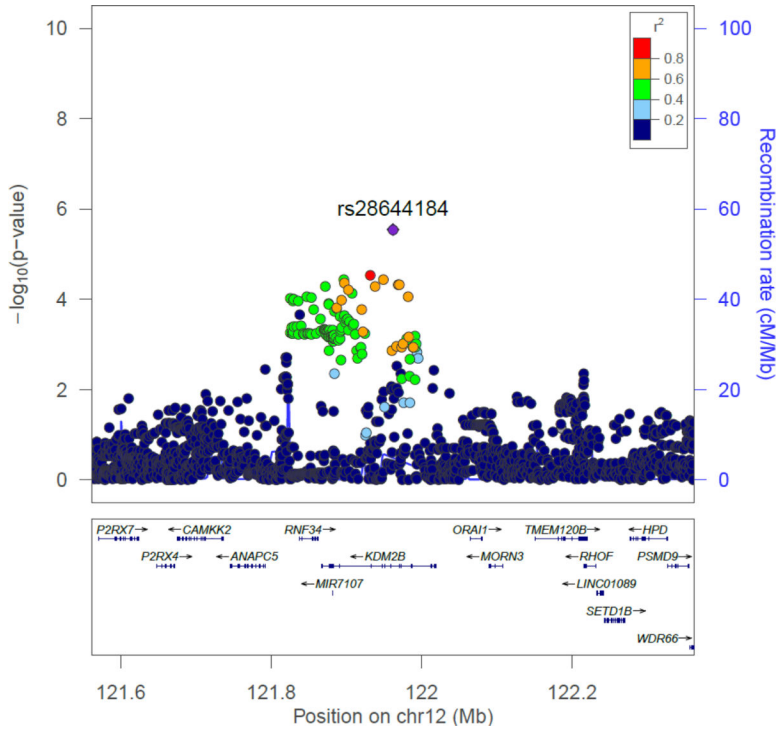

Figure 3A: Regional association plot of the *KDM2B* gene on chromosome 12 in which the intronic single nucleotide variant (rs28644184) with suggestive association is located.

Association of −log10 (p-values) with single nucleotide variants are plotted as points and the colors indicate the degree of linkage disequilibrium with the index variant.

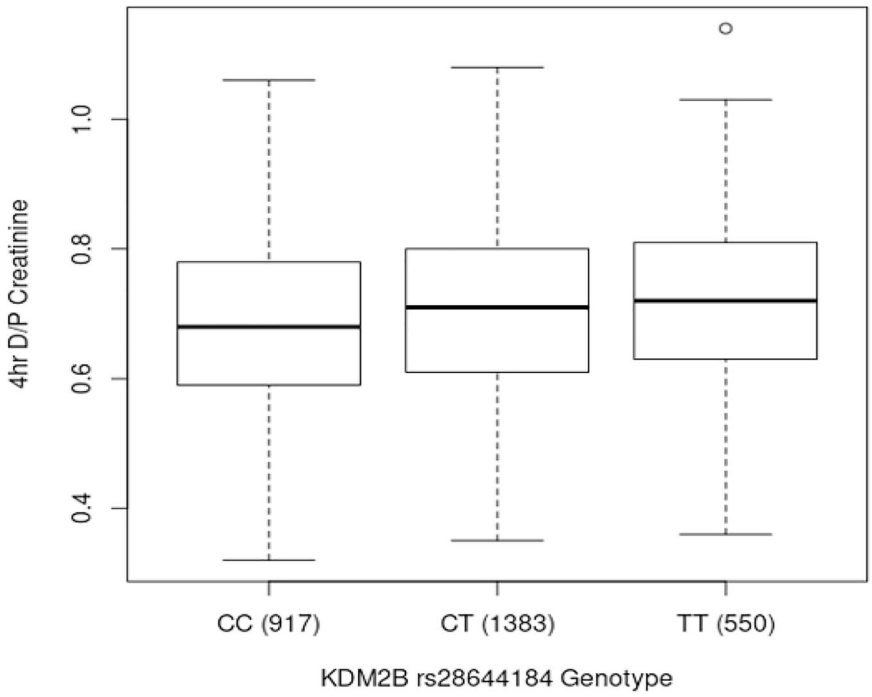

Figure 3B: Box plots for PSTR by *KDMB2* rs28644184 genotype.

The median (IQR) 4-h D/P creatine by genotype were: CC (n=917), 0.68 (0.59, 0.78); CT (n=1383), 0.71 (0.61, 0.80), and TT (n=550), 0.72 (0.63, 0.81).

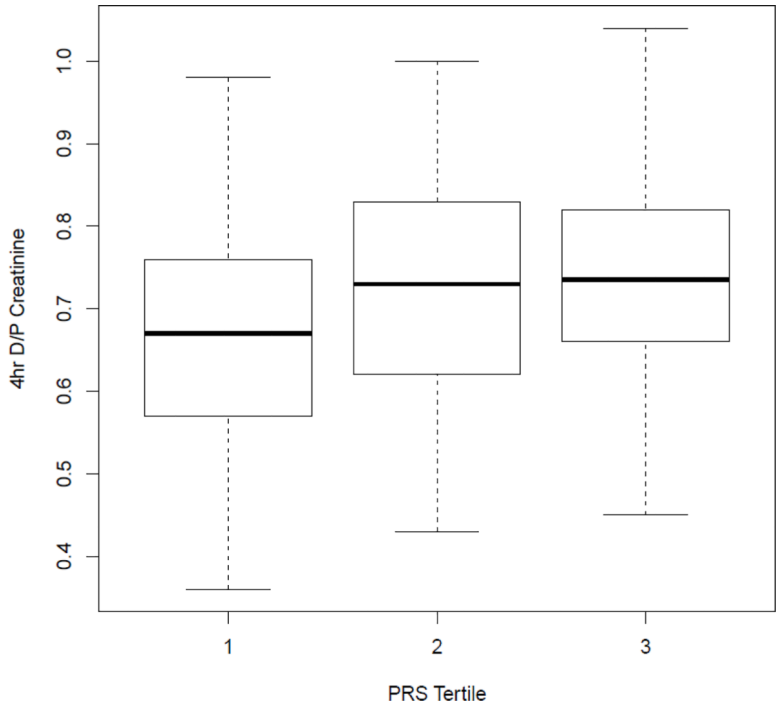

Figure 4: Association of polygenic risk with peritoneal solute transfer rate.

Association of tertiles of polygenic risk score with peritoneal solute transfer rate as measured by 4-h D/P creatinine on peritoneal equilibration test (n=299). The median (interquartile range) of 4-h D/P creatinine ratio: tertile 1, 0.67 (0.57–0.76); tertile 2, 0.73 (0.62–0.84), and tertile 3, 0.74 (0.66–0.82) (p=0.0002 for difference across tertiles).

Table 1.

Demographic and clinical characteristics of participants, by ancestry, included in the genome wide association study of peritoneal solute transfer rate.

	European (N=2212)	African (N=181)	Asian (N=109)	Admixed/Other (N=348)	Total (N=2850)
Sex Female, N (%)	803 (36)	102 (56)	44 (40)	135 (39)	1084 (38)
Age years, Mean ± SD*	59.8 ± 15.8	52.7 ± 15.5	54.6 ± 15.8	54.7 ± 14.7	58.5 ± 15.8
Self-Reported Race, N (%)					
White	2212 (100)	0 (0)	0 (0)	81 (23)	2293 (80)
Black	0 (0)	181 (100)	0 (0)	8 (2)	189 (7)
Asian	0 (0)	0 (0)	109 (100)	85 (25)	194 (7)
Native American/Pacific Islander	0 (0)	0 (0)	0 (0)	29 (8)	29 (1)
Not Reported	0 (0)	0 (0)	0 (0)	145 (42)	145 (5)
Country, N (%)					
Australia	34 (1)	0 (0)	10 (9)	19 (5)	63 (2)
Belgium	233 (11)	11 (6)	8 (7)	6 (2)	258 (9)
Canada	135 (6)	12 (7)	26 (24)	42 (12)	215 (8)
Sweden	174 (8)	0 (0)	0 (0)	16 (5)	190 (7)
UK	1357 (61)	36 (20)	27 (25)	155 (44)	2575 (55)
USA	279 (13)	122 (67)	38 (35)	110 (32)	549 (19)
Diabetes, N (%)*	636 (29)	70 (39)	44 (40)	156 (45)	906 (32)
Cause of Kidney Failure, N (%)					
Diabetes	462 (21)	37 (20)	34 (31)	126 (36)	659 (23)
Glomerular Disease	463 (21)	34 (19)	21 (19)	60 (17)	578 (20)
Hypertension	215 (10)	49 (27)	17 (16)	35 (10)	316 (11)
Cystic kidney disease	235 (11)	3 (2)	1 (1)	19 (6)	258 (9)
Other/Unknown	837 (37)	58 (32)	36 (33)	108 (31)	1039 (37)
BMI kg/m^2, Mean ± SD*	27.8 ± 5.8	28.6 ± 7.0	26.0 ± 6.1	27.8 ± 5.8	27.2 ± 6.0
Dialysate Dextrose for PET, N (%)					
2.5%	1709 (77)	161 (89)	79 (73)	300 (86)	2249 (79)
4.25%	358 (16)	16 (9)	22 (20)	28 (8)	424 (15)
1.5%	145 (7)	4 (2)	8 (7)	20 (6)	177 (6)
PD Start-PET Interval days, Median (IQR)	62 (37, 120)	67 (39, 110)	80 (52, 182)	64 (37, 112)	63 (28, 120)

	European (N=2212)	African (N=181)	Asian (N=109)	Admixed/Other (N=348)	Total (N=2850)
4 h D/P Creatinine, Mean ± SD*	0.71 ± 0.13	0.68 ± 0.14	0.71 ± 0.11	0.68 ± 0.13	0.70 ± 0.13

Table 2.

Regions of the genome showing the strongest association signals with peritoneal solute transfer rate as measured by 4-h D/P creatinine in participants of European ancestry (n=2212).

Genomic Region	Variant ID	Chromosome	Position	P value	Beta (95% CI)	R^2*	Minor Allele Frequency, %	Minor Allele	Major Allele
LINC01800 5' ~40 kb	rs76108553	2	65039700	9.2×10^{-7}	−0.05 (−0.07, −0.03)	1.0	3.2	T	C
LINC01800 5' ~1 kb	rs111976243		65072210	2.4×10^{-6}	−0.05 (−0.07, −0.03)	0.87	3.0	T	C
GIMAP6 5' ~12 kb**	rs73474862	7	150341555	3.8×10^{-6}	−0.02 (−0.03, −0.01)	1.0	18.4	C	T
	rs12154435		150343708	3.9×10^{-6}	−0.02 (−0.03, −0.01)	1.0	18.3	A	G
	rs12154436		150343784	3.9×10^{-6}	−0.02 (−0.03, −0.01)	1.0	18.3	A	G
	rs1316352		150346270	3.9×10^{-6}	−0.02 (−0.03, −0.01)	1.0	18.3	T	C
	rs62491829		150349768	4.4×10^{-6}	−0.02 (−0.03, −0.01)	1.0	18.2	C	A
	rs35329030		150350564	3.9×10^{-6}	−0.02 (−0.03, −0.01)	1.0	18.3	G	C
	rs34030180		150350735	3.9×10^{-6}	−0.02 (−0.03, −0.01)	1.0	18.3	A	G
LINC01505 intron	rs13288836	9	109233842	1.2×10^{-6}	0.02 (0.01, 0.03)	1.0	28.8	A	C
	rs7039680		109243327	1.2×10^{-6}	0.02 (0.01, 0.03)	1.0	43.0	C	A
	rs11789496		109243344	3.9×10^{-7}	0.02 (0.01, 0.03)	1.0	30.3	T	G
	rs11789956		109244009	1.5×10^{-6}	0.02 (0.01, 0.03)	1.0	29.0	T	C
	rs11792623		109244902	2.0×10^{-6}	0.02 (0.01, 0.03)	1.0	42.9	C	T
	rs10512347		109245178	1.5×10^{-6}	0.02 (0.01, 0.03)	1.0	29.0	T	C
	rs1387591		109246563	7.6×10^{-7}	0.02 (0.01, 0.03)	1.0	29.8	G	C
	rs11794795		109254458	2.3×10^{-6}	0.02 (0.01, 0.03)	1.0	43.2	C	T
	rs4742997		109255208	3.6×10^{-6}	0.02 (0.01, 0.03)	0.99	27.2	T	C
PCDH9 5'~450kb	rs11840701	13	68253904	4.7×10^{-6}	0.02 (0.01, 0.03)	1.0	19.8	G	C
	rs11843673		68262519	4.4×10^{-6}	0.02 (0.01, 0.03)	1.0	19.8	C	T
	rs7325638		68263150	4.4×10^{-6}	0.02 (0.01, 0.03)	0.99	19.8	G	A
	rs7337043		68269911	4.0×10^{-6}	0.02 (0.01, 0.03)	0.99	19.8	C	G
	rs57521059		68278456	4.6×10^{-6}	0.02 (0.01, 0.03)	0.99	19.8	C	T

All analyses are adjusted for age, sex, diabetes (yes/no), body mass index, log transformed PD start-PET interval, dialysate tonicity for PET, country of enrollment, and principal components (PC) 1–10 of ancestry, as covariates

*R^2=imputation quality

**Regions/variants associated with evidence of eQTL RNAs in GTEx data

Table 3.

Meta-analysis of stratified European (n=2212), African (n=181), Asian (n=109) and Admixed-Other (n=348) ancestry groups.

Genomic Region	Variant ID	Chromosome	Position	P value	Beta (95% CI)	R^{2*}	Minor Allele Frequency, %	Minor/Major Allele	Direction***	n
LINC01800 5' ~40 kb	rs76108553	2	65039700	1.1×10^{-6}	−0.05 (−0.07, −0.03)	1.0	3.2	T/C	???−	2212
LINC01800 5' ~1 kb	rs111976243		65072210	2.4×10^{-6}	−0.05 (−0.07, −0.03)	0.87	3.0	T/C	???−	2212
LINC01561, PLPP4 3' ~5kb**	rs2901257	10	122358463	4.5×10^{-6}	0.02 (0.01, 0.02)	1.0	52.6	A/G	++−+	2850
KCNC2 5' '20 kb	rs117559199	12	75424551	3.9×10^{-6}	−0.04 (−0.06, −0.03)	0.87	3.8	A/C	?−?−	2560
KDM2B intron**	rs28644184	12	121961947	2.9×10^{-6}	0.02 (0.01, 0.02)	1.0	43.6	T/C	++++	2850

All analyses are adjusted for age, sex, diabetes (yes/no), body mass index, log transformed PD start-PET interval, dialysate tonicity for PET, country of enrollment, and principal components (PC) 1–10 of ancestry, as covariates

*R^2=imputation quality

**Regions/variants associated with evidence of eQTL RNAs in GTEx data

***1st position Asian, 2nd position Admixed/Other, 3rd position African, 4th European Ancestry,? indicates not included, +/− Effect Direction