Genetic Variation and Ultrafiltration with Peritoneal Dialysis

A Genome-Wide Association Study

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Key Points

- There is a large person-to-person variability in ultrafiltration with peritoneal dialysis at the time of starting treatment.
- In this international cohort study, heritability of peritoneal ultrafiltration with peritoneal dialysis was estimated at 50%.
- In genome-wide association study, two single-nucleotide variants reached genome-wide significance—rs72631501 in CRK intron with European ancestry and rs1416265, intergenic, with South Asian ancestry.

Abstract

Background There is a large person-to-person variability in ultrafiltration volume with peritoneal dialysis (PD), most of which cannot be accounted for by demographic and clinical differences. In this article, we tested the hypothesis that common genetic variants are associated with peritoneal ultrafiltration and explored one mechanistic pathway identified by genetic studies.

Methods We generated estimates of heritability and undertook genome-wide and gene-wise association studies, adjusted for peritoneal solute transfer rate, to test associations of genetic variation with ultrafiltration on peritoneal equilibration test conducted at PD initiation in 2723 participants in the international Biological Determinants of PD (Bio-PD) study. We used a mouse model of PD to study the mechanistic basis for the association of *PTGES* gene with peritoneal ultrafiltration.

Results The peritoneal equilibration test was conducted at a median of 61 (interquartile range, 38–118) days from PD start with a median 4-hour ultrafiltration volume of 250 (interquartile range, 25–465) ml. The heritability of peritoneal ultrafiltration was estimated to be 50% ($P = 0.001$). In single-nucleotide variant–wise multiancestry genome-wide association study using TRACTOR software, one single-nucleotide variant reached genome-wide significance in participants with European local ancestry (rs72631501, *CRK* intron, $P = 2.6\times10^{-8}$) and one in participants with South Asian local ancestry (rs1416265, intergenic, $P = 4.2\times10^{-8}$). Gene-wise analyses showed significant association of 21 genes at false discovery rates (FDRs) <0.10 in the European strata, notably *PTGES* (FDR=0.053), *SLC24A3* (FDR=0.0003), and *CRK* (FDR=0.04). *SLC24A3* remained significant (FDR=0.03) in meta-analysis of the four ancestry strata. Using single-cell RNA sequencing, *PTGES* localized in peritoneal adipocytes. In a mouse PD model, pharmacologic modulation of prostaglandin E synthase altered dialysate PGE2 levels with changes in adipocyte volume, peritoneal small solute transfer rate, and ultrafiltration volume.

Conclusions Common genetic variants accounted for a substantial proportion of the variability in peritoneal ultrafiltration with potential associations with 21 genes, including *CRK*, *PTGES*, and *SLC24A3*. Functional studies substantiated a potential role for prostaglandin E synthase/prostaglandin E2 in regulating peritoneal ultrafiltration.

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See related editorial, "Genetic Architecture of Peritoneal Ultrafiltration: Lessons from the Bio-PD Study," on pages 4–5.

Introduction

Peritoneal dialysis (PD), a home dialysis modality, is used by 11% of patients undergoing long-term dialysis worldwide.[1] During PD, dextrose-based dialysate drives solute and water across the peritoneum. Convergent physiologic studies in humans and animals have provided an understanding of the pathways involved in movement of solutes and water across the peritoneum.[2–8] Solute and water removal are central to effectively managing uremia with PD, but the peritoneal solute transfer rate (PSTR) and ultrafiltration rate are highly variable from one person to another.[9–17] Demographic and clinical variables explain only a small part of this variability, leading to the long-proposed hypothesis that some of this variation is genetic. Yet, no meaningful progress had been made until recently, given the challenges in enrolling patients for genetic association studies for PD phenotypes: Worldwide, fewer than 450,000 patients are treated with PD spread across 6000 dialysis centers. The Biological Determinants of PD (Bio-PD) study is the first large cohort of patients treated with PD with genetic data that enrolled participants from 70 centers worldwide, finally allowing for genetic association studies for PD phenotypes. Even without any additional cohorts worldwide to validate these findings, these first genetic association studies mark a major advance.

Our first analyses from the Bio-PD study demonstrated that about 20% of the variation in PSTR is genetically determined.[17] Only one previous study examined the relationship of genetic variation with the other phenotype important for PD, ultrafiltration, using a candidate gene approach (*AQP1*).[8] Despite a known reciprocal relationship between PSTR and peritoneal ultrafiltration, PSTR explains only a small part of the variability in ultrafiltration.[9,15,18,19] Considering the different mechanisms involved in these two processes, the contributions of genetic variation to PSTR and ultrafiltration are likely largely distinct.

As such, we undertook this study to test the hypothesis that common genetic variation is associated with variability in ultrafiltration at the time of starting PD, separately from the effects from variation in PSTR. We tested the biologic plausibility of one of the genes, *PTGES*, with functional studies in a mouse model of PD.

Methods

Study Population

The Bio-PD study enrolled 3817 participants undergoing PD at 70 centers across Australia, Belgium, Canada, Hong Kong, Sweden, the United Kingdom, and the United States.[17] In brief, participants were enrolled (*1*) prospectively from 54 centers (NCT02694068, $n=1677$; Australia, Canada, the United Kingdom, and the United States), and (2) DNA was procured for participants enrolled in other studies from 36 centers ($n=2140$; Belgium, Hong Kong, Sweden, and the United Kingdom). This present analysis comprised 2723 (71%) participants in Bio-PD (Supplemental Figure 1). The study was approved by the Institutional Review Board (IRB) of the University of Washington, with additional ethics approvals from participating institutions. All participants enrolled prospectively provided written informed consent, and the consent forms from previous studies were reviewed by the University of Washington IRB to ensure data could be used for this analysis.

Phenotype and Other Covariates

The phenotype was peritoneal ultrafiltration, defined as net ultrafiltration volume at 4 hours with a 2 L dwell during the first peritoneal equilibration test (PET) conducted after initiation of PD.[9] The continuous outcome of ultrafiltration was calculated as the drain volume at 4-hour drain minus the instilled volume for PET in milliliters (net ultrafiltration=drain volume−instilled volume). The phenotype data were obtained from the first PET when starting PD using unit-specific protocols. Additional data collected included self-reported race, country/territory, age, sex, diabetes mellitus, body mass index, cause of kidney failure, tonicity of dialysate for PET (1.5%, 2.5%, or 4.25% dextrose), days from the start of PD to PET, and PSTR (4-hour dialysate-to-plasma [D/P], creatinine ratio).

Genotyping, Imputation, and Quantitative Trait Locus

Genotyping for single-nucleotide variants (SNVs) was conducted with the Illumina InfiniumOmni2-5 array in three batches, with genotypic imputation using the Michigan Imputation Server (HRC1.1).[17,20–22] Imputed variants with an imputation quality $r^2>0.8$ and minor allele frequency (MAF) >0.02 were included. SNVs within one megabase of a gene's transcription site were queried in the genotype tissue expression (GTEx) dataset for quantitative trait locus (QTL) RNA transcriptomic associations for expression and splice variants in all tissues where data were available.[23]

Functional Assessment of Prostaglandin E Synthase in a Mouse Model

Studies were undertaken to elucidate the link between *PTGES*, a gene that consistently met the false discovery threshold in gene-wise genome-wide association study (GWAS). Detailed methods for animal treatments and analytic and experimental procedures are provided in Supplemental Methods. All experiments were conducted using male C57BL/6J mice (Charles Rivers, Brussels, Belgium) aged 8–12 weeks. Animals were housed in an air-conditioned room with a 12/12-hour dark-light cycle and acclimatized to the new environment for 1 week before experiments. Mice were allowed free access to standard laboratory diet (Scientific Animal Food & Engineering, Augy, France) and tap water. The effect of modulating prostaglandin E synthase (PTGES) on prostaglandin E2 (PGE2) levels and peritoneal parameters was evaluated with a PET with 2.5 ml of 4.25% dextrose.[24,25]

We investigated the effect of modulating PTGES expression on PGE2 levels and peritoneal function using an inhibitor (Cay10526; Cayman Chemical, Ann Arbor, MI; 5 mg/kg intraperitoneally [i.p.]) or activator (all-trans retinoic acid [AtRA]; Sigma-Aldrich, St. Louis, MO; 10 mg/kg i.p) of PTGES, administered 3 hours before PET.[26–28] We investigated the effects of acute exposure to lipopolysaccharide (LPS) (*Escherichia coli* serotype O111: B4, Sigma-Aldrich; 10 mg/kg i.p., 6 hours before PET), alone or with Cay10526, as it is an inducer of PTGES and a regulator of peritoneal function.[29–33] We studied direct effects of PGE2 (Santa Cruz Biotechnology, Dallas, TX; 0.1–10 nM in

dialysate during PET) on peritoneal function. The role of the PGE2 receptors was addressed using specific inhibitors for E-prostanoid receptor 2 (EP2) (TG11-77; Axon Medchem BV, Groningen, The Netherlands; 10 mg/kg i.p.) or E-prostanoid receptor 3 (EP3) (L798.106; Santa Cruz Biotechnology; 5 mg/kg i.p.), injected 1 hour before PET.[34,35]

Statistical Analyses

Of the 3817 participants, genotyping that passed quality control was completed for 3611 individuals. Participants who did not have data on ultrafiltration (n=604), or were genetically related (n=54), or had PET fill-volume that was not 2 L (n=230) were excluded, yielding the analytic cohort of 2723 participants (Supplemental Figure 1). Missing covariate data were accounted for with five multiple imputations.[36] Extreme values of time on PD were winsorized and log-transformed and centered and scaled, as described previously.[17,37]

Linkage disequilibrium (LD) pruning of autosomal chromosomes was performed with plink v1.90b6.21 using the parameters (–maf 0.02 –geno 0.1 –mind 0.1 –indep-pairwise 1000 50 0.7)[38]; the hg19 regions (chr5: 44000000–51500000, chr6: 25000000–33500000, chr8: 8000000–12000000, and chr11: 45000000–57000000) were excluded. Principal component (PC; plink–PC analysis) Identity-By-Descent (IBD; plink –genome) analyses were performed on these LD-pruned genotypes. Participants were excluded if they were duplicates/twins, and one participant was retained from related individuals (IBD0 <0.83 and IBD1 >0.1; n=54). Hardy–Weinberg Equilibrium statistics were calculated among participants who self-reported as White and of European ancestry by k-means clustering of the first two PCs. SNVs with large deviations from Hardy–Weinberg Equilibrium ($P < 10^{-6}$) were removed.

As a first step, a linear regression analysis model including demographic and clinical variables, including 4-hour D/P creatinine as a measure of PSTR, was built. For genetic analyses, data from countries with small number of participants were pooled with their nearest geographic neighbors (Belgium with Sweden and Canada with the United States) or the largest regional cohort for efficiency (Australia with the United Kingdom).

Heritability of ultrafiltration was estimated with genome-wide complex trait analysis (version 1.93.2 beta) genomic-restricted maximum likelihood analysis method with 200 kb LD score regions stratified into four high to low LD genetic relationship matrices after excluding the HLA/MHC region (chr6: 25000000–33500000).[39] A SNV-wise multiancestry GWAS was performed with the TRACTOR software (v1.1.0) with local ancestry[40] assessed using the 1000 Genomes European, African, East Asian, and South Asian participants and RFmix.[41] This analysis included 5,891,995 SNVs adjusted for age, sex, body mass index, country/territory, diabetes, dialysate dextrose concentration, log of days from PD start to PET, 4-hour D/P creatinine, and genetic ancestry (PC1–10). Exploratory analyses were performed without 4-hour D/P creatinine as a covariate. We interpreted the European ancestry tract from TRACTOR as the primary analysis. We meta-analyzed the four ancestry tracts using METAL.[42] A P value of 5×10^{-8} was considered to indicate genome-wide significance. Analyses were performed five times with the multiple imputation for missing data, the summary statistics combined using the mean of the individual estimates (Rubin rules), and P values summarized using the median P value rule.[43,44] LD-independent SNVs at loci were tested for independence by conditioning on the residuals of the other independent SNVs. We also estimated heritability and observed the LD intercept using LD score regression of the summary statistics from the European track of the TRACTOR analysis.[45,46] Gene-wise GWAS with the Generalized Berk–Jones test was performed using the data for genes with more than two variants within and 5 kb flanking each of the 18,208 genes within the European TRACTOR track summary statistics and 18,273 genes using the summary statistics meta-analyzed across ancestry strata.[47,48] The Generalized Berk–Jones test took the marginal statistics from a set of tests and tested if the group of marginal scores was associated with the outcome. A gene-wise false discovery rate of <0.10 was set for multiple testing.

The results from all functional data in a mouse model of PD are expressed as mean±SD. This study was exploratory in nature, with the primary aim of evaluating the effect of PGE2 on net ultrafiltration. A sample size of n=6 per group was chosen based on ethical considerations, consistent with similar preclinical studies. Differences between groups were assessed by unpaired t test, one-way ANOVA, followed by Tukey multiple comparisons test (to assess the effect of increasing concentrations of PGE2-supplemented dialysate), two-way ANOVA (to assess inhibitors effect in control and PGE2-supplemented dialysate), using GraphPad Software (San Diego, CA). A P value < 0.05 was considered statistically significant.

Results

Study Participants

Of the 3817 participants, 2723 (71%) were included (Supplemental Figure 1). There were no meaningful differences in characteristics of participants included or excluded from analyses (Supplemental Table 1). The largest number of participants (49%) were from the United Kingdom, and 72% identified as White (Table 1). The self-reported race clustered with expected genetic ancestry (Supplemental Figure 2). The k-means clustering of PC1 and PC2 identified 2116 individuals with European ancestry.

The PET was conducted at a median of 61 (interquartile range, 38–118) days from start of PD and with 2.5% dextrose in 2197 (81%) participants. The mean (±SD) 4-hour D/P creatinine ratio was 0.70±0.13 (Table 1). The 4-hour ultrafiltration varied by tonicity of dextrose with a median of 250 (interquartile range, 25–465 ml) ml (Table 1).

In participants where PET was conducted with 2.5% dextrose (n=2197), the multivariable model with demographic and clinical covariates and estimates of ancestry explained 6% of the variance in ultrafiltration (Supplemental Table 2); in the entire cohort (n=2723), including tonicity of dextrose as a covariate, the model explained 21% of the variance (Supplemental Table 3); further, including 4-hour D/P creatinine, the clinical model explained 36% of the variance in ultrafiltration (Supplemental Table 3).

Table 1. Demographic and clinical characteristics of participants in the Bio-PD study included in the analyses of association of genetic variation with peritoneal

Characteristic	Total (*N*=2723)
Age, yr, mean±SD	59±16
N-missing	8
Men, *n* (%)	1731 (64)
Self-reported race, *n* (%)	
American Indian	5 (0.2)
Asian	458 (17)
Black	163 (6)
Not reported	104 (4)
Pacific Islander	19 (0.7)
White	1974 (72)
Country/territory of enrollment, *n* (%)	
Australia	46 (2)
Belgium	258 (10)
Canada	172 (6)
Hong Kong	310 (11)
Sweden	169 (6)
United Kingdom	1337 (49)
United States	431 (16)
Diabetes, *n* (%)	938 (38)
N-missing	272
Body mass index, kg/m^2, mean±SD	27±6
N-missing	92
Cause of kidney failure, *n* (%)	
Cystic	236 (9)
Diabetes	706 (26)
GN	561 (21)
Hypertension	288 (11)
Other	891 (33)
N-missing	41
Dialysate dextrose for PET, *n* (%)	
1.5%	161 (6)
2.5%	2197 (81)
4.25%	365 (13)
Interval from PD start to PD, d, median (IQR)	61 (38–118)
N-missing	4
4 h D/P creatinine, mean±SD	0.70±0.13
4-h net UF, ml, median (IQR)	250 (25–465)
1.5% dextrose	0 (−125 to 200)
2.5% dextrose	220 (0–400)
4.25% dextrose	590 (365–800)

Bio-PD, Biological Determinants of PD; D/P, dialysate-to-plasma; IQR, interquartile range; PD, peritoneal dialysis; PET, peritoneal equilibration test; UF, ultrafiltration.

Heritability

The covariate-adjusted genomic-restricted maximum likelihood analysis heritability of ultrafiltration was 50% (SEM 15%, $P = 0.001$). When analyses were restricted to 2116 participants of European ancestry, the heritability was 25% (SEM 18%, $P = 0.39$). The heritability estimates after excluding HLA were similar. Using the alternative method of LD score regression from the European track of the TRACTOR summary statistics, the heritability was estimated to be 36% (SEM 0.27, $P = 0.09$).

GWASs

In analyses within European ancestry, 5,560,973 variants (MAF >0.02) passed quality parameters with lambda for genomic inflation of 1.11 with a LD score regression intercept of 1.10. The quantile-quantile (QQ) *P* value plots are presented in Supplemental Figure 3. One SNV (rs72631501, chr17: 1344282, MAF 0.09, $P = 2.6\times10^{-8}$) in an intron of the *CRK* gene reached genome-wide significance ($P < 5\times10^{-8}$; Figure 1A and Table 2).

In analyses within South Asian ancestry, the lambda for genomic inflation was 1.05 (Supplemental Figure 4). One SNV reached genome-wide significance for association with ultrafiltration (rs1416265, chr10: 72754371, intergenic between *PCBD1* and *UNC5B*, MAF=0.05, $P = 4.2\times10^{-8}$; Figure 1B and Table 2) and the ultrafiltration varied by genotype (Supplemental Figure 5).

No SNV reached genome-wide significance in analyses within other ancestry groups (Supplemental Figure 6, A–D) or in meta-analyses across four ancestry groups (Supplemental Figure 6, E and F) or in analyses without 4-hour D/P creatinine as a covariate (Supplemental Figures 3, B and C, 4, B and C, and 6, G–L). The previously reported association between *AQP1* promoter SNV rs2075574 and ultrafiltration was not statistically significant in any ancestry-specific analyses ($P = 0.83$) or in the meta-analysis or in analyses limited to participants with PET conducted with 4.25% dextrose.[8]

A sensitivity analysis that included genotype imputation batch as a covariate in the GWAS yielded the same results as above.

Gene-Wise GWASs

In gene-wise analyses within European ancestry, 21 genes were associated with ultrafiltration (Figure 1C and Table 3); the data for analyses without 4-hour D/P creatinine as a covariate are summarized in Supplemental Table 4. On meta-analysis of all four ancestry tracts, one gene—*SLC24A3*—was significantly associated with ultrafiltration (Supplemental Figure 7, false discovery rate=0.03). There was no significant association between *AQP1* gene and peritoneal ultrafiltration in any gene-wise analyses. The association summary statistics of all gene-wise analyses are summarized in Supplemental Spreadsheet 1.

The European ancestry regional association plots of *CRK* and *MYO1C* genes showed one primary signal (rs72631501) among the SNVs in LD (Supplemental Figure 8). The European regional association plot of *PTGES* gene showed two independent signals among the SNVs in LD (Figure 2): The SNV with the strongest association was rs10118377 (chr9: 132523860, $P = 1.3\times10^{-6}$, MAF=0.26) and is reported as an expression QTL in GTEx in ten tissues, with the strongest association in esophageal mucosa (normalized effect size, −0.31, $P = 2.7\times10^{-26}$). The second SNV, rs12004095 (chr9: 132503432, $P = 1.4\times10^{-5}$, MAF=0.07), is not reported as a QTL in GTEx. Regression analysis of the residuals conditioning on the effect of the respective *PTGES* SNVs showed both variants maintained nominal significance (rs10118377, $P = 0.00002$, adjusted R^2, 0.009; rs12004095, $P = 0.0007$, adjusted R^2, 0.007). Ultrafiltration also varied by *PTGES* genotype for both SNVs (Figure 2).

The *SLC24A3* locus had two independent signals in participants of European ancestry (rs728481, chr20: 19341331, $P = 1.34\times10^{-6}$, MAF=0.43; rs6046109, chr20: 19442549, $P = 3.08\times10^{-6}$, MAF=0.42; Supplemental Figure 9). Meta-analyses of four ancestries yielded similar results (Supplemental Spreadsheet 1). Both signals remained significant when conditioning on the other variant

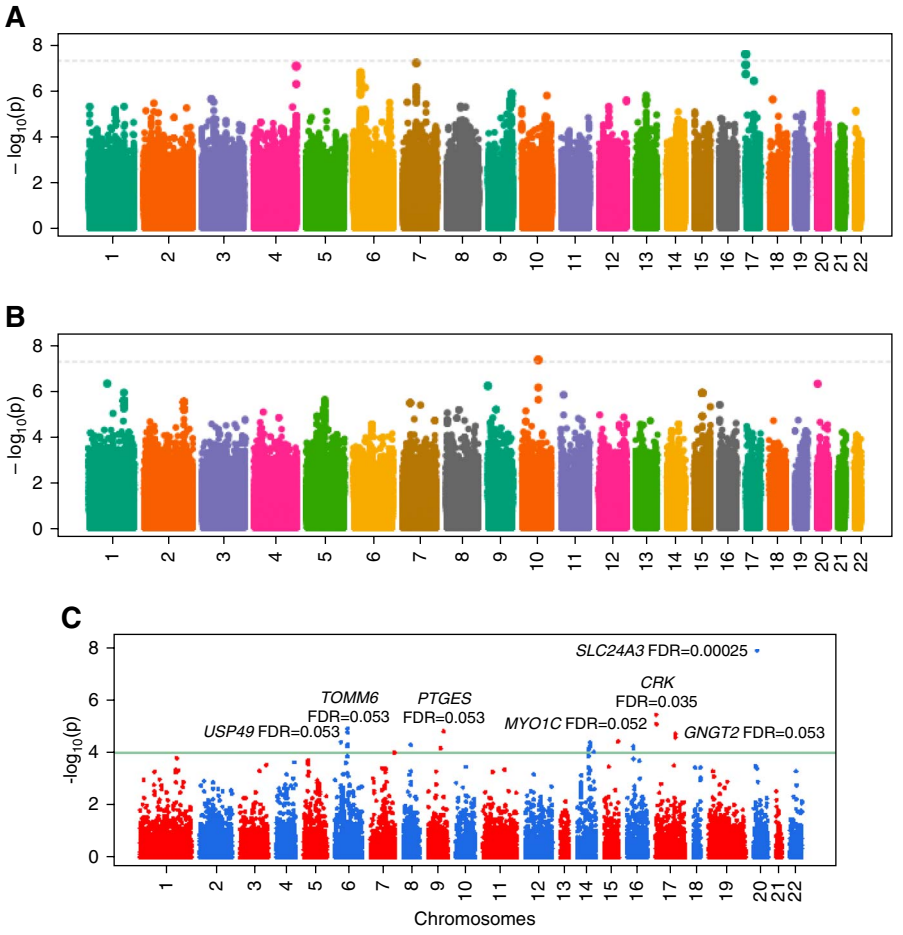

Figure 1. GWAS for the association of common genetic variants with peritoneal ultrafiltration. (A) Results of the GWAS among participants with European local ancestry, as −log10 *P* plot (Manhattan plot). The association of peritoneal ultrafiltration in approximately 2000 individuals with European local ancestry enrolled in the Bio-PD study. The association of one SNV reached genome-wide significance (rs72631501 [*CRK* intron], $P = 2.6\times10^{-8}$). Analyses were adjusted for age, sex, diabetes (yes/no), body mass index, dialysate tonicity used for the PET, log-transformed interval from the start of PD to the date of PET in days, country of enrollment, 4-hour D/P creatinine, and PCs 1–10 of ancestry as covariates. (B) Results of the GWAS among participants with South Asian local ancestry, as −log10 *P* plot (Manhattan plot). The association of peritoneal ultrafiltration in individuals with South Asian local ancestry enrolled in the Bio-PD study. The association of one SNV reached genome-wide significance (rs1416265, intergenic between *PCBD1* and *UNC5B*, $P = 4.2\times10^{-8}$). Analyses were adjusted for age, sex, diabetes (yes/no), body mass index, dialysate tonicity used for the PET, log-transformed interval from the start of PD to the date of PET in days, country of enrollment, 4-hour D/P creatinine, and PCs 1–10 of ancestry as covariates. (C) Results of the primary gene-wise Generalized Berk–Jones test as −log10 *P* plot (Manhattan plot) from the European track TRACTOR summary statistics. The association of peritoneal ultrafiltration in approximately 2000 European individuals enrolled in the Bio-PD study. Twenty-one genes were significant at a FDR of <0.1. Analyses were adjusted for age, sex, diabetes (yes/no), body mass index, dialysate tonicity used for the PET, log-transformed interval from the start of PD to the date of PET in days, country of enrollment, 4-hour D/P creatinine, and PCs 1–10 of ancestry as covariates. Bio-PD, Biological Determinants of PD; D/P, dialysate-to-plasma; FDR, false discovery rate; GWAS, genome-wide association study; PC, principal component; PD, peritoneal dialysis; PET, peritoneal equilibration test; PTGES, prostaglandin E synthase; SNV, single-nucleotide variant.

(rs728481, chr20: 19341331, $P = 0.0002$, $R^2=0.005$; rs6046109, chr20: 19442549, $P = 0.02$, adjusted $R^2=0.002$). The SNV rs728481 is a splice QTL in four tissues, most significant in the esophageal mucosa ($P = 2\times10^{-14}$, normalized effect size=0.44). Table 4 summarizes the genes associated at each locus and the most significant variant identified in the region.

Functional Evaluation of PTGES

We selected *PTGES* for further evaluation because of its association with ultrafiltration in gene-wise analyses, ease of pharmacologic accessibility, and relevant prostaglandin pathways in epithelial and vascular tissues. Using public single-cell and single-nucleus RNA sequencing in human and mouse omentum (white adipose tissue), *PTGES* mRNA was mostly expressed in the adipose cell progenitors and adipocytes, whereas *AQP1* mRNA was strongly expressed in endothelial cells (Supplemental Figure 10). In the human and mouse peritoneum, PTGES colocalized with the adipocyte marker perilipin-1 (PLIN), whereas no colocalization between aquaporin 1 (AQP1) and PTGES was observed (Figure 3 and Supplemental Figure 11).

In a mouse model of PD, treatment with Cay10526, an inhibitor of PTGES, led to a lower tissue expression of

Table 2. Single-nucleotide variants associated with 4-hour peritoneal ultrafiltration from the peritoneal equilibration test at genome-wide level of significance in the genome-wide association study in the Bio-PD study using single-nucleotide variant–wise TRACTOR local ancestry analysis

Ancestry	SNV ID	Chromosome	Position	Local Ancestry, *N*	Effect Allele	Reference Allele	MAF	Effect Estimate	Standard Error	*P* Value
European	rs72631501	17	1344282	2000	A	G	0.09	83.5	14.9	2.56×10^{-8}
South Asian	rs1416265	10	72754371	111	A	G	0.05	453.8	75.8	4.15×10^{-8}

Bio-PD, Biological Determinants of PD; MAF, minor allele frequency; SNV, single-nucleotide variant.

PTGES in the visceral peritoneum and lower dialysate PGE2 levels. Conversely, treatment with AtRA, an activator of PTGES, resulted in higher tissue expression of PTGES in the visceral peritoneum and higher dialysate PGE2 levels (Figure 4, A–D). Changes in dialysate PGE2 levels were reflected by changes in ultrafiltration: lower PGE2 levels with Cay10526 were associated with higher ultrafiltration, while higher PGE2 levels with AtRA were associated with lower ultrafiltration (Figure 4E and Supplemental Table 5). These changes were paralleled by changes in PSTR, measured by D/P urea (Figure 4F).

Since the PTGES/PGE2 pathway is induced by inflammation, we investigated the structural and functional consequences of acute peritonitis induced by LPS in mice.[32] Exposure to LPS led to significant upregulation of PTGES and AQP1 in the peritoneum, higher dialysate PGE2, and lower ultrafiltration along with increase in PSTR; these effects were blocked by Cay10526 (Figure 4, G–K, and Supplemental Table 6). PETs with progressively higher dialysate concentrations of PGE2 demonstrated a strong inverse relationship between PGE2 concentration and ultrafiltration and a progressively higher PSTR (Figure 5 and Supplemental Table 7). Exposure to PGE2 also led to a dose-dependent increase in adipocyte size (Figure 5C), peritoneal infiltration with macrophages (F4/80-positive) and neutrophils (lymphocyte antigen 6, family member B, (Ly-6B)-positive; Supplemental Figure 12), and higher dialysate IL-6 levels (Figure 5D).

PGE2 exerts its effects through PG G-coupled E-prostanoid (EP) receptors, which activate different downstream signaling pathways (Figure 5E). Analysis of the available single-cell and single-nucleus RNA sequencing data indicated that two receptors, EP2 (macrophages and neutrophils) and EP3 (adipocytes and mesothelial cells), are expressed in the peritoneum (Supplemental Figure 13). To clarify the mechanism of action of PGE2 during PD, we used selective antagonists of EP2 and EP3, TG11.77, and L798.106, respectively (Figure 5E and Supplemental Table 8). Under baseline conditions, EP2 or EP3 inhibition led to higher ultrafiltration without changes in PSTR (Figure 5, F and G). Furthermore, EP2 inhibition (TG11.77) decreased dialysate IL-6 levels

Table 3. Results of the primary gene-wise genome-wide association study analysis with the Generalized Berk–Jones test, with genes associated with 4-hour peritoneal ultrafiltration from the peritoneal equilibration test with adjustment for 4-hour dialysate-to-plasma creatinine

Gene	Gene ID	Chromosome	Start	Stop	Estimate[a]	*P* Value	FDR
SLC24A3	57419	20	19193290	19703541	16.3	1.4×10^{-8}	0.0003
CRK	1398	17	1325440	1359544	11.6	3.8×10^{-6}	0.04
MYO1C	4641	17	1367480	1396001	11.0	8.6×10^{-6}	0.05
TOMM6	100188893	6	41755181	41757634	11.2	1.3×10^{-5}	0.05
PTGES	9536	9	132500615	132515344	10.2	1.7×10^{-5}	0.05
USP49	25862	6	41765383	41863099	10.5	1.8×10^{-5}	0.05
GNGT2	2793	17	47283596	47287936	10.2	2.1×10^{-5}	0.06
ABI3	51225	17	47287589	47300587	9.9	2.8×10^{-5}	0.06
MCTP2	55784	15	94841430	95027181	9.3	4.0×10^{-5}	0.07
HLA-A	3105	6	29910247	29913661	9.7	4.2×10^{-5}	0.07
ENTPD5	957	14	74433172	74486026	9.6	4.4×10^{-5}	0.07
BYSL	705	6	41888965	41900784	9.8	5.2×10^{-5}	0.07
CRH	1392	8	67088612	67090846	9.1	5.4×10^{-5}	0.07
C14ORF45	80127	14	74486059	74532795	9.1	5.9×10^{-5}	0.07
RPS15A	6210	16	18794277	18801656	9.2	6.0×10^{-5}	0.07
PRICKLE4	29964	6	41748500	41755110	9.6	6.1×10^{-5}	0.07
TTLL11	158135	9	124584204	124855885	9.0	7.2×10^{-5}	0.07
ARL6IP1	23204	16	18802991	18812857	9.3	7.3×10^{-5}	0.07
GPHN	10243	14	66974125	67648525	8.6	7.9×10^{-5}	0.08
PAPOLA	10914	14	96968720	97033448	8.5	9.9×10^{-5}	0.09
PRKAG2	51422	7	151253200	151574316	8.6	1.1×10^{-4}	0.09

FDR, false discovery rate.
[a]Obtained from the Generalized Berk–Jones test.

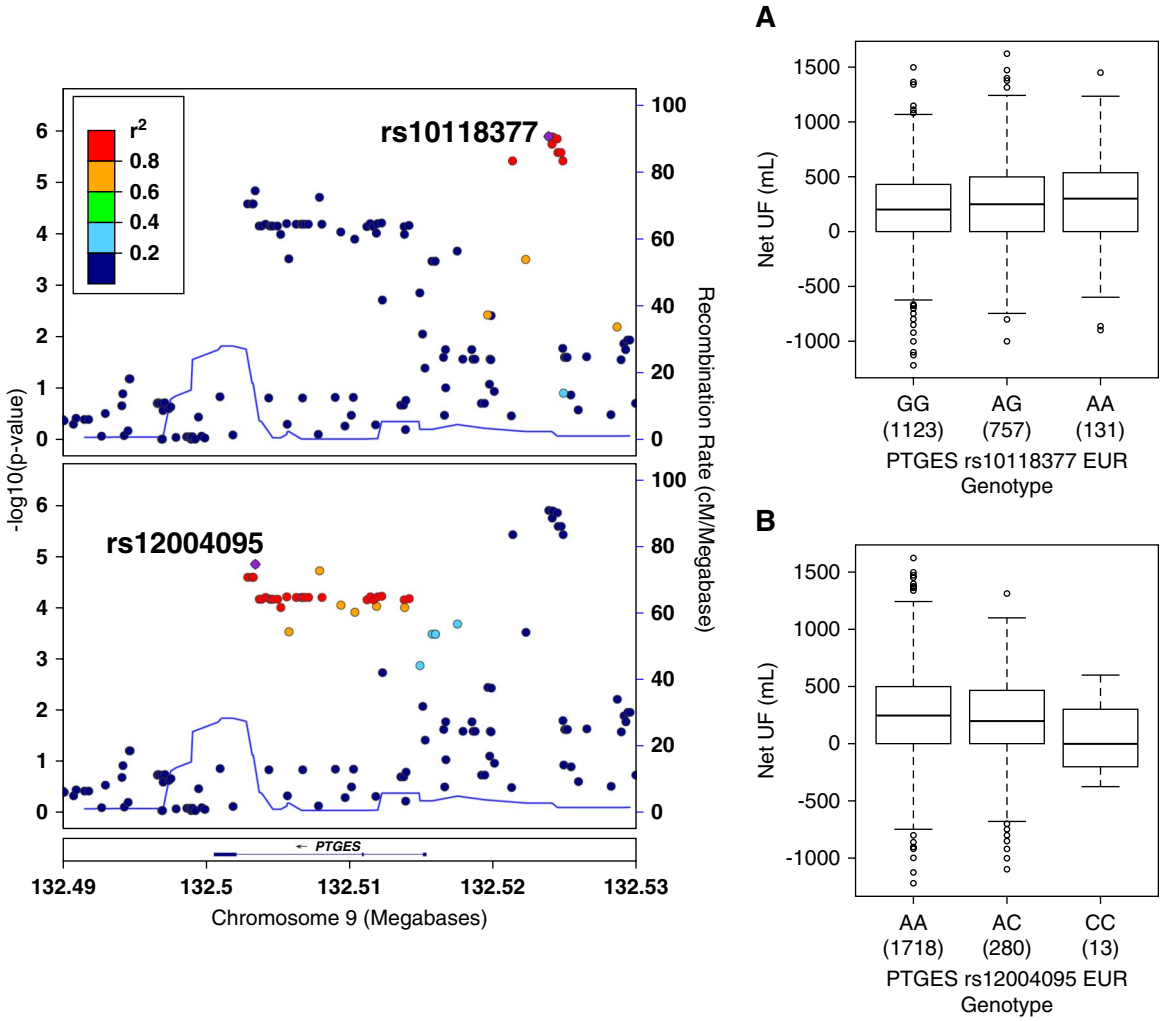

Figure 2. European local ancestry TRACTOR regional association with peritoneal ultrafiltration plot of *PTGES* gene on chromosome 9. Association of −log10 (*P* values) with SNVs within gene are plotted as points, and the colors indicate the strength of association of the SNV with peritoneal ultrafiltration; with boxplots of peritoneal ultrafiltration by *PTGES* genotypes. (A) For SNV rs10118377, ultrafiltration with genotypes GG (*N*=1123, median peritoneal ultrafiltration, 200 ml, IQR, 0–429 ml), AG (*N*=757, median ultrafiltration, 250 ml, IQR, 0–500 ml), and AA (*N*=131, median ultrafiltration, 300 ml, IQR, 5–539 ml). (B) For SNV rs12004095, ultrafiltration with genotypes AA (*n*=1718, median peritoneal ultrafiltration, 247 ml, IQR, 0–500 ml), AC (*n*=280, median peritoneal ultrafiltration, 200 ml, IQR, 0–465 ml), and CC (*n*=13, median peritoneal ultrafiltration, 0 ml, IQR, –200 to 300 ml). AC, apoptotic cell; EUR, European; IQR, interquartile range; UF, ultrafiltration.

(Figure 5H), while EP3 inhibition (L798.106) resulted in a reduction in adipocyte size (Figure 5I). In the presence of high levels of PGE2 in the dialysate, inhibiting either EP2 or EP3 increased ultrafiltration (Figure 5F). Notably, EP3 inhibition resulted in significant reduction of adipocyte size without affecting PSTR, while EP2 inhibition decreased IL-6 levels and reduced PSTR (Figure 5, G–I).

To confirm the direct effect of PGE2 on adipocytes, we treated adipocytes with PGE2 and PGE2 receptor inhibitors, followed by lipid quantification using Oil Red O staining (Supplemental Figure 14). Consistent with *in vivo* observations, PGE2 exposure increased lipid accumulation, whereas inhibition of EP3 with its antagonist L7988.106 (1 μM, for 3 hours) reduced lipid accumulation regardless of whether PGE2 was added to the medium. However, inhibition of EP2 with its antagonist TG11-77 (1 μM, for 3 hours) had no effect on lipid accumulation. Together, these findings suggest that EP2 may influence ultrafiltration by modulating dialysate IL-6 levels and changing PSTR, while EP3 may influence adipocyte size without affecting PSTR (Figure 6 and Table 5).

Discussion

This study of a large international cohort presents three findings that advance our understanding of the biology of peritoneal ultrafiltration. First, genetic variation accounted for a large part of the person-to-person variability in peritoneal ultrafiltration, and we provide the first estimates of heritability of this trait. Second, the association of ultrafiltration with *PTGES* on gene-wise analysis and functional studies in a mouse model of PD supports the role of PTGES/PGE2 in peritoneal ultrafiltration, with differential effect on PSTR and adipocytes. Third, data suggest that several additional genes such as *SLC24A3* and *CRK* may

Table 4. Summary of known functional significance of genes identified to be associated with peritoneal ultrafiltration in either the SNV-wise or gene-wise association studies

Gene	Gene ID	Association Type	Population Strata	Locus Region Top SNV	NCBI Gene Functional Knowledge Context
CRK	1398	Gene and SNV wise	European	rs72631501	Adapter protein that binds tyrosine-phosphorylated proteins in signaling pathways
MYO1C	4641	Gene wise	European	rs72631501	Actin-based molecular motor found in the cytoplasm and nucleus
Intergenic	NA	SNV wise	South Asian	rs1416265	Between *SGPL1* and *UNC5B*
SLC24A3	57419	Gene wise	European and meta-analysis	rs728481	Plasma membrane sodium/calcium exchanger solute carrier
PTGES	9536	Gene wise	European	rs107118377	Prostaglandin E2 synthase, terminal pathway enzyme
TOMM6	100188893	Gene wise	European	rs9381096	Protein transporter located in mitochondrion
USP49	25862	Gene wise	European	rs9381096	Enables histone binding, peptidase, mRNA splicing, regulation of signal transduction, and protein deubiquitination. In the nucleoplasm and cytoplasm
GNGT2	2793	Gene wise	European	rs7219226	G protein γ family phototransduction in photoreceptor cones
ABI3	51225	Gene wise	European	rs7219226	Adaptor protein with proline rick and SH3 domain in the Abi/WAVE holoenzyme. Regulates actin polymerization
MCTP2	55,784	Gene wise	European	rs7176435	Cytosol, membrane, and nucleoplasm localized and enables calcium ion binding activity
HLA-A	3105	Gene wise	European	rs2471863	Presents peptides from the endoplasmic reticulum lumen for recognition by cytotoxic T cells
ENTPD5	957	Gene wise	European	rs58894370	Extracellular nucleotide catabolism
BYSL	705	Gene wise	European	rs3806113	Binds troponin and tastin along with cytokeratins in the trophectoderm cells at the time of zygote implantation in the placentas
CRH	1392	Gene wise	European	rs80021978	Corticotropin-releasing hormone secreted by the hypothalamus to stimulate adrenocorticotrophic hormone release from pituitary gland
C14ORF45	80127	Gene wise	European	rs75773875	Also known as *BBOF1*. Sperm axoneme assembly, flagellum, cilium movement, cell motility, microtubule depolymerization, and protein stabilization
RPS15A	6210	Gene wise	European	rs11646808	Encodes a ribosomal protein 40S subunit holoenzyme component located in the cytoplasm
PRICKLE4	29964	Gene wise	European	rs9381093	Prickle planar cell polarity protein 4
TTLL11	158135	Gene wise	European	rs4837905	Tubulin-binding and tubulin-glutamic acid ligase activity in microtubule cytoskeleton and ciliary basal body organization
ARL6IP1	23204	Gene wise	European	rs2606565	Protein transport and cell signaling during hematopoietic maturation. Encodes a transmembrane protein localized to intracytoplasmic membranes in myeloid progenitor cells
GPHN	10243	Gene wise	European	rs1457421	Anchors inhibitory neurotransmitter receptors to the postsynaptic cytoskeleton by binding to tubulin dimers. Required for molybdenum cofactor biosynthesis in nonneuronal tissues
PAPOLA	10914	Gene wise	European	rs76171690	Poly(A) polymerase family gene that adds adenosines for the polymerization of mRNA 3′-poly(A) tails

NA, not applicable; NCBI, National Center for Biotechnology Information; SH3, Src-homology 3; SNV, single-nucleotide variant; WAVE, Wiskott–Aldrich syndrome protein-family verprolin-homologous protein.

affect ultrafiltration, indicating that the trait is polygenic. It is important to acknowledge the larger context for these findings that the peritoneum in humans did not evolve to allow for ultrafiltration with PD and our findings reflect unique gene–environment interactions.

Peritoneal ultrafiltration with any given concentration of dextrose varies widely between people such that it can range as much as from net reabsorption to net ultrafiltration of 1000 ml at 4 hours with 2.5% dextrose.[9,15,18,19] Consistent with previous studies, demographic and clinical factors explained 6% of the variability in ultrafiltration with 2.5% dextrose. By contrast, genome-wide genetic variation explained 50% of the variability in the entire cohort. The high heritability of the peritoneal ultrafiltration trait was consistent in different analyses such as in participants of European ancestry or after excluding HLA genes or with LD score regression. These heritability estimates are higher than for the PSTR (ultrafiltration, 50% versus 4-hour D/P creatinine in our prior work, 19%).[17] The phenotypes of solute transfer and ultrafiltration leveraged for PD are different than other biologic traits, in that there would have been little natural selection to provide survival advantage. PD is an innovation of the 20th century, and the factors leading to the high heritability likely have nothing to do with functional elements relevant to PD.

It has long been recognized that there is a reciprocal relationship between PSTR and ultrafiltration. However, differences in PSTR explain a small fraction of variance in ultrafiltration.[9,15,18,19] Accordingly, adding 4-hour D/P creatinine as a covariate explained only 36% of variance in

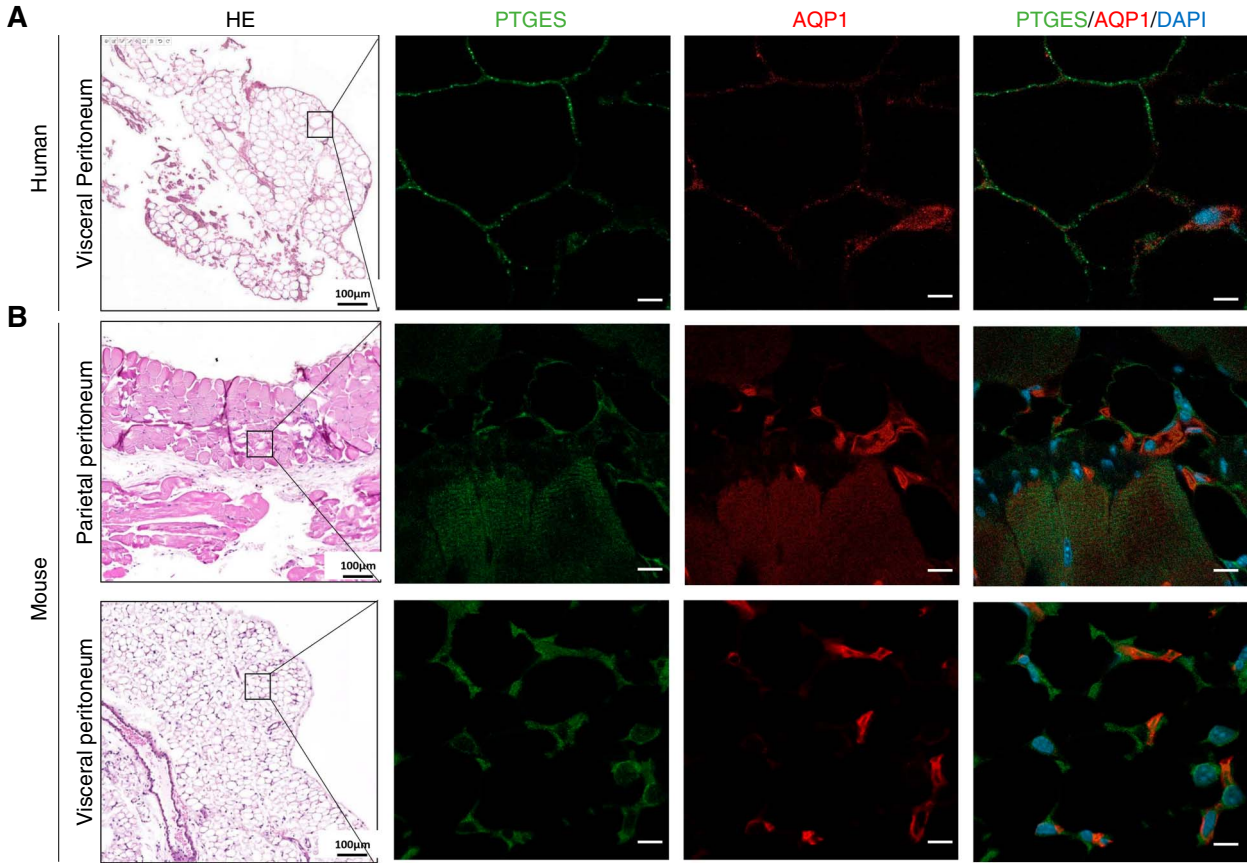

Figure 3. Immunolocalization of PTGES and AQP1 in human and mouse omentum. (A) Representative immunostaining for PTGES (green channel) and AQP1 (red channel) in the human visceral peritoneum. PTGES is mostly expressed in adipocytes, contrasting with the localization of AQP1 in the microvascular endothelial cells. Scale bars: HE, 50 μm, 10×; immunostaining, 10 μm, 63×. (B) Representative immunostaining for PTGES (green channel) and AQP1 (red channel) in the mouse visceral and parietal peritoneum. PTGES is mostly expressed in adipocytes, whereas AQP1 is located in the microvascular endothelial cells. Scale bars: HE, 50 μm, 10×; immunostaining, 10 μm, 63×. AQP1, aquaporin 1; DAPI, 4′,6-diamidino-2-phenylindole; HE, hemtaoxylin-eosin.

ultrafiltration compared with 50% with genome-wide genetic variance. This suggests that a large part of heritability of ultrafiltration is independent of the genetic determinants of PSTR. This supports the view that biologic processes affecting ultrafiltration (*e.g.*, osmotic conductance to glucose, aquaporins, PTGES/PGE2) are largely different from those affecting PSTR.

Our study also highlights several biologic pathways where genetic variation may influence person-to-person variation in ultrafiltration. Two SNVs reached genome-wide significance, and gene-wise analysis identified 21 genes associated with ultrafiltration (Tables 3 and 4). We explored one of these mechanistic pathways to further understand the biologic regulation of peritoneal ultrafiltration. *PTGES* encodes for PGE synthase, a 152-amino acid protein that is the terminal enzyme in the production of PGE2.[49] Several considerations lend support to the premise that variation in *PTGES* affects peritoneal ultrafiltration. Previous studies have shown PGE2 and PTGES production to be highly heritable.[50] We evaluated two independent SNVs, rs10118377 and rs12004095, with associations with ultrafiltration on the regional association plot for *PTGES*. Genotypic variation in each of the two SNVs was independently associated with variation in ultrafiltration. The association is biologically plausible, as *PTGES* encodes for PGE synthase, the terminal enzyme in the production of PGE2.[51–53] The PTGES/PGE2 pathway is induced by inflammation, a major driver of peritoneal function, and it has been involved in the regulation of peritoneal function in human and various animal models.[29,54,55]

Our functional studies substantiate the potential role of PTGES and PGE2 in regulating ultrafiltration. PTGES does not colocalize with AQP1 in the peritoneum and is highly expressed in adipocytes; the volume/size of adipocytes has previously been associated with changes in ultrafiltration.[25] Pharmacologic activation or inhibition of PTGES, reflected by higher or lower levels of PGE2, respectively, was associated with corresponding changes in ultrafiltration and PSTR. Direct exposure to PGE2 in dialysate led to lower ultrafiltration and higher PSTR with marked structural changes including larger adipocyte size and an inflammatory infiltrate that may drive the release of IL-6. Mechanistically, our data suggest that the effect of PGE2 on adipocyte enlargement is through the EP3 receptor, and the changes in adipocyte size in the peritoneum may affect ultrafiltration independently of the effect on PSTR. These different lines of evidence collectively provide support for the importance of genetic variation in *PTGES* on peritoneal ultrafiltration.

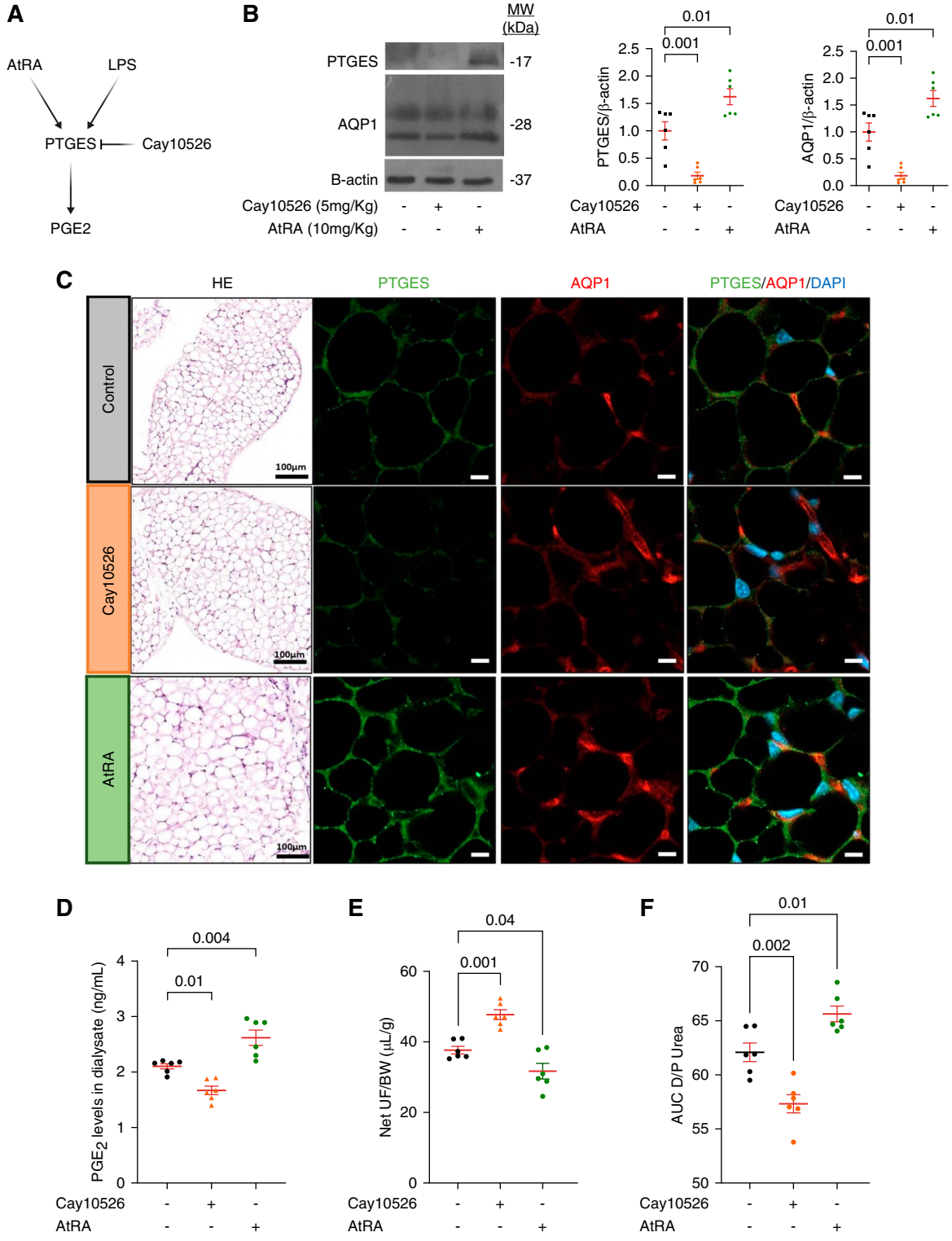

Figure 4. Modulation of PTGES influences PGE2 production and transport parameters in a mouse model of PD. (A) Pharmacologic regulators of the PTGES and PGE2 pathway. (B) Representative immunoblots and densitometry analyses showing the effects of AtRA and Cay10526 on the expression of PTGES and AQP1 (signal normalized to β-actin) in the visceral peritoneum. Twenty microgram of proteins were loaded in each lane. (C) Representative immunofluorescence of the mouse visceral peritoneum showing signals for PTGES and AQP1 after treatment with Cay10526 and AtRA. Original magnification for HE ×10; scale bar 50 μm; immunostaining, 10 μm, 63×. (D–F) Effects of PTGES inhibitor (Cay10526) and activator (AtRA) on PGE2 levels in the dialysate (D) and ultrafiltration (E) and peritoneal small solute transfer rate (PSTR, AUC of D/P urea; F) during the PET: changes in PGE2 levels inversely correlate with ultrafiltration levels. (G) Representative immunoblots and densitometry analyses showing that LPS upregulates both PTGES and AQP1 in

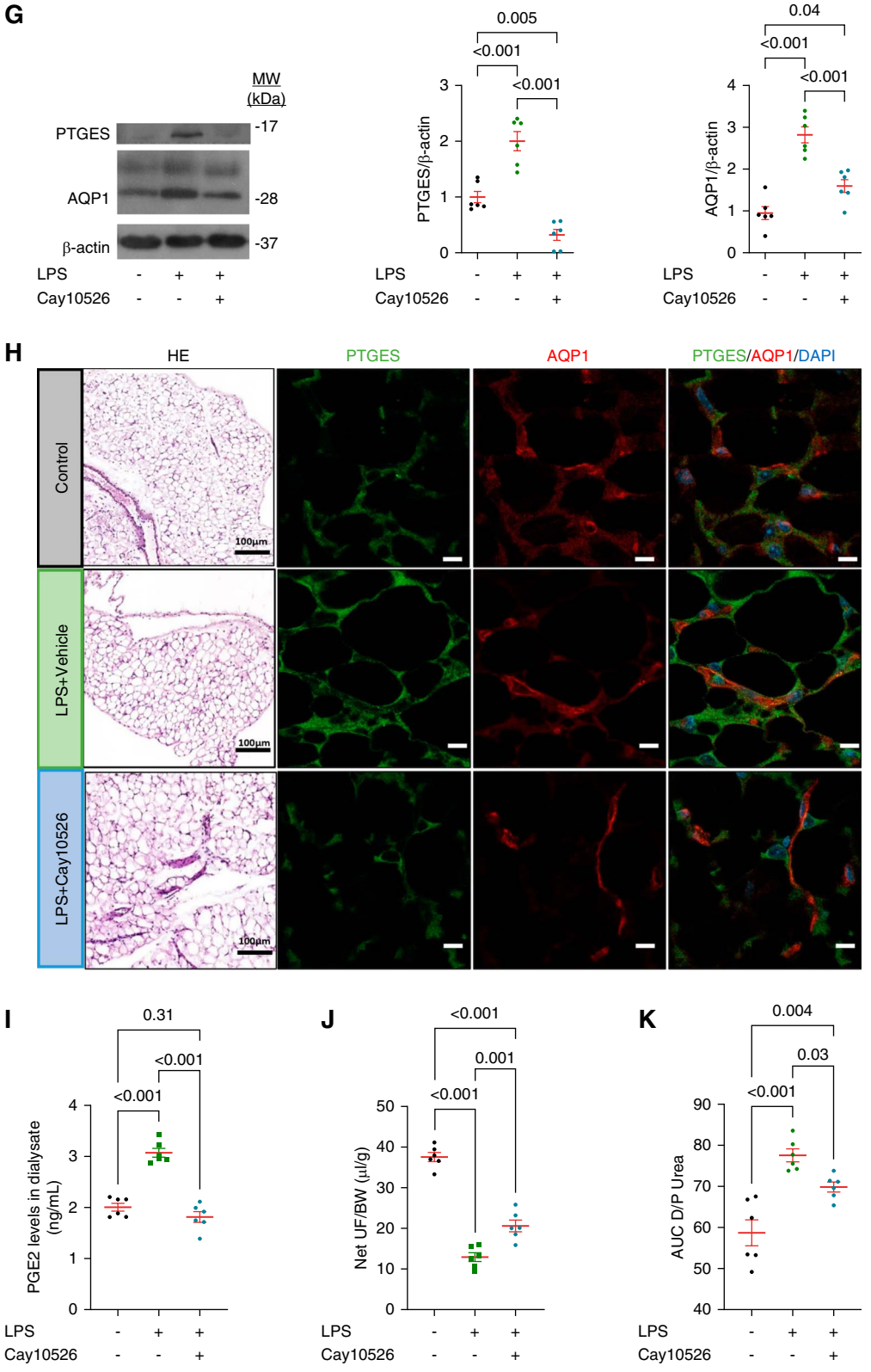

Figure 4. *Continued.* the visceral peritoneum. Treatment with Cay10526 reduces the LPS-induced effect on PTGES and AQP1. (H) Representative immunofluorescence of the mouse visceral peritoneum showing induction of PTGES and AQP1 after treatment with LPS and the blocking effect of Cay10526. Original magnification for HE ×10; scale bar 50 μm; immunostaining, 10 μm, 63×. (I–K) Effects of LPS and Cay10526 on PGE2 levels in the dialysate (I), ultrafiltration (J), and peritoneal small solute transfer rate (K) changes in PGE2 levels inversely correlate with UF levels. Differences between groups were assessed using ANOVA followed by Tukey multiple comparisons test. AtRA, all-trans retinoic acid; AUC, area under the curve; BW, body weight; LPS, lipopolysaccharide; MW, molecular weight; PGE2, prostaglandin E2; PSTR, peritoneal solute transfer rate.

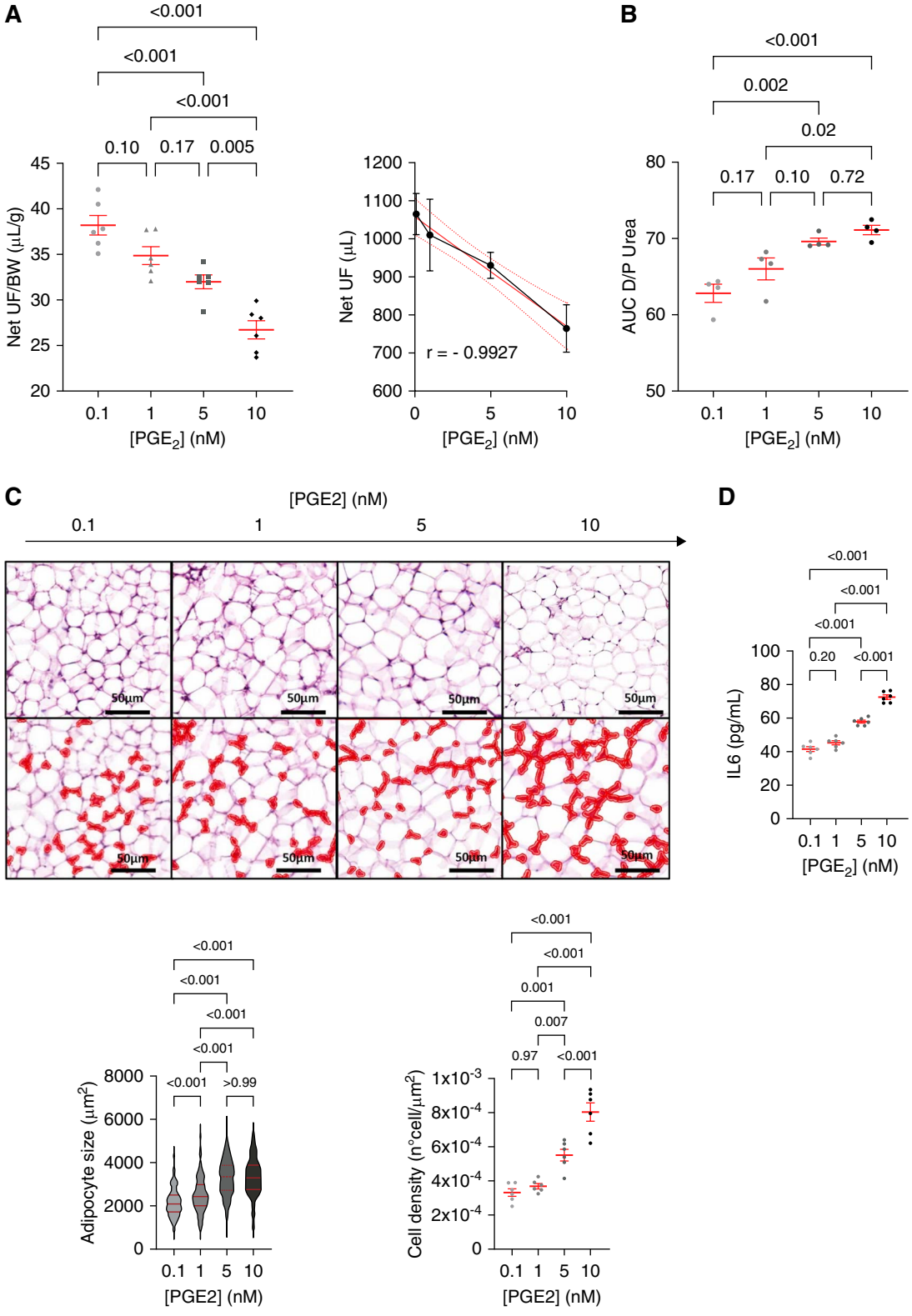

Figure 5. Influence of PGE2 signaling on the structure and function of the mouse peritoneum. (A and B) Effect of increasing concentration of PGE2 in the dialysate on (A) ultrafiltration and (B) peritoneal small solute transfer rate (PSTR, AUC of D/P urea) during the PET in mouse. (C) Effects of exposure to increased PGE2 concentrations on the structure of the peritoneal membrane: Increased levels of PGE2 lead to a progressive increase in the size of adipocytes (upper row) and an inflammatory infiltrate (lower row) in the visceral peritoneum. Scale bar: 50 μm. Original magnification, ×40. (D) Effect of increased PGE2 levels on IL-6 levels in the dialysate. (E) Graphical representation of the main types of EP receptors (EP2 and EP3) involved in PGE2 signaling. (F–I) Effect of EP2 and EP3

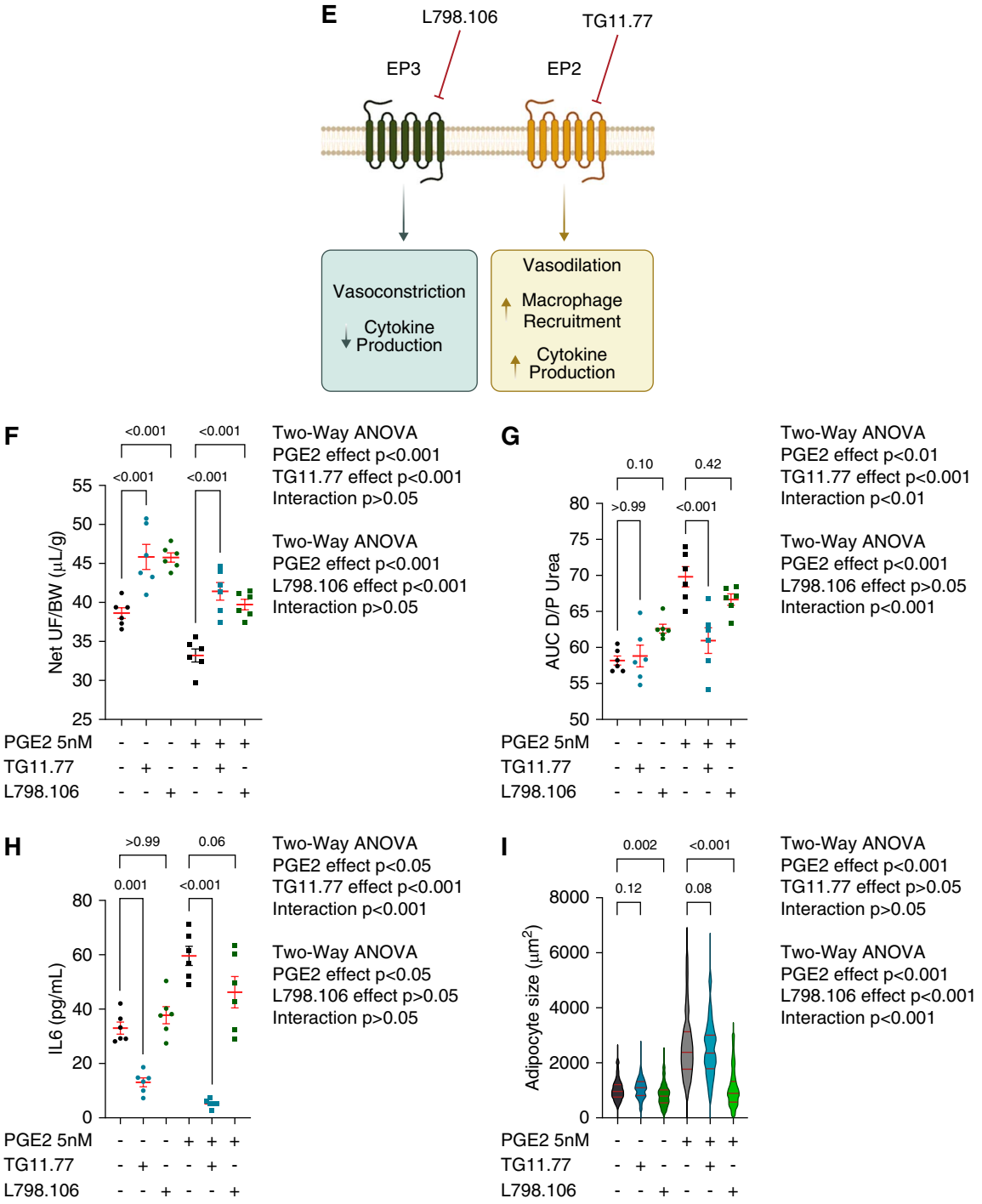

Figure 5. *Continued.* antagonists on ultrafiltration (F), peritoneal small solute transfer rate (G), IL-6 levels in dialysate (H), and adipocyte size (I) at baseline and on exposure to 5 nM PGE2. Differences between groups were assessed using ANOVA followed by Tukey multiple comparisons test. EP, E-prostanoid; EP2, E-prostanoid receptor 2; EP3, E-prostanoid receptor 3.

Our work also suggests the potential role of variation in other genes. The association with *SLC24A3* was evident in gene-wise analyses in models with and without adjustment for PSTR. The gene encodes for solute carrier family 24-member three protein, a 72 KD potassium-dependent sodium/calcium exchanger protein. The association is biologically plausible as genetic variation in *SLC24A3* is associated with changes in vascular tone and with hypertension.[56,57] Furthermore, ultrafiltration was associated with *CRK* and *MYO1C* genes, but the signal at *CRK* has two variants in high LD in the gene *MYO1C* (Supplemental Figure 7). Collectively, this makes discerning between *CRK* and *MYO1C* difficult.

Our study has several strengths. It is the first genome-wide analysis to determine the effect of genetic variation on ultrafiltration and has yielded the first estimates of heritability of the trait. Two SNVs reached genome-wide significance, and gene-wise analysis identified 21 genes

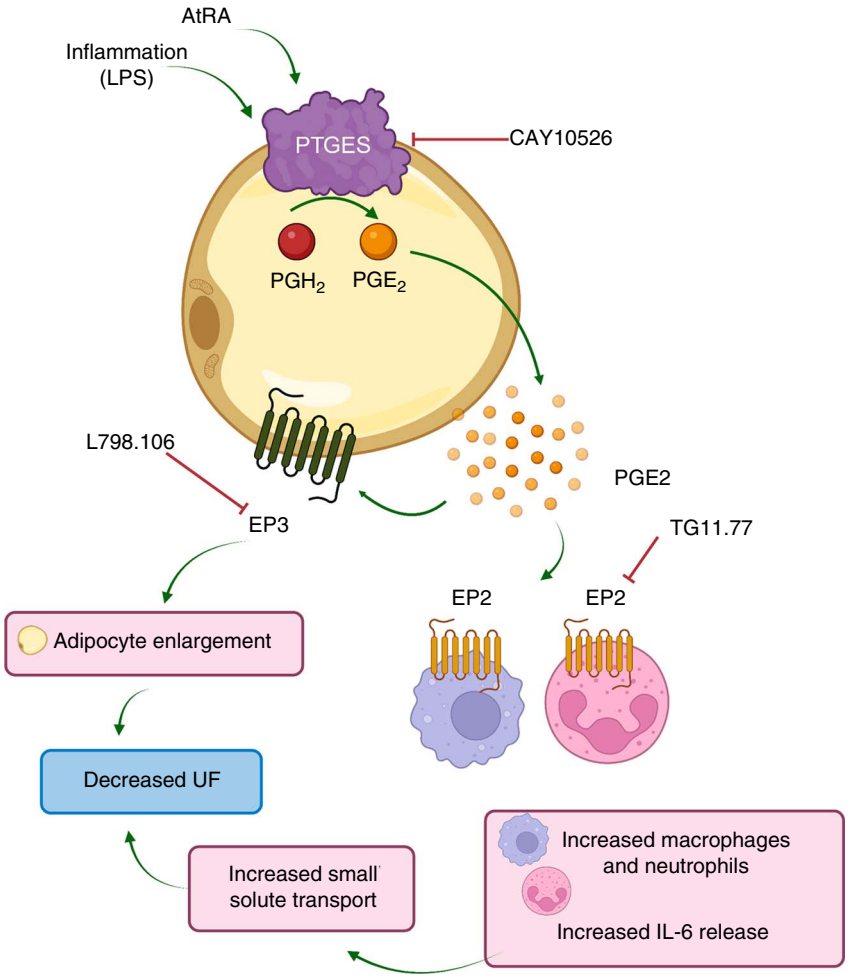

Figure 6. Proposed mechanism for the PTGES/PGE2 effect on the peritoneum. PTGES converts PGH2 into PGE2 in the adipocytes on the peritoneum. PTGES can be induced by LPS and AtRA and inhibited by Cay10526. Once released from adipocytes, PGE2 acts as a potent proinflammatory mediator through its binding to specific receptors, known as EP receptors. EP3 is the predominant receptor in the peritoneum, primarily expressed in adipocytes and mesothelial cells. Conversely, EP2 is mainly expressed in immune cells such as macrophages and neutrophils. Elevated levels of PGE_2 in the peritoneal cavity activate EP3 in peritoneal adipocytes, leading to their enlargement. Simultaneously, the activation of EP2 triggers the recruitment of immune cells to the peritoneal cavity and stimulates the release of IL-6. Together, these changes in the peritoneal membrane culminate in increased PSTR and a reduction in ultrafiltration. PGH2, prostaglandin H2.

of potential interest. Importantly, we provide strongly supportive experimental data for the biologic plausibility for the association of *PTGES* with ultrafiltration. Our cohort was assembled from 70 centers in seven countries/regions, providing significant external validity. Furthermore, our cohort was primarily of European ancestry, our analyses

Table 5. Effect of EP2 and EP3 antagonists at baseline and following exposure to PGE2-supplemented dialysate on peritoneal ultrafiltration, solute transfer rate, adipocyte size, and IL-6 levels in a mouse model of peritoneal dialysis

Variable	Baseline		PGE2 5 nM	
	EP2 Antagonist	EP3 Antagonist	EP2 Antagonist	EP3 Antagonist
Net UF/body weight, μl/g	Increased[a]	Increased[a]	Increased[a]	Increased[a]
AUC D/P urea	Unchanged	Unchanged	Decreased[a]	Unchanged
Adipocyte size, μm^2	Unchanged	Decreased[a]	Unchanged	Decreased[a]
IL-6, pg/ml	Decreased[a]	Unchanged	Decreased[a]	Unchanged

Results are derived from n=4 mice per group. AUC D/P urea, area under the curve for dialysate to plasma concentration of urea; the differences were assessed by unpaired t test; EP2, E-prostanoid receptor 2; EP3, E-prostanoid receptor 3; PGE2, prostaglandin E2; UF, ultrafiltration.
[a]$P < 0.05$.

controlled for local ancestry, and hence, the findings are unlikely to be affected by population stratification.

The limitations include a modest sample size for GWAS, albeit we were able to identify association of two SNVs with ultrafiltration at genome-wide level of significance in two ancestry strata. The signal in the South Asian portion of the cohort should be interpreted with caution as the analyses included approximately 100 people and the variants occurred at lower frequency and are not supported by association in the other ancestries. Similarly, the European-specific variant at *CRK* was not supported in other ancestries. The study population had limited diversity by ancestry, comprised primarily of participants of European ancestry, and hence, care should be exercised in extending our findings to non-European populations. Our assessments of heritability were performed in the full cohort to have adequate statistical power, but we additionally provided European strata estimates using two different methods. Furthermore, assessment of ultrafiltration was made once, albeit under standardized conditions of a PET. There was also heterogeneity in the tonicity of dextrose used for PET.[58]

In conclusion, our findings indicate that genetic variation exerts a strong polygenic influence on peritoneal ultrafiltration. Ultrafiltration is highly heritable, with genetic determinants that are independent of those associated with PSTR. Two SNVs reached genome-wide level of significance. Gene-wise analysis identified associations of ultrafiltration with 21 genes. Functional studies in a mouse model of PD substantiated the role of PTGES/PGE2 in regulating ultrafiltration. This work sets the stage for further investigation into the genetic and structural basis of peritoneal biology relevant to PD and to advance the principles of precision medicine in delivering PD therapy.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/JSN/F328.

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Declarative Statements

This study includes clinical experimentation and received Institutional Review Board or Ethics Committee approval. All patients provided written informed consent. This study includes clinical experimentation and complies with the Declaration of Helsinki. All animal experiments were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals or an equivalent standard that meets or exceeds the ethical and welfare requirements outlined in the NIH Guide. All protocols were approved by the appropriate institutional animal care and use committee.

Data Availability Statements

Original data generated for the study are available in a public access repository. Data Type: Raw Data/Source Data. The investigators have deposited the phenotype-genotype data from participants enrolled prospectively in Australia, Canada, and the United States to the database of Genotype and Phenotypes (National Center for Biotechnology Information database of Genotype and Phenotypes phs002996.v1.p1 National Institute of Diabetes and Digestive and Kidney Diseases PD Outcomes). The IRB 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 are 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.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/JSN/F329, http://links.lww.com/JSN/F330.

Supplemental Methods

Supplemental Table 1. Demographic and clinical characteristics of participants in the Bio-PD study not included in this analysis, compared with those included.

Supplemental Table 2. Multivariable models for the association of demographic and clinical covariates with peritoneal ultrafiltration in the entire analytic cohort (n=2723), without and with 4-hour D/P creatinine as a covariate.

Supplemental Table 3. Multivariable models for association of demographic and clinical covariates with peritoneal ultrafiltration in participants who had the PET conducted with 2.5% dextrose (n=2131), without and with 4-hour D/P creatinine as a covariate.

Supplemental Table 4. Results of the European strata gene-wise GWAS analysis with the Generalized Berk–Jones test, with genes associated with 4-hour peritoneal ultrafiltration from the PET, not adjusted for 4 hours D/P creatinine as covariate.

Supplemental Table 5. Effect of PTGES modulation on peritoneal ultrafiltration and solute transfer rate at baseline in a mouse model of PD.

Supplemental Table 6. Effect of LPS and PTGES modulation on peritoneal ultrafiltration and solute transfer rate in a mouse model of PD.

Supplemental Table 7. Effect of increasing PGE2 concentration on peritoneal ultrafiltration and solute transfer rate in a mouse model of PD.

Supplemental Table 8. Effect of PTGES receptor modulation on peritoneal ultrafiltration and solute transfer rate with PGE2 exposure in a mouse model of PD.

Supplemental Figure 1. A flow diagram of building the study cohort. The number of participants enrolled, who underwent genotyping, and who were included in the final analytic cohort, and the reasons for exclusion of participants at each step.

Supplemental Figure 2. Genomic PC analysis of genetic ancestry and self-reported race plotted for PC1 and PC2.

Supplemental Figure 3. Plots for GWAS of peritoneal ultrafiltration in participants in the European ancestry tract (A) QQ plot with 4-hour D/P creatinine as covariate (lambda 1.11); (B) −log10 P plot (Manhattan plot); and (C) QQ plot for model without 4-hour D/P creatinine as covariate (lambda 1.12).

Supplemental Figure 4. Plots for GWAS of peritoneal ultrafiltration in participants in the South Asian ancestry tract (A) QQ plot with 4-hour D/P creatinine as covariate (lambda 1.05); and (B) −log10 P plot (Manhattan plot) and (C) QQ plot for model without 4-hour D/P creatinine as covariate (lambda 0.92).

Supplemental Figure 5. Net 4-hour ultrafiltration volume on the PET, by genotype, in participants with South Asian ancestry for rs1416265.

Supplemental Figure 6. Results of GWAS of peritoneal ultrafiltration in participants in African and East Asian ancestry tracts and meta-analysis across ancestries: (A) −log10 P plot (Manhattan plot) in participants in African ancestry tract; (B) QQ plot in participants in African ancestry tract; (C) −log10 P plot (Manhattan plot) in participants in East Asian ancestry tract; (D) QQ plot in participants in East Asian ancestry tract; (E) meta-analysis of all four ancestry tracts; (F) QQ plot for meta-analyses of all four ancestry tracts; (G) −log10 P plot (Manhattan plot) in participants in African ancestry tract without 4-hour D/P creatinine as covariate; (H) QQ plot in participants in African ancestry tract without 4-hour D/P creatinine as covariate; (I) −log10 P plot (Manhattan plot) in participants in East Asian ancestry tract without 4-hour D/P creatinine as covariate; (J) QQ plot in participants in East Asian ancestry tract without 4-hour D/P creatinine as covariate; (I) meta-analysis of all four ancestry tracts without 4-hour D/P creatinine as covariate; and (J) QQ plot for meta-analyses of all four ancestry tracts without 4-hour D/P creatinine as covariate.

Supplemental Figure 7. Results of the gene-wise analyses from the Generalized Berk–Jones test as −log10 P plot (Manhattan plot): (A) European ancestry tracts without 4-hour D/P creatinine as covariate; (B) meta-analyses of the results for four ancestry tracts, with 4-hour D/P creatinine as covariate; and (C) meta-analyses of the results for four ancestry tracts, without 4-hour D/P creatinine as a covariate.

Supplemental Figure 8. (A) Regional association plots for SNVs in the *CRK* and *MYO1C* in participants in the European ancestry tract, adjusted for 4-hour D/P creatinine; and (B) boxplot of net ultrafiltration volume by rs72631501 genotype in participants in the European ancestry tract.

Supplemental Figure 9. *SLC24A3* regional association plot of meta-analyzed TRACTOR results adjusted for 4-hour D/P creatinine and boxplots for peritoneal ultrafiltration by genotype in participants across all ancestries for two LD independent SNVs in the *SLC24A3* LD blocks with the strongest association with peritoneal ultrafiltration: (A) rs728481; and (B) rs6046109.

Supplemental Figure 10. Differential expression of PTGES and AQP1 mRNAs in human and mouse visceral adipose tissue. (A–C) Differential expression of PTGES and AQP1 mRNAs in human white/visceral adipose tissue. (A) Uniform manifold approximation and projection (UMAP) plot of human visceral adipose tissue showing 16 distinct cell populations. Feature and dot plots showing expression levels of PTGES (B) and AQP1 (C) in the different cell clusters. (D–F) Differential expression of Ptges and Aqp1 mRNAs in mouse white/perigonadal adipose tissue. (D) UMAP plot of mouse perigonadal adipose tissue showing 17 distinct cell populations. Feature and dot plots showing expression levels of Ptges (E) and Aqp1 (F) in the different cell clusters.

Supplemental Figure 11. Immunolocalization of PTGES in mouse omentum. Representative immunostaining for PTGES (green channel) and the marker of adipocytes—PLIN (red channel) in the mouse visceral peritoneum. There is a strong co-localization between PTGES and PLIN in the adipocytes (yellow signal). Scale bars: HE, 50 μm, 10×; immunostaining, 20 μm, 20×; (B) representative immunostaining for PTGES (green channel) and the marker of mesothelial cells—carbonic anyhdrase, IX, (red channel) in the mouse visceral peritoneum. There is minimal co-localization between PTGES and CAIX, in mesothelial cells. Scale bars: HE, 50 μm, 10×; immunostaining, 20 μm, 20×.

Supplemental Figure 12. Effect of PGE2 on inflammatory cell recruitment in the peritoneal membrane. (A) Impact of increasing concentrations of PGE2 in the dialysate (in nM, for 2 hours) on the accumulation of macrophages (F4/80) and neutrophils (Ly-6B) in the peritoneal membrane. The quantification of fluorescent cell densities for F4/80 (B) and Ly-6B (C) were assessed on whole slide images. n=4 in each group.

Supplemental Figure 13. Differential expression of PTGER2 and PTGER3 mRNAs in human and mouse visceral adipose tissue. (A–C) Differential expression of PTGER2 and PTGER3 mRNAs in human white/visceral adipose tissue. (A) UMAP plot of human visceral adipose tissue showing 16 distinct cell populations. Feature and dot plots showing expression levels of PTGER2 (B) and PTGER3 (C) in the different cell clusters. (D–F) Differential expression of Ptger2 and Ptger3 mRNAs in mouse white/perigonadal adipose tissue. (D) UMAP plot of mouse perigonadal adipose tissue showing 17 distinct cell populations. Feature and dot plots showing expression levels of Ptger2 (E) and Ptger3 (F) in the different cell clusters.

Supplemental Figure 14. Influence of PGE2 signaling on lipid accumulation in adipocytes *in vitro*. (A) Adipocytes were treated with PGE2 (5 nM) alone or in combination with receptor-specific antagonists (EP3: L7988.106 or EP2: TG11-77; 1 μM) for 3 hours, followed by Oil Red O staining to assess lipid content. (B) Impact of PGE2 and EP2 antagonist TG11-77 or EP3 antagonist L798.106 on the accumulation of lipids in adipocytes.

Supplemental Spreadsheet 1. Complete results of genetic association studies of gene-wise analyses by the Generalized Berk–Jones test for peritoneal ultrafiltration.

References

1. Fresenius Medical Care. *Annual Report 2019*; 2022.
2. Rippe B. A three-pore model of peritoneal transport. *Perit Dial Int.* 1993;13(2 suppl):S35–S38. doi:10.1177/089686089301302s09
3. Öberg CM, Rippe B. Optimizing automated peritoneal dialysis using an extended 3-pore model. *Kidney Int Rep.* 2017;2(5):943–951. doi:10.1016/j.ekir.2017.04.010
4. Flessner MF, Dedrick RL, Schultz JS. A distributed model of peritoneal-plasma transport: theoretical considerations. *Am J Physiol.* 1984;246(4 Pt 2):R597–R607. doi:10.1152/ajpregu.1984.246.4.R597
5. Morelle J, Stachowska-Pietka J, Öberg C, et al. ISPD Recommendations for the evaluation of peritoneal membrane dysfunction in adults: classification, measurement, interpretation, and rationale for intervention. *Perit Dial Int.* 2021;41(4):352–372. doi:10.1177/0896860820982218
6. Devuyst O. Aquaporin-1 and osmosis: from physiology to precision in peritoneal dialysis. *J Am Soc Nephrol.* 2024;35(11):1589–1599. doi:10.1681/ASN.0000000000000496
7. Ni J, Verbavatz JM, Rippe A, et al. Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. *Kidney Int.* 2006;69(9):1518–1525. doi:10.1038/sj.ki.5000285
8. Morelle J, Marechal C, Yu Z, et al. AQP1 promoter variant, water transport, and outcomes in peritoneal dialysis. *N Engl J Med.* 2021;385(17):1570–1580. doi:10.1056/NEJMoa2034279
9. Karl ZJT, Khanna ONR, Leonor BFP, Ryan P, Moore HL, Nielsen MP. Peritoneal equilibration test. *Perit Dial Int.* 1987;7(3):138–148. doi:10.1177/089686088700700306
10. Cueto-Manzano AM, Díaz-Alvarenga A, Correa-Rotter R. Analysis of the peritoneal equilibration test in Mexico and factors influencing the peritoneal transport rate. *Perit Dial Int.* 1999;19(1):45–50. doi:10.1177/089686089901900108
11. Mujais S, Vonesh E. Profiling of peritoneal ultrafiltration. *Kidney Int.* 2002;62(81):S17–S22. doi:10.1046/j.1523-1755.62.s81.4.x
12. Davies SJ. Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. *Kidney Int.* 2004;66(6):2437–2445. doi:10.1111/j.1523-1755.2004.66021.x
13. Rumpsfeld M, McDonald SP, Johnson DW. Higher peritoneal transport status is associated with higher mortality and technique failure in the Australian and New Zealand peritoneal dialysis patient populations. *J Am Soc Nephrol.* 2006;17(1):271–278. doi:10.1681/ASN.2005050566
14. Lambie M, Chess J, Donovan KL, et al. Independent effects of systemic and peritoneal inflammation on peritoneal dialysis survival. *J Am Soc Nephrol.* 2013;24(12):2071–2080. doi:10.1681/ASN.2013030314
15. Mehrotra R, Ravel V, Streja E, et al. Peritoneal equilibration test and patient outcomes. *Clin J Am Soc Nephrol.* 2015;10(11):1990–2001. doi:10.2215/CJN.03470315
16. La Milia V, Cabiddu G, Virga G, et al. Peritoneal equilibration test reference values using a 3.86% glucose solution during the first year of peritoneal dialysis: results of a multicenter study of a large patient population. *Perit Dial Int.* 2017;37(6):633–638. doi:10.3747/pdi.2017.00004
17. Mehrotra R, Stanaway IB, Jarvik GP, et al. A genome-wide association study suggests correlations of common genetic variants with peritoneal solute transfer rates in patients with kidney failure receiving peritoneal dialysis. *Kidney Int.* 2021;100(5):1101–1111. doi:10.1016/j.kint.2021.05.037
18. Davies SJ, Brown B, Bryan J, Russell GI. Clinical evaluation of the peritoneal equilibration test: a population-based study. *Nephrol Dial Transplant.* 1993;8(1):64–70. doi:10.1093/oxfordjournals.ndt.a092275
19. Davies SJ. Monitoring of long-term peritoneal membrane function. *Perit Dial Int.* 2001;21(2):225–232. doi:10.1177/089686080102100222
20. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. *Nat Genet.* 2016;48(10):1284–1287. doi:10.1038/ng.3656
21. Loh PR, Danecek P, Palamara PF, et al. Reference-based phasing using the haplotype reference consortium panel. *Nat Genet.* 2016;48(11):1443–1448. doi:10.1038/ng.3679
22. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet.* 2016;48(10):1279–1283. doi:10.1038/ng.3643
23. Aguet F, Anand S, Ardlie KG, et al. The GTEx consortium atlas of genetic regulatory effects across human tissues. *Science.* 2020;369(6509):1318–1330. doi:10.1126/science.aaz1776
24. Ni J, Cnops Y, Debaix H, Boisdé I, Verbavatz JM, Devuyst O. Functional and molecular characterization of a peritoneal dialysis model in the C57BL/6J mouse. *Kidney Int.* 2005;67(5):2021–2031. doi:10.1111/j.1523-1755.2005.00304.x
25. Costa IPD, Hautem N, Schiano G, Uchida S, Nishino T, Devuyst O. Fasting influences aquaporin expression, water transport and adipocyte metabolism in the peritoneal membrane. *Nephrol Dial Transplant.* 2023;38(6):1408–1420. doi:10.1093/ndt/gfac318
26. Wang T, Jing B, Xu D, et al. PTGES/PGE(2) signaling links immunosuppression and lung metastasis in Gprc5a-knockout mouse model. *Oncogene.* 2020;39(15):3179–3194. doi:10.1038/s41388-020-1207-6
27. Lenz M, Eichler A, Kruse P, et al. All-trans retinoic acid induces synaptopodin-dependent metaplasticity in mouse dentate granule cells. *elife.* 2021;10:e71983. doi:10.7554/eLife.71983
28. Mamidi S, Hofer TP, Hoffmann R, Ziegler-Heitbrock L, Frankenberger M. All-trans retinoic acid up-regulates prostaglandin-E synthase expression in human macrophages. *Immunobiology.* 2012;217(6):593–600. doi:10.1016/j.imbio.2011.10.022
29. Hautem N, Morelle J, Sow A, et al. The NLRP3 inflammasome has a critical role in peritoneal dialysis-related peritonitis. *J Am Soc Nephrol.* 2017;28(7):2038–2052. doi:10.1681/ASN.2016070729
30. Xiao L, Ornatowska M, Zhao G, et al. Lipopolysaccharide-induced expression of microsomal prostaglandin E synthase-1 mediates late-phase PGE2 production in bone marrow derived macrophages. *PLoS One.* 2012;7(11):e50244. doi:10.1371/journal.pone.0050244
31. Díaz-Muñoz MD, Osma-García IC, Cacheiro-Llaguno C, Fresno M, Iñiguez MA. Coordinated up-regulation of cyclooxygenase-2 and microsomal prostaglandin E synthase 1 transcription by nuclear factor kappa B and early growth response-1 in macrophages. *Cell Signal.* 2010;22(10):1427–1436. doi:10.1016/j.cellsig.2010.05.011
32. Ni J, McLoughlin RM, Brodovitch A, et al. Nitric oxide synthase isoforms play distinct roles during acute peritonitis. *Nephrol Dial Transplant.* 2010;25(1):86–96. doi:10.1093/ndt/gfp415
33. Murakami M, Naraba H, Tanioka T, et al. Regulation of prostaglandin E2 biosynthesis by inducible membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2. *J Biol Chem.* 2000;275(42):32783–32792. doi:10.1074/jbc.M003505200
34. Banik A, Amaradhi R, Lee D, et al. Prostaglandin EP2 receptor antagonist ameliorates neuroinflammation in a two-hit mouse model of Alzheimer's disease. *J Neuroinflammation.* 2021;18(1):273. doi:10.1186/s12974-021-02297-7
35. Leng J, Zhao W, Guo J, et al. E-prostanoid 3 receptor deficiency on myeloid cells protects against ischemic acute kidney injury via breaking the auto-amplification loop of necroinflammation. *Kidney Int.* 2023;103(1):100–114. doi:10.1016/j.kint.2022.08.019
36. Buuren Sv, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Softw.* 2011;45(3):1–67. doi:10.18637/jss.v045.i03

37. Hastings C, Mosteller F, Tukey JW, Winsor CP. Low moments for small samples: a comparative study of order statistics. *Ann Math Stat.* 1947;18(3):413–426. doi:10.1214/aoms/1177730388
38. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience.* 2015;4:7. doi:10.1186/s13742-015-0047-8
39. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet.* 2011;88(1):76–82. doi:10.1016/j.ajhg.2010.11.011
40. Atkinson EG, Maihofer AX, Kanai M, et al. Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power. *Nat Genet.* 2021;53(2):195–204. doi:10.1038/s41588-020-00766-y
41. Maples BK, Gravel S, Kenny EE, Bustamante CD. RFMix: a discriminative modeling approach for rapid and robust local-ancestry inference. *Am J Hum Genet.* 2013;93(2):278–288. doi:10.1016/j.ajhg.2013.06.020
42. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics.* 2010;26(17):2190–2191. doi:10.1093/bioinformatics/btq340
43. Eekhout I, van de Wiel MA, Heymans MW. Methods for significance testing of categorical covariates in logistic regression models after multiple imputation: power and applicability analysis. *BMC Med Res Methodol.* 2017;17(1):129. doi:10.1186/s12874-017-0404-7
44. van de Wiel MA, Berkhof J, van Wieringen WN. Testing the prediction error difference between 2 predictors. *Biostatistics.* 2009;10(3):550–560. doi:10.1093/biostatistics/kxp011
45. Bulik-Sullivan BK, Loh PR, Finucane HK, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet.* 2015;47(3):291–295. doi:10.1038/ng.3211
46. Finucane HK, Bulik-Sullivan B, Gusev A, et al. Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat Genet.* 2015;47(11):1228–1235. doi:10.1038/ng.3404
47. Sun R, Lin X. Genetic variant set-based tests using the generalized Berk-Jones statistic with application to a genome-wide association study of breast cancer. *J Am Stat Assoc.* 2020;115(531):1079–1091. doi:10.1080/01621459.2019.1660170
48. Sun R, Hui S, Bader GD, Lin X, Kraft P. Powerful gene set analysis in GWAS with the Generalized Berk-Jones statistic. *PLoS Genet.* 2019;15(3):e1007530. doi:10.1371/journal.pgen.1007530
49. Samuelsson B, Morgenstern R, Jakobsson PJ. Membrane prostaglandin E synthase-1: a novel therapeutic target. *Pharmacol Rev.* 2007;59(3):207–224. doi:10.1124/pr.59.3.1
50. Vila L, Martinez-Perez A, Camacho M, et al. Heritability of thromboxane A2 and prostaglandin E2 biosynthetic machinery in a Spanish population. *Arterioscler Thromb Vasc Biol.* 2010;30(1):128–134. doi:10.1161/ATVBAHA.109.193219
51. Ozen G, Gomez I, Daci A, et al. Inhibition of microsomal PGE synthase-1 reduces human vascular tone by increasing PGI(2): a safer alternative to COX-2 inhibition. *Br J Pharmacol.* 2017;174(22):4087–4098. doi:10.1111/bph.13939
52. Avendaño MS, García-Redondo AB, Zalba G, et al. mPGES-1 (microsomal prostaglandin E synthase-1) mediates vascular dysfunction in hypertension through oxidative stress. *Hypertension.* 2018;72(2):492–502. doi:10.1161/HYPERTENSIONAHA.118.10833
53. Hao H, Hu S, Wan Q, et al. Protective role of mPGES-1 (microsomal prostaglandin E synthase-1)-derived PGE(2) (prostaglandin E(2)) and the endothelial EP4 (prostaglandin E receptor) in vascular responses to injury. *Arterioscler Thromb Vasc Biol.* 2018;38(5):1115–1124. doi:10.1161/ATVBAHA.118.310713
54. Leypoldt JK, Kamerath CD, Gilson JF. Acute peritonitis in a C57BL/6 mouse model of peritoneal dialysis. *Adv Perit Dial.* 2007;23:66–70. PMID: 17886606
55. Zemel D, Struijk DG, Dinkla C, Stolk LM, ten Berge IJ, Krediet RT. Effects of intraperitoneal cyclooxygenase inhibition on inflammatory mediators in dialysate and peritoneal membrane characteristics during peritonitis in continuous ambulatory peritoneal dialysis. *J Lab Clin Med.* 1995;126(2):204–215. PMID: 7636393
56. Citterio L, Simonini M, Zagato L, et al. Genes involved in vasoconstriction and vasodilation system affect salt-sensitive hypertension. *PLoS One.* 2011;6(5):e19620. doi:10.1371/journal.pone.0019620
57. Dong H, Jiang Y, Triggle CR, Li X, Lytton J. Novel role for K+-dependent Na+/Ca2+ exchangers in regulation of cytoplasmic free Ca2+ and contractility in arterial smooth muscle. *Am J Physiol Heart Circ Physiol.* 2006;291(3):H1226–H1235. doi:10.1152/ajpheart.00196.2006
58. Morelle J, Davies S, Devuyst O. AQP1 promoter variant, water transport, and outcome in peritoneal dialysis. Reply. *New Engl J Med.* 2022;386(11):1098. doi:10.1056/NEJMc2118244

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