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Glutathione-S-transferase P1 may predispose children to a decline in pulmonary function after stem cell transplant

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Abstract

RATIONALE—Pulmonary complications after hematopoietic stem cell transplant (SCT) are associated with increased mortality. Genetic markers for those at risk for pulmonary impairment post-SCT have not been widely investigated.

METHODS—Forty-nine patients were retrospectively selected from a single institution's biorepository with linked clinical data. All subjects performed pre-SCT PFTs. Genotyping was conducted using the Infinium Exome-24 BeadChip. Four single nucleotide polymorphisms (SNPs) were selected (rs1800871, rs1695, rs1800629, rs12477314) and evaluated for association with PFT parameters as change over time from baseline. Associations between SNPs and PFT parameters were assessed and adjusted for the following confounding variables: age, gender, and race.

RESULTS—Using the recessive genetic model, patients with one or two minor alleles for the *glutathione S-transferase P1* (*GSTP1*) SNP rs1695 had a lower decline in FEV_1 and $FEF_{25–75}$ at one-year post-SCT compared to patients who were homozygous for the ancestral allele (adjusted p-values <0.01 and 0.02, respectively). No other SNPs were significantly associated with other PFT parameters.

CONCLUSIONS—Our findings suggest that *GSTP1* genotype may be associated with lung function during the first year post-SCT. Identifying and investigating genes that predispose patients to pulmonary complications after SCT may allow for more personalized patient management based on pre-emptive genetic testing. The *glutathione S-transferase* gene merits further investigation.

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Introduction

Hematopoietic stem cell transplantation (SCT) has been increasingly used in pediatric patients to treat both malignant and non-malignant diseases. Advances in supportive care and techniques that prevent complications of SCT have allowed for treatment of a wider variety of diseases with improved outcomes. For supportive care, we have expanded our use of prophylactic antimicrobial therapy in this population. More targeted approaches to therapy, including decreased use of total body irradiation, have been implemented. Furthermore, improved skills in the care of critically ill pediatric patients have increased patient post-SCT survival. Regardless of these advances, pulmonary complications after SCT commonly occur and are a significant source of post-SCT morbidity and mortality.

Pulmonary complications after SCT have been estimated to occur in 40–60% of patients in adult studies, which can be separated into infectious and noninfectious etiologies (1). In a recent pediatric study, noninfectious pulmonary complications were reported to occur in 28% of patients, and survival at 10 years was 76% in patients without early pulmonary complications in comparison to 18% in patients with early pulmonary complications (2). Early complications were defined as those occurring within the first 100 days post-SCT. The predominant pulmonary complication observed was idiopathic pneumonia syndrome (IPS). Pleural effusion, pulmonary hemorrhage, reactive airway disease, bronchiectasis, and bronchiolitis obliterans were other noted pulmonary complications after SCT.

Furthermore, lung function abnormalities noted on pulmonary function tests (PFTs) have been documented in patients after SCT. Decreased diffusion capacity is the most common abnormality identified, followed by restriction. Diffusion and restrictive impairments have been reported to improve with time (3). Restriction often occurs with IPS and has been linked to acute graft-versus-host disease (GVHD) (4). Bronchiolitis obliterans, the most concerning pulmonary complication, causes progressive pulmonary compromise. Obstructive impairment as noted in bronchiolitis obliterans has been linked to chronic GVHD.

Previous studies have attempted to create models that predict pulmonary outcomes after SCT based on pre-SCT PFTs. A large adult study in 2005 demonstrated that a decrease in all lung function parameters pre-SCT was associated with a stepwise increase of developing early respiratory failure and death post-SCT (5). This study also constructed a “Lung Function Score” (LFS), which correlated well with risk of early respiratory failure and death. The score was calculated using forced expiratory volume in one second (FEV_1) and diffusing capacity (DL_{CO}). In 2010, a similar study was completed in a smaller cohort of pediatric patients, and the LFS was validated in this population (6). In spite of studies such as these, no scoring system for pulmonary risk is universally used in SCT patients prior to transplant.

Given the impact of pulmonary complications on survival, identifying patients who are at risk has the potential to impact prognosis and improve patient outcomes. However, using PFT data alone to predict post-SCT pulmonary complications provides only general knowledge of those who are at risk for pulmonary complications post-transplant.

Increasingly, the desire for personalized medicine has driven evaluation of genetic variation in predicting disease outcomes. Differences in single nucleotide polymorphism (SNPs) have been investigated as modulators of common pulmonary diseases such as asthma (7, 8). Our objective was to compare lung function indices over time to four selected SNPs previously reported to be associated with lung disease after SCT or etiologies leading to restrictive and/or obstructive pulmonary impairment. The overall goal of this study was to identify SNPs, and their corresponding genes, that may be associated with pulmonary complications after SCT. We hypothesized that genes related to obstructive and restrictive changes in other underlying lung disease etiologies would be associated with similar impairment in PFTs after SCT.

Materials and Methods

Patients who underwent SCT from 2004 to 2010 at Riley Children's Hospital were retrospectively selected for analysis (Indianapolis, IN) (Table 1). A total of 98 patients who underwent SCT were included in the study cohort. Three patients were excluded who underwent autologous SCT. Of the remaining 95 patients, 62 completed PFTs prior to SCT (65%). Of these 62, 49 had samples available for exon SNP genotyping, which was completed using a PCR-based assay.

The Infinium Exome-24 BeadChip was used to analyze SNPs of functional exonic variants from patient exomes. The BeadChip consists of greater than 240,000 markers that represent European, African American, Chinese, and Hispanic populations. DNA samples from the subjects were obtained from left over clinical samples in the medical genetics laboratory, for which consent had been previously obtained for storage and further analysis. DNA was extracted from whole blood using the Qiagen DNA Blood Mini Kit and quantified using Fisher Scientific's Quant-iT BR dsDNA reagent kit with the Quant-iT fluorometer. All samples were collected prior to SCT such that no donor DNA was represented in the samples. The Indiana Retrospective HSCT Biobank as well as this sample and data utilization project were reviewed and approved by the Indiana University School of Medicine Institutional Review Board (IRB).

Lung function tests were performed based on American Thoracic Society/European Respiratory Society criteria. Spirometry, plethysmography and diffusing capacity were evaluated for all 49 patients. All parameters were assessed as a change from baseline, with the baseline being the PFTs obtained prior to SCT. Changes in FEV_1, FEV_1/FVC (forced vital capacity), and forced expiratory flows between 25% and 75% of forced vital capacity ($FEF_{25–75}$) were assessed. Total lung capacity (TLC) was used to identify restrictive change. Diffusion capacity was adjusted for hemoglobin (DL_{co}). All PFTs were normalized for age, gender, weight, and height using z-scores.

Available follow up PFTs were collected for the 49 patients. Baseline, or pre-SCT, PFTs were obtained an average of one month, but no more than two months, prior to SCT. Seventeen patients died or were otherwise unable to complete follow-up PFTs. Thirty-one patients completed post-SCT PFTs at one year; one patient did not complete PFTs until two

years post-SCT. Follow up PFTs at two, three, four, and five years were also recorded, but were less consistently performed.

Based on a review of the current literature using Ovid, four SNPs were selected within the exomes of four distinct genes: rs1800629 (*tumor necrosis factor α*, or *TNFα*), rs1800871 (*interleukin 10*, or *IL-10*), rs1695 (*glutathione-s-transferase P1*, or *GSTP1*), and rs12477314 (*Histone deacetylase 4*, or *HDAC4*). Key phrases searched in the Ovid were "single nucleotide polymorphism," with either "pulmonary restriction" or "pulmonary obstruction." Articles that described specific SNPs in the exome were used. These SNPs were selected because they have been implicated in modifying severity of lung diseases which cause restriction and obstruction such as asthma and α_1-antitrypsin deficiency (7, 8, 9). Each SNP has a known "ancestral allele," referred to as the "wild type" in animal models, which is the more common nucleotide found in the population. There is also a documented variant allele, which we refer to as the "minor allele."

Once SNPs were selected, each SNP was analyzed with three different models to ensure that the different combinations were all tested: a dominant model, a recessive model, and an additive model. In the dominant model, the group of individuals with two minor alleles was compared to a group of subjects having one or two of the ancestral alleles, considered the dominant group. In the recessive model, individuals with one or both minor alleles were grouped together, considered the recessive group, and compared to those having only ancestral alleles. In the additive model the number of minor alleles were treated as an ordinal outcome, with participants being categorized as having 0, 1, or 2 minor alleles.

ANOVA models were used to evaluate for associations between each SNP model and PFT outcomes as change from baseline to each follow-up time point. ANCOVA models were used to adjust for possible confounding variables: age, gender, and race. All analytic assumptions were verified and all analyses were performed using SAS v9.4 (SAS Institute, Cary, NC). Repeated measures analyses were not performed, due to low sample sizes at the later follow-up periods. P values were corrected for multiple comparisons. Since four SNPs were assessed, the standard P-value of 0.05, which normally designates significance, was adjusted to 0.0125. Z-scores for spirometry were calculated with the SAS GLI macro, using the Global Lungs Initiative algorithms (10, 11). Z-scores for DL_{co} and TLC were calculated using published references standards (12, 13, 14).

Results

Using the recessive genetic model, patients who were homozygous for the ancestral allele of the *glutathione-S-transferase P1* (*GSTP1*) SNP (rs1695) had a larger decline in FEV_1 (adjusted p-value < 0.01) and $FEF_{25–75}$ (adjusted p-value = 0.02) values at one-year post-SCT compared to patients with one or two minor alleles (Figure 1). This association was not significant in subsequent post-SCT years. Using the adjusted P-value of 0.0125 for significance, $FEF_{25–75}$ becomes narrowly outside the area of significance using the recessive model. FEV_1 remains significant. No other SNPs were significant on statistical analysis in comparison with other PFT parameters (Table 2).

Death was divided into death from primary disease and transplant-related mortality. Neither death overall nor transplant-related mortality were significantly associated with any of the SNPs using any genetic model. Of the patients included in this study cohort who died, the average time to death post-SCT was approximately one year (380 days).

Discussion

We report that patients who were homozygous for the ancestral allele of the *GTSP1* SNP rs1695 had a greater decline in lung function at one year after SCT compared to those who had at least one minor allele of the *GTSP1* SNP rs1695. Specifically, FEV_1 significantly declined and there was evidence of airflow limitation with diminished $FEF_{25–75}$ values at one-year post-SCT in those homozygous for the ancestral allele of the *GTSP1* SNP rs1695. Though FVC and TLC decreased post-transplant, the change was not significantly associated with the four identified SNPs. Given this, the decline in FEV_1 and $FEF_{25–75}$ in those homozygous for the ancestral allele of the *GTSP1* SNP rs1695 is more indicative of an obstructive pattern than a restrictive one. Airway obstruction is one of the more concerning findings on spirometry because these findings are often associated with bronchiolitis obliterans.

The association between FEV_1 and *GSTP1* was not demonstrated on the PFTs in subsequent years post-SCT. There are a couple of possible explanations. Unfortunately, follow up after a year was limited in our patient population leading to a smaller sample size for those that completed PFTs at two, three, four, and five years. The data may have been skewed by this smaller sample size. It is also known, however, that pulmonary function in general improves with time after SCT in patients who survive early complications. A retrospective study performed at Riley Hospital for Children in 2012 demonstrated a decline in PFTs (FEV_1 and TLC) 1-year post-SCT, which largely recovered at 2 years post-SCT (15).

The four SNPs selected for this study were chosen because of previous reports demonstrating that they mediate severity of pulmonary disease after SCT or in other underlying etiologies known to cause restrictive and obstructive disease, such as asthma and α_1-antitrypsin deficiency. Each of these follows a common disease pathway, yet there are a wide variety of clinical presentations, suggesting variability in other genetic modifiers. From the limited literature available in this area, we chose the SNPs within the following genes: *TNFα*, *IL-10*, *HDAC4,* and *GSTP1*.

Previously, *TNFα* was assessed in a study of cytokine expression in bronchoalveolar lavage samples from patients with pulmonary complications after SCT (16). *TNFα* expression was demonstrated to be significantly increased in patients with both infectious and non-infectious pulmonary complications, and this elevation correlated with a poorer prognosis overall. *IL-10* was demonstrated to be a genetic modifier for severity of chronic obstructive pulmonary disease (COPD) in patients with α_1-antitrypsin deficiency (9). Finally, a preliminary study revealed that *HDAC4* genetic variation may be associated with the development of asthma and COPD as patients age (17). Although all three of these genes seemed like promising candidates for this study, none were shown to be significantly associated with PFT outcomes in our patient population.

As stated, *Glutathione-S-transferase P1* (*GSTP1*) was significantly associated with lung function in our patient population. *Glutathione-S-transferase* is a superfamily of metabolic enzymes involved in the conjugation of reduced glutathione (18). These reactions are generally considered detoxifying and protective from cytotoxic agents, but they have also been noted to create intermediate metabolites that are more toxic than their precursors (19). In addition, these enzymes are known to metabolize chemotherapeutic agents and are often over expressed in tumors that are refractory to chemotherapy. *GSTP1* is widely found in human epithelium, especially the lungs, esophagus, and placenta. *GSTP1* is most abundantly expressed in the alveoli, alveolar macrophages, and bronchioles and has been studied for its role in ameliorating the effects of air pollution, tobacco smoke, and α_1-antitrypsin deficiency (7, 8, 20).

The SNP that we investigated within the *GSTP1* gene is a substitution of adenosine (the ancestral allele) for guanine (the minor allele) at position 105. This leads to a missense mutation and causes the amino acid isoleucine to be replaced by valine. In a 2004 study in Taiwan, patients coding for isoleucine at this site were demonstrated to be at increased risk of developing asthma when exposed to air pollution. These findings correlate well with our results, demonstrating that the ancestral allele leads to diminished FEV_1 values and more airflow limitation in SCT patients one year post-transplant. In contrast, a 2006 publication reported a higher susceptibility to asthma in children who were exposed to tobacco smoke and had the minor allele, which codes for valine, at the 105 position. Though these are conflicting reports, they emphasize the importance of GSTP1 in modifying disease severity and demonstrate the need for further research into the mechanism of action of *GSTP1*.

In our study population, there was no correlation identified between *GSTP1* and transplant-related mortality. The average time of death in this study, however, was around one year. This correlates chronologically with decrease in FEV_1 and $FEF_{25–75}$ related to *GSTP1*. Given the fact that not all transplant-related mortality was secondary to pulmonary complications, it is not surprising that the two are not strongly correlated.

Further investigation of *GSTP1* needs to be performed to assess its utility as a biomarker for pulmonary complications after SCT. In this study, patients with one or more minor allele for *GSTP1* had better PFTs one-year post-SCT. One possible mechanism of action for this finding is that the minor allele leads to increased function of the *GSTP1* gene; thereby, providing more protection against cytotoxic agents administered in preparation for and during SCT. Murine models have confirmed that the pro-inflammatory state following SCT leads to an increased production of reactive oxygen species (21, 22). *GSTP1* may be an important modulator of these effects after transplant.

Identifying best management approaches that decrease the morbidity and mortality of SCT is critical. Previous studies have suggested that depletion of T cells in the transplant itself provides protection against GVHD and subsequently, serious pulmonary complications (23). This benefit must be weighed against the loss of important graft-versus-leukemia effects as well as the associated increased degree of immunosuppression and prolonged time to immune reconstitution when T cell depletion is performed. Newer therapies such as Alemtuzumab, or Campath, are being implemented to suppress T and B cells after SCT with

fewer negative side effects than T cell depletion (24). If *GSTP1* genotype is validated as a marker for poor pulmonary outcomes, and patients are found to be at risk prior to transplant, the management of T and B cells pre-SCT and post-SCT is one of many areas of intervention.

Other possible strategies include reducing the intensity of the preparation used for transplant. Specifically, treatments known to have significant pulmonary side effects, such as busulfan and total body irradiation, could potentially be avoided. Finally, other tactics for decreasing pulmonary inflammation such as inhaled corticosteroids could be studied.

This pilot study has several limitations. The initial sample size of patients who underwent SCT during the given time period was larger than the selected population. As noted above, patients were excluded who did not undergo pre-SCT PFTs and exome SNP array PCR analysis. There were 25 patients who were too young to perform baseline PFTs and were excluded. Generally, the patients who did not perform baseline PFTS were those who were less than 5 years of age. In patients who performed pre-SCT PFTs, follow up at one year was excellent unless the patient died or was too sick to perform PFTs.

Our sample size was too small to correct for confounders such as total body irradiation and chemotherapy received prior to SCT. In order to ameliorate this issue, each patient's PFT parameters were compared to his or her own personal baseline PFTs just prior to transplant. The change from baseline was compared between patients due to the variability in pulmonary impairment prior to SCT. However, due to the small sample size, a more restrictive change post-SCT in those homozygous for the ancestral allele of the *GTSP1* SNP rs1695 may not have been fully delineated.

After correcting for multiple comparisons, the association between FEV_1 and the *GSTP1* SNP remained significant at one year; however, $FEF_{25–75}$ did not have a strong enough association to retain its significance. A decrease in FEV_1 without a significant decreased in TLC, coupled with the airflow limitation noted in the $FEF_{25–75}$ values as seen in our study, is suggestive of airway obstruction, one of the more concerning pulmonary complications noted after SCT. A mild restrictive change is often seen post-SCT. In our study, patients who were homozygous for the ancestral allele of *GSTP1* were observed to develop a more accelerated decline in FEV_1 and $FEF_{25–75}$ 1 year post-SCT.

In comparison to the other three SNPS that were investigated in this study, *GSTP1* stood out as an excellent candidate for further research in regards to SCT. As we move towards an era of personalized medicine in which genetic variation is widely assessed and applied clinically to patients, identifying genes becomes increasingly important. *GSTP1* certainly merits further investigation.

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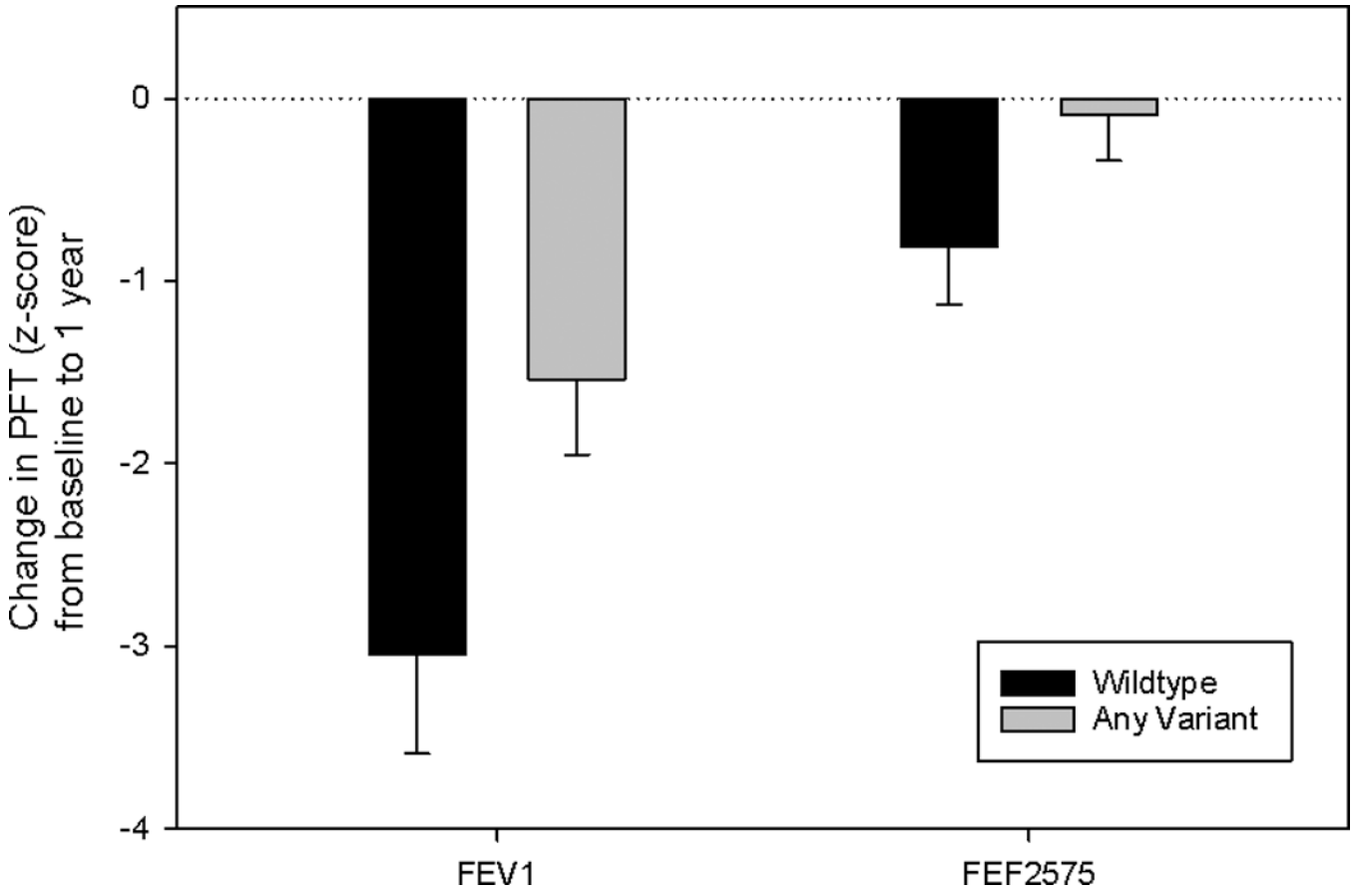

Figure 1.

Table 1

Demographics

Age (years)	12.4 (4.3)
Height (cm)	150.1 (20.7)
Weight (kg)	49.3 (19.2)
Sex	
Male	27 (55%)
Female	22 (45%)
Ethnicity	
Black	4 (8%)
Hispanic	2 (4%)
White	43 (88%)
Reason for SCT	
Malignant disease	37 (75.5)
Non-malignant disease	12 (24.5)
Baseline FEV1 (z-score)	−0.25 (1.4)
Baseline FVC (z-score)	−0.36 (1.4)
Baseline FEV1/FVC (z-score)	−0.07 (1.2)
Baseline FEF2575 (z-score)	−0.25 (1.3)
Baseline DLCO (z-score)	−2.57 (2.2)
Baseline TLC (z-score)	−2.23 (0.6)
Busulfan	15 (30.6%)
TBI	30 (61.2%)

Values are means (standard deviation) for continuous variables and frequency (percent) for categorical variables.

Table 2

Recessive Model for the *GSTP1* SNP

			FEV_1	FVC	Dlco	FEF_{25-75}	FEV1/FVC	TLC
Decline in PFT z-score at each year compared to baseline (pre-SCT)	1-year	W/W (n=9)	3.05 (0.54)	1.89 (0.56)	0.05 (0.93)	0.81 (0.32)	−0.09 (0.35)	0.19 (0.10)
		W/V and V/V (n=23)	1.54 (0.41)	1.08 (0.42)	−0.54 (0.79)	0.09 (0.25)	−0.27 (0.26)	0.11 (0.08)
		Adj P-value	0.0052	0.1234	0.4402	0.0205	0.5683	0.3358
	2-year	W/W (n=5)	1.17 (1.11)	1.07 (1.13)	0.09 (0.92)	0.24 (0.87)	0.30 (0.68)	0.06 (0.10)
		W/V and V/V (n=11)	0.76 (0.92)	0.84 (0.94)	0.03 (0.65)	0.06 (0.72)	0.03 (0.57)	0.06 (0.09)
		Adj P-value	0.6057	0.7750	0.9620	0.7761	0.5900	0.9360
	3-year	W/W (n=2)	2.13 (0.79)	−0.26 (0.94)	−2.56 (1.30)	0.41 (0.59)	0.20 (0.57)	0.36 (0.19)
		W/V and V/V (n=10)	0.95 (0.59)	−0.93 (0.70)	−2.76 (0.91)	−0.44 (0.44)	−0.73 (0.42)	0.15 (0.20)
		Adj P-value	0.3333	0.6340	0.9210	0.3467	0.2922	0.5513
	4-year	W/W (n=3)	0.61 (0.69)	0.11 (0.22)	0.46 (1.23)	0.50 (0.86)	1.13 (0.92)	−0.18 (0.04)
		W/V and V/V (n=5)	1.10 (0.75)	1.31 (0.23)	0.54 (1.10)	−0.41 (0.93)	−0.41 (1.00)	0.28 (0.03)
		Adj P-value	0.5998	0.0196	0.9669	0.4511	0.2631	0.0651
	5-year	W/W (n=0)	n/a	n/a	n/a	n/a	n/a	n/a
		W/V and V/V (n=5)	0.09 (0.63)	0.16 (0.73)	−1.90 (1.74)	−0.10 (0.15)	−0.36 (0.35)	0.25 (0.26)
		Adj P-value	n/a	n/a	n/a	n/a	n/a	n/a