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# Variation in *PTX3* Is Associated with Primary Graft Dysfunction after Lung Transplantation

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**Rationale:** Elevated long pentraxin-3 (*PTX3*) levels are associated with the development of primary graft dysfunction (PGD) after lung transplantation. Abnormalities in innate immunity, mediated by *PTX3* release, may play a role in PGD pathogenesis.

**Objectives:** Our goal was to test whether variants in the gene encoding *PTX3* are risk factors for PGD.

**Methods:** We performed a candidate gene association study in recipients from the multicenter, prospective Lung Transplant Outcomes Group cohort enrolled between July 2002 and July 2009. The primary outcome was International Society for Heart and Lung Transplantation grade 3 PGD within 72 hours of transplantation. Targeted genotyping of 10 haplotype-tagging *PTX3* single-nucleotide polymorphisms (SNPs) was performed in lung transplant recipients. The association between PGD and each SNP was evaluated by logistic regression, adjusting for pretransplantation lung disease, cardiopulmonary bypass use, and population stratification. The

## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

There is expanding evidence of a central role for innate immune dysregulation in the development of primary graft dysfunction (PGD) after lung transplantation, and innate immunity is a target for evolutionary selection from infectious sources. Long pentraxin-3 (*PTX3*) is an innate immune mediator that has been shown to be a plasma marker in PGD, but the genetics of this relationship are incompletely understood.

### What This Study Adds to the Field

We performed a candidate gene association study of long *PTX3*, an innate immune mediator, and PGD in the Lung Transplant Outcomes Group, a multicenter cohort of lung transplant recipients. We identified a significant association between polymorphisms in *PTX3* and PGD, and functional evaluation revealed that PGD-associated *PTX3* variants regulate plasma *PTX3* levels.

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The participating centers for this study were as follows: University of Pennsylvania, Columbia University, University of Alabama at Birmingham, Vanderbilt University, Stanford University, Johns Hopkins University, University of Michigan, Duke University, University of Pittsburgh, and University of Chicago.

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association between SNPs and plasma *PTX3* levels was tested across genotypes in a subset of recipients with idiopathic pulmonary fibrosis.

**Measurements and Main Results:** Six hundred fifty-four lung transplant recipients were included. The incidence of PGD was 29%. Two linked 5' region variants, rs2120243 and rs2305619, were associated with PGD (odds ratio, 1.5; 95% confidence interval, 1.1 to 1.9;  $P = 0.006$  and odds ratio, 1.4; 95% confidence interval, 1.1 to 1.9;  $P = 0.007$ , respectively). The minor allele of rs2305619 was significantly associated with higher plasma *PTX3* levels measured pretransplantation ( $P = 0.014$ ) and at 24 hours ( $P = 0.047$ ) after transplantation in patients with idiopathic pulmonary fibrosis. **Conclusions:** Genetic variants of *PTX3* are associated with PGD after lung transplantation, and are associated with increased *PTX3* plasma levels.

**Keywords:** primary graft dysfunction; single-nucleotide polymorphism; long pentraxin 3; lung transplantation

Primary graft dysfunction (PGD), with an incidence of 10–30%, is a major cause of early morbidity and mortality after lung

transplantation (1–4). Ischemia–reperfusion injury is a significant contributor to the development of PGD (5, 6). Furthermore, ischemia–reperfusion injury is also known to result in activation and propagation of the innate immune response (7–11).

Innate immune responses appear to be regulated by germline-encoded receptors, and their polymorphic variants influence response to infection and inflammatory conditions (12). Long pentraxin-3 (*PTX3*) is a phylogenetically conserved mediator of the innate immune response (13). We previously demonstrated that plasma *PTX3* levels after lung transplantation were significantly associated with PGD, with the strongest relationship seen in transplant recipients with idiopathic pulmonary fibrosis (IPF) (14).

*PTX3* is produced at sites of inflammation or injury by dendritic cells and other antigen-presenting cells as a result of IL-1 and Toll-like receptor-4 (TLR4) signaling pathways (13, 15–18). *PTX3* blood levels are elevated under inflammatory and ischemic conditions, including myocardial infarction, acute lung injury, and sepsis (19–24). The *PTX3* promoter responds to tumor necrosis factor- $\alpha$  and IL-1 $\beta$  stimulation and contains binding sites for nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B) (25). On the basis of our prior findings of an association of plasma *PTX3* levels with PGD, we performed a candidate gene analysis of *PTX3* with the hypothesis that polymorphisms in *PTX3* in lung transplant recipients are significantly associated with the development of severe PGD. On the basis of the previously identified association of elevated *PTX3* plasma protein levels in IPF recipients with PGD, we further evaluated the association of *PTX3* polymorphisms in IPF recipients with PGD. Some of the results of these studies have been previously reported in the form of an abstract (26).

## METHODS

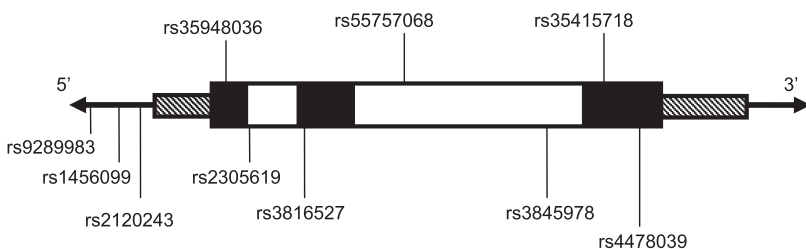
Please see the online supplement for further details on PGD grading, genotyping method, measurement of *PTX3* concentration, and statistical analysis, including power calculations.

### Study Design and Subject Selection

Study subjects were enrolled from the multicenter Lung Transplant Outcomes Group cohort and patient-level data were collected prospectively as previously described (3, 4, 14, 27–29). This study was approved by the institutional review boards at each site and subjects provided consent for enrollment.

Phase 1 was a candidate gene association study evaluating the association of *PTX3* single nucleotide polymorphisms (SNPs) and the risk of PGD after lung transplantation. Patients enrolled consecutively in the Lung Transplant Outcomes Group from July 2002 through July 2009 were included for analysis.

Phase 2 was a functional assessment of the SNPs identified in phase 1. Plasma *PTX3* concentrations were measured in a subset of subjects with IPF (14). On the basis of a previously identified association of *PTX3* plasma concentration in IPF recipients with PGD, this analysis was performed on the overall cohort and a subgroup limited to transplant recipients with IPF.



**Figure 1.** Gene structure of pentraxin-3 (*PTX3*), with approximate positions of single-nucleotide polymorphisms (SNPs) included for analysis. Exons are depicted as solid rectangles, whereas introns are open rectangles, and 5' and 3' untranslated regions (UTRs) are hatched.

## PGD Grading

PGD was defined as any episode of grade 3 PGD developing within 72 hours of allograft reperfusion, determined according to International Society for Heart and Lung Transplantation criteria, with grade 3 indicated by the presence of diffuse alveolar infiltrates in the allograft, a  $\text{PaO}_2/\text{FiO}_2$  (fraction of inspired oxygen) ratio less than 200, and the exclusion of secondary causes (27, 30, 31). As a sensitivity analysis, grade 3 PGD present 48 or 72 hours after transplantation was used as an alternative PGD definition.

## Genotyping Strategy

SNPs were selected to capture at least 50% of the variation in *PTX3* at a minor allele frequency (MAF) greater than 5%, with additional SNPs selected to include known coding variants (Figure 1). Genotyping of 10 *PTX3*-tagging SNPs selected from HapMap and 1000 Genomes was performed with a combination of TaqMan polymerase chain reaction and the IBC chip (Illumina, San Diego, CA), a gene-centric array designed to assay SNPs in candidate genes affecting vascular, pulmonary, and metabolic phenotypes with a robust set of ancestry informative markers, filtered for the *PTX3* gene (32–34).

## Measurement of *PTX3* Concentration

Plasma *PTX3* concentrations were determined with a sandwich ELISA (Alexis Biochemicals, Lausen, Switzerland) in a previously measured subset of the patients with IPF (14).

## Statistical Analysis

Subject characteristics were compared using *t* tests, Wilcoxon rank sum, or Kruskal-Wallis testing as appropriate. An odds ratio (OR) for PGD was calculated according to genotype for the seven SNPs with a minor allele frequency greater than 5%, with significance determined by  $\chi^2$  test, assuming an additive model of genetic risk in PLINK (35). Genetically inferred ancestry was determined by principal components analysis and the approximately 1,800 ancestry informative markers (AIMs) on the IBC chip (36). To account for population stratification and potential clinical confounders, analyses included adjustment for key clinical covariates (cardiopulmonary bypass, predisposing lung disease) and two principal components derived from AIMs, using logistic regression. A Bonferroni-adjusted  $P < 7.1 \times 10^{-3}$  was considered significant to account for the seven SNPs tested. We also performed analyses in the IPF subgroup and performed sensitivity analyses using altered outcome definitions. Haplotype analyses were performed with Haploview and PLINK (35, 37), using the confidence intervals method (38). Plasma *PTX3* levels were analyzed across SNP genotypes, using the nonparametric test for trend. Except where noted, statistical analyses were performed with Stata 11.2 software (STATA Corp., College Station, TX).

## RESULTS

### Patient Characteristics

Overall, 654 patients were included for analysis, with an incidence of PGD of 29% (189 of 654). The patient characteristics of the study subjects with and without PGD are described in Table 1. Subjects with PGD had a significantly higher usage of cardiopulmonary bypass compared with those without PGD

TABLE 1. SUBJECT CHARACTERISTICS

Covariate	PGD (n = 189)	Non-PGD (n = 465)	P Value
Recipient variables			
Age, mean (95% CI)	52 (50, 54)	52 (51, 54)	0.6
Male sex, n (%)	97 (51)	240 (52)	0.7
Pulmonary diagnosis, n (%)			<0.001
COPD	59 (31)	209 (45)	
IPF	73 (39)	143 (31)	
CF	14 (7)	71 (15)	
Other	43 (23)	42 (9)	
Race, n (%)			0.004
Caucasian	147 (78)	406 (87)	
African American	31 (16)	30 (6)	
Other	11 (6)	29 (6)	
Operative variables			
Cardiopulmonary bypass use, yes, n (%)	99 (52)	133 (29)	<0.001
Pulmonary arterial systolic pressure, mean (95% CI)	34.6 (30.2, 39.0)	30.4 (27.9, 33.0)	0.1

Definition of abbreviations: CF = cystic fibrosis; CI = confidence interval; COPD = chronic obstructive pulmonary disease; IPF = idiopathic pulmonary fibrosis; PGD = primary graft dysfunction. Percentages may not equal 100% because of rounding.

(52 vs. 29%;  $P < 0.001$ ). Age and sex were not significantly different between subjects with or without PGD.

### SNP Associations with PGD

After adjustment for pretransplantation diagnosis, genetically inferred ancestry using population stratification, and cardiopulmonary bypass use, two SNPs met our prespecified level of significance (Table 2). One SNP, rs2120243, resides in the 5' promoter region and the minor allele is significantly associated with PGD (OR, 1.5; 95% confidence interval [CI], 1.1 to 1.9;  $P = 0.006$ ). Variant rs2305619 is in the first intron and the minor allele at this position is also associated with PGD (OR, 1.4; 95% CI, 1.1 to 1.9;  $P = 0.007$ ). The minor alleles at both SNP positions were common in the transplant population, with MAFs greater than 0.45.

### Sensitivity Analysis for SNP Associations with Alternative PGD Definitions

When using grade 3 PGD present 48 hours after transplantation as an alternative outcome definition, 91 subjects met the criteria for PGD. The association between the minor alleles at the identified risk SNPs, rs2120243 (OR, 1.5; 95% CI, 1.04 to 2.0;  $P = 0.03$ ) and rs2305619 (OR, 1.6, 95% CI, 1.1, 2.2,  $P = 0.01$ ), and PGD is attenuated, based on the Bonferroni-corrected  $P$  value cutoff, in the setting of a smaller sample size but remains of similar magnitude to the primary outcome. Similarly, when using grade 3 PGD present 72 hours after transplantation as a secondary

PGD definition (n = 78), the direction and magnitude of effect appeared similar to the overall population, although the result was similarly not statistically significant with the smaller sample size (for rs2120243: OR, 1.6; 95% CI, 1.1 to 2.3;  $P = 0.01$ ; for rs2305619: OR, 1.6; 95% CI, 1.1 to 2.3;  $P = 0.01$ ). The associations between the *PTX3* SNPs and PGD at both alternative time points are significant when using a  $P < 0.05$  cutoff.

### Haplotype Analysis

With two SNPs in *PTX3* demonstrating significant association with PGD, we defined the linkage disequilibrium (LD) between markers and investigated whether *PTX3* haplotypes, or combinations of alleles at different loci, were also associated with PGD. Two haplotype blocks were defined in our population for tested variants with MAF equal to or greater than 0.05 (Figure 2). Haplotype 1 blocks GA and AT and haplotype 2 blocks CCTCC and ATGCC were associated with PGD. Block 2 CCTCC ( $P = 0.02$ ) and ATGCC ( $P = 0.03$ ), defined by the 2 PGD-associated SNPs, demonstrated the strongest association (Table 3). There was significant linkage across the SNPs tested, with rs2120243 and rs2305619 demonstrating tight LD ( $r^2 = 0.83$ ). Furthermore, both markers from block 1 displayed moderate LD with block 2. Block 1 haplotypes were linked to the PGD-associated block 2 haplotypes; 73% of patients with haplotype block 1 AT had haplotype block 2 CCTCC while 98% of patients with haplotype 1 block GA had haplotype block 2 ATGCC.

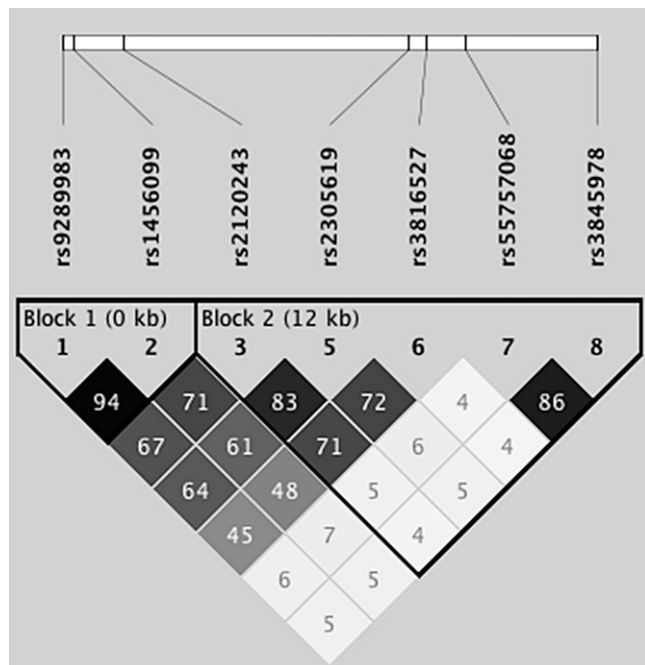
TABLE 2. SINGLE-NUCLEOTIDE POLYMORPHISM ANALYSIS FOR ASSOCIATION WITH PRIMARY GRAFT DYSFUNCTION

rs Number	Minor Allele	Risk Allele	MAF Affected	MAF Unaffected	OR (95% CI)	P Value	Location
rs9289983	G	A	0.41	0.50	0.8 (0.6, 1.0)	0.04	5' upstream
rs1456099	A	T	0.43	0.51	0.8 (0.6, 1.0)	0.05	5' upstream
rs2120243	A	A	0.49	0.42	1.5 (1.1, 1.9)	0.006	5' upstream
rs35948036	—	—	0.009	0.009	—	—	First exon synonymous
rs2305619	T	T	0.54	0.46	1.4 (1.1, 1.9)	0.007	Intron
rs3816527	G	G	0.43	0.40	1.3 (1.0, 1.6)	0.1	Second exon nonsynonymous
rs55757068	C	T	0.06	0.07	0.7 (0.4, 1.3)	0.1	Intron
rs3845978	C	T	0.06	0.06	0.7 (0.4, 1.3)	0.3	Intron
rs35415718	—	—	0.02	0.01	—	—	Third exon nonsynonymous
rs4478039	—	—	0.00	0.00	—	—	Third exon nonsynonymous

Definition of abbreviations: CI = confidence interval; MAF = minor allele frequency; OR = odds ratio.

OR and  $P$  values are based on an additive model.  $P$  for significance =  $7.1 \times 10^{-3}$ , based on the testing of seven single-nucleotide polymorphisms.

Analysis is corrected for first two principal components derived from ancestry informative markers, cardiopulmonary bypass use, and preoperative lung disease.



**Figure 2.** Linkage disequilibrium (LD) structure of *PTX3* in the study population. LD values and shading represent  $R^2$  values, with higher numbers and darker shading reflecting a higher degree of LD. Each single-nucleotide polymorphism in the haplotype is listed by its reference sequence (rs) number.

### SNP Associations with PGD in IPF Subgroup

The results of the SNP-association study among patients with a preoperative diagnosis of IPF are presented in Table E1 (in the online supplement). When the analysis was restricted to subjects with IPF only, the direction and magnitude of effect appeared similar to the overall population, though the result was not statistically significant with the smaller sample size.

### Functional Evaluation

*PTX3* SNP genotypes and plasma *PTX3* levels were obtained from 82 subjects in the overall cohort, comprising subjects with varying preoperative diagnoses. Of these, 23 subjects (28%) had PGD and 59 (72%) did not have PGD. *PTX3* plasma levels 24 hours after transplantation were higher with the presence of the risk allele at rs2305619, but did not achieve statistical significance (median [*PTX3*] C/C, 20.3 ng/ml; C/T, 29.6 ng/ml; T/T, 53.5 ng/ml) ( $P = 0.07$ ) (Figure 3A).

Our prior work demonstrated a wider variability in plasma *PTX3* levels among patients with IPF compared with those with chronic obstructive pulmonary disease. Of the 47 recipients with IPF who had both *PTX3* genotyping and plasma *PTX3* levels determined, 13 subjects (28%) had PGD and 34 (72%) did not have PGD. Circulating *PTX3* plasma levels 24 hours after transplantation (median [*PTX3*] C/C, 19.5 ng/ml; C/T, 29.8 ng/ml; T/T, 46.0 ng/ml;  $P = 0.047$ ) were significantly different by genotype for SNP rs2305619 (Figure 3B). *PTX3* plasma levels 24 hours after transplantation were likewise higher with the presence of the risk allele at rs2120243, but did not achieve statistical significance (median [*PTX3*] C/C, 22.0 ng/ml; C/A, 29.2 ng/ml; A/A, 73.3 ng/ml) ( $P = 0.3$ ) (Figure E1). Pretransplantation *PTX3* levels were significantly associated with the genotype for SNP rs2305619 (median [*PTX3*] C/C, 1.7 ng/ml; C/T, 1.9 ng/ml; T/T, 7.9 ng/ml) ( $P = 0.014$ ) (Figure E2).

**TABLE 3. HAPLOTYPE ANALYSIS FOR ASSOCIATION WITH PRIMARY GRAFT DYSFUNCTION**

Haplotype	Frequency in PGD	Frequency in Non-PGD	OR	<i>P</i> Value
<b>Block 1</b>				
GA	0.59	0.49	1.3	0.048
AT	0.47	0.50	0.8	0.04
GT	0.01	0.01	1.1	0.8
<b>Block 2</b>				
CCTCC	0.46	0.49	0.7	0.02
ATGCC	0.38	0.36	1.3	0.03
CCTTT	0.05	0.05	0.7	0.3
ATTCC	0.05	0.04	1.8	0.05
CTGCC	0.02	0.03	0.7	0.5
CTTCC	0.02	0.02	1.4	0.4

*Definition of abbreviations:* OR = odds ratio; PGD = primary graft dysfunction.

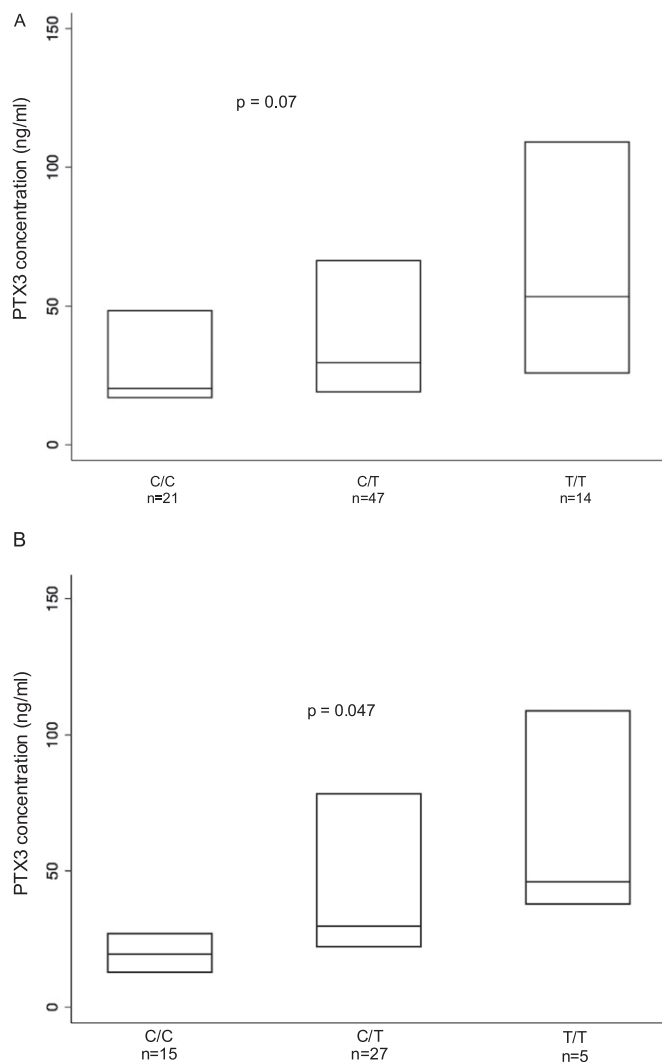
ORs for PGD for individual haplotypes are based on logistic regression controlling for population stratification, using principal component analysis, use of cardiopulmonary bypass, and preoperative pulmonary diagnosis. The alleles encoded by the identified risk single-nucleotide polymorphisms, rs2120243 and rs2305619, are the first two alleles in block 2; the risk alleles are A and T, respectively.

### DISCUSSION

In a large diverse cohort of lung transplant recipients, we demonstrated two SNPs in *PTX3* that were significantly associated with PGD after transplantation. The haplotypes defined by PGD-associated SNPs were also significantly associated with PGD after lung transplantation. Variation in one SNP, rs2305619, was also associated with plasma *PTX3* concentration at baseline and 24 hours after transplantation in lung transplant recipients with IPF. We used a carefully defined phenotype for PGD that is widely accepted in the literature (27, 30, 39). Elevated plasma levels of the protein product of the *PTX3* gene have been associated with PGD (14). The high-risk SNPs identified in *PTX3* are in strong LD and are associated with a significant difference in *PTX3* protein plasma levels, suggesting that PGD-associated SNPs or their LD partners may be functional. Our results are consonant with previous studies demonstrating associations between genetic variation in other innate immune genes with acute cellular rejection and bronchiolitis obliterans syndrome after lung transplantation (40–44).

Genetic variation in *PTX3* is likely important in the development of PGD and may lead to functional differences in innate immune activity. Genetic variation in *PTX3* has previously been associated with altered susceptibility to *Pseudomonas aeruginosa* colonization in patients with cystic fibrosis and altered pulmonary tuberculosis risk in West Africans (45, 46). Our identification of a *PTX3*–PGD association provides evidence to support the significance of altered innate immune activation in the development of PGD. We have previously demonstrated that elevated *PTX3* concentrations after transplantation were associated with PGD in IPF transplant recipients (14). We have extended our understanding of the association between innate immunity and PGD by demonstrating the association of genetic variation in *PTX3* with PGD and also by highlighting the association of the genetic variation with changes in plasma *PTX3* concentrations. SNP level variation in *PTX3* may explain some of the variance in post-transplantation *PTX3* plasma concentrations, although the results are preliminary.

The region of *PTX3* demonstrating association with PGD spanned the 5' promoter region (rs2120243) and the first intron (rs2305619). Variation at these sites may alter transcriptional regulation, which might explain the variation in circulating *PTX3* plasma levels observed in subjects with IPF. This is consistent with the observation that the *PTX3* promoter increases gene transcription in response to the proinflammatory mediators



**Figure 3.** Box plot of plasma pentraxin-3 (PTX3) concentration 24 hours after transplantation stratified genotype at rs2305619 locus. (A) Eighty-two patients with *PTX3* genotyping and plasma concentration measurements. (B) Forty-seven patients with a preoperative diagnosis of idiopathic pulmonary fibrosis (IPF) with *PTX3* genotyping and plasma concentration measurements. Each horizontal line indicates median concentration. The upper and lower limits of each box indicate the interquartile range. The *P* value reported is from nonparametric test for trend.

tumor necrosis factor- $\alpha$  and IL-1 $\beta$  and binding of the transcription factor NF- $\kappa$ B (25). Alternatively, variation in the 5' and first intronic region might result in abnormal splicing, or altered translational dynamics in the setting of acute ischemia-reperfusion. Alternatively spliced isoforms of PTX3 have not been reported to date. It is equally possible that these SNPs merely tag an untyped functional variant. Our genotyping was designed to test the reported coding variants in *PTX3*, but three of four known coding SNPs were rare in our population. The only common exonic SNP, rs3816527, displays moderate LD with the PGD-associated SNPs but did not itself demonstrate association with the PGD phenotype, perhaps because of low MAF. Given the high LD observed across *PTX3*, it may be necessary to pursue further sequencing and *in vitro* promoter assays, including fine mapping and mutagenesis studies, to more fully assess functionality.

Small-molecule and monoclonal antibody innate immune modulators are under investigation in models of acute lung injury,

lentiviral infection, and inflammatory disorders (20, 47, 48). Eritoran, a small-molecule antagonist of TLR4, an upstream mediator of PTX3 production, is currently under investigation for treating severe sepsis (49). The potential role of therapies aimed at mitigating or preventing PGD through modification of host innate immune responses might be the subject of future trials. Proper modulation of PTX3 levels and activity are likely key to normal function of the innate immune responses to infection and inflammation, which may be particularly relevant for an injury response such as PGD. In *PTX3* knockout mice, PTX3 deficiency was associated with more severe LPS-induced experimental lung injury whereas in wild-type mice, PTX3 overexpression was strongly associated with LPS-induced lung injury (19, 20). Differences in the timing and magnitude of PTX3 generation and release may explain some of these differences. Given the evidence for a potential role played by transcriptional regulation in the association between genetic variation in *PTX3* and altered susceptibility to PGD, genotype may be an important consideration in future trial design for innate immune modulators.

We have previously demonstrated that post-transplantation biomarker profiles differ across pretransplantation diagnostic categories and have hypothesized that cellular pathways leading to PGD may be dependent on pretransplantation diagnosis (4, 14). On the basis of the observed correlation of genetic variation in *PTX3* and PTX3 plasma concentrations in patients with IPF, there may be a genetic underpinning to these differences. There is also expanding evidence for the role played by innate immune mediators, including CXCL17, TLRs, and surfactant proteins, in the pathogenesis of interstitial lung diseases (50–54). The role of PTX3 and genetic variation in innate immune genes in the development of pulmonary fibrosis and the interplay between fibrotic lung disease and post-transplantation PGD are areas of future study.

There are several limitations to our study. The *PTX3* SNP–PGD association has yet to be confirmed in a replication cohort. Supporting the veracity of the *PTX3*–PGD association are the previous association of PTX3 plasma levels with PGD, the single-gene design of our genetic association study, and the regulation of PTX3 plasma level by genotype. We focused on the relationship between *PTX3* genotype and circulating PTX3 among subjects with IPF because subjects with IPF demonstrate the most variability in post-transplantation PTX3 concentrations. It will be important to assess the association between *PTX3* polymorphisms and plasma protein levels in patients with other preoperative diagnoses as well as in the alveolar compartment.

As this was a candidate gene association study, we evaluated the influence of variation in *PTX3* alone. There may be important variation in other innate immune genes, including TLRs, that impact the risk of developing the PGD phenotype, and different innate immunity loci may interact to modify PGD risk. Furthermore, it may be that PGD is a phenotype influenced by both donor and recipient genotype. Our analysis focused on allograft recipients and was essentially blinded to the potential influence of donor innate immune responses. Further work to elucidate the loci or environmental stimuli regulating the expression of PTX3 after transplantation is warranted.

In summary, we identified an association between polymorphisms in *PTX3* and risk of PGD after lung transplantation. Furthermore, we identified a correlation between a PGD-associated *PTX3* SNP and pre- and post-transplantation PTX3 plasma concentrations in patients with IPF. Improved mechanistic understanding of the genetic and clinical risk factors for PGD may allow improved prognostication pretransplantation and may aid in the development of personalized post-transplantation therapy tailored to an individual recipient's risk.

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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