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Genome-wide association study evaluating single-nucleotide polymorphisms and outcomes in patients with advanced stage serous ovarian or primary peritoneal cancer: An NRG Oncology/ Gynecologic Oncology Group study☆,,☆☆

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Conflict of interest statement

The authors report the following conflicts of interest: K. Moore reports advisory board participation for Astra Zeneca, Clovis, Immunogen, Tesaro, Genentech/Roche, Advaxis, VBL Therapeutics and Janssen. L. van Lee reports clinical trial grants from Astra Zeneca and Morphotek. K Tewari reports speakers bureau participation for Genentech/Roche, Merck, Astra Zeneca, Vermillion, and Clovis. He also reports steering committee participation with Mateon and consultancy with CARIS. R.Wenham reports speakers bureau participation for Genentech/Roche and Janssen as well as steering committee participation for Tesaro. M Bookman reports advisory board participation with Astra Zenca, Tesaro, Endocyte, Pfizer and Clovis. He reports steering committee participation for Genentech/Roche, Mateon and Abbvie and employment with McKesson Specialty Health and USOR. D. Tritchler, K. Kaufman, H. Lankes, M Quinn, A Berchuck, F Backes, R Lee, J Kesterson, D Armstrong, T Krivak and M Birrer have nothing to disclose.

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Abstract

Objective—This study evaluated single nucleotide polymorphisms (SNPs) associated with progression free (PFS) and overall survival (OS) in patients with advanced stage serous EOC.

Methods—Patients enrolled in GOG-172 and 182 who provided specimens for translational research and consent were included. Germline DNA was evaluated with the Illumina's HumanOMNI1-Quad beadchips and scanned using Illumina's iScan optical imaging system. SNPs with allele frequency > 0.05 and genotyping rate > 0.98 were included. Analysis of SNPs for PFS and OS was done using Cox regression. Statistical significance was determined using Bonferroni corrected *p*-values with genomic control adjustment.

Results—The initial GWAS analysis included 1,124,677 markers in 396 patients. To obtain the final data set, quality control checks were performed and limited to serous tumors and self-identified Caucasian race. In total 636,555 SNPs and 289 patients passed all the filters. The pre-specified statistical level of significance was $7.855e^{-08}$. No SNPs met this criteria for PFS or OS, however, two SNPs were close to significance (rs10899426 *p*-$2.144e^{-08}$) (rs6256 *p*-$9.774e^{-07}$) for PFS and 2 different SNPs were identified (rs295315 *p*-$7.536e^{-07}$; rs17693104 *p*-$7.734e^{-07}$) which were close to significance for OS.

Conclusions—Using the pre-specified level of significance of 1×10^{-08}, we did not identify any SNPs of statistical significance for OS or PFS, however several were close. The SNP's identified in this GWAS study will require validation and these preliminary findings may lead to identification of novel pathways and biomarkers.

Keywords

Genome-wide association; Advanced stage serous ovarian; Primary peritoneal cancer

1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic oncology malignancy. In 2017 there will be approximately 22,440 newly diagnosed cases leading to 14,080 deaths in the United States. The overall high mortality seen in patients with EOC may be in large part due to 70% being diagnosed at an advanced stage [1]. Treatment of patients with advanced stage EOC includes a combination of platinum based chemotherapy and cytoreductive surgery [2,3]. A majority of patients will respond to this aggressive approach and achieve complete clinical remission. However, approximately 20% of patients will have platinum resistant disease and progress within six months of primary therapy. Patients who relapse within six months of completing initial treatment are classified as being primary platinum-resistant and have a poor response to secondary treatment with response rates of 7–12% [4–6]. These patients are often not just resistant to platinum but resistant to all cytotoxic therapies making them chemotherapy resistant. Historically, patients with primary platinum-resistant disease have an estimated overall survival of 12 months from the time platinum resistance is identified [7]. Patients who relapse >6 months following primary platinum therapy are termed platinum-sensitive and have better response to secondary platinum-based chemotherapy with response rates of 30–60% depending on the initial platinum free interval. Eventually, those patients with platinum-sensitive disease will develop resistance to platinum therapies and can be classified as acquired platinum-resistant [4–6].

Mechanisms that underlie resistance to platinum chemotherapy are most likely multi-factorial [8,9]. Broadly, resistance to anticancer platinum agents can be classified into two categories: first, platinum compounds may not reach intracellular levels needed for response due to inadequate delivery; and second, increased DNA damage repair mechanisms may lead to increased viability of tumor cells, and hence resistance [10,11]. For example, carboplatin works by binding to DNA and forming DNA adducts leading to intrastrand or interstrand cross-links which disrupt the structure of the DNA molecule, leading to steric changes in the helix. Alteration in the structure of the DNA molecule leads to cellular DNA damage recognition and repair which can result in the continued viability of the cell resulting in platinum-resistance [12].

Changes in front line schedule and delivery of chemotherapy, better supportive care and increased availability of effective agents for use at the time of recurrence have resulted in modest improvements in overall survival. [13] The development of novel targeted agents, germline BRCA screening, and emphasis on personalized therapies is starting to change the landscape for managing patients with ovarian cancer.

Factors that determine the aggressiveness of cancer as well as response to chemotherapy may be related to germ line genetic variants other than those related to homologous recombination, which has garnered the most interest and resulted in development of targeted therapies in the form of PARP inhibitors. GWAS studies performed by the international

ovarian cancer association consortium (OCAC) have identified 18 common SNPs associated with ovarian cancer risk [14]. Five additional common ovarian cancer risk SNPs were identified in a meta-analysis of cancer GWAS studies [15]. Studies using GWAS have also been performed to identify common genetic variants that impact progression free and/or overall survival (PFS and OS) of ovarian cancer. An OCAC study by Bolton et al. revealed 2 SNPs at 19p13.11 (rs8170, rs2363956) that were associated with survival in an initial replication, but not in a second phase of replication [16]. Johnatty et al. recently published a large OCAC GWAS of ~2.8 million genotyped and imputed SNPs in 2900 ovarian cancer cases. None of the SNPs reached genome wide significance, but three of the top five loci for survival were associated with long non-coding RNAs [17].

This study used GWAS to identify common SNPs associated with PFS and OS among patients diagnosed with advanced stage epithelial ovarian cancer treated on Gynecologic Oncology Group (GOG) protocols 172 and 182. Identification and validation of prognostic and predictive SNPs for PFS and OS could provide candidate SNPs for prospective validation in other GOG phase III trials.

2. Patient and methods

Study population: Patients enrolled on GOG 172 and 182 who had genomic DNA available. DNA was extracted from WBCs recovered from whole blood using the Puregene DNA purification kit (GentraSystems Inc., Minneapolis, MN) or the ABI PRISM 6100 Nucleic Acid Prep Station (Applied Biosystems Inc., Foster City, CA). All studies received approval from their respective human research ethics committees, and all participants provided written informed consent.

2.1. GOG 172

Patients enrolled on GOG protocol 172 had stage III EOC with residual disease ≤1 cm following primary cytoreductive surgery (pCRS) and a GOG performance status of 0–2 and normal blood counts. Patients were randomly assigned to receive either 135 mg/m^2 IV paclitaxel over 24 h day 1 followed by 75 mg/m^2 of IV cisplatin day 2 or 135 mg/m^2 of IV paclitaxel over 24 h day 1 followed by 100 mg/m^2 of intraperitoneal (IP) cisplatin day 2 and 60 mg/m^2 of IP paclitaxel day 8. Six total cycles given at 21 days intervals were planned. The primary study endpoints were PFS and OS which were measured from the date of randomization. Full details of the eligibility and results are available in the published manuscript [18].

2.2. GOG 182

Patients enrolled on GOG protocol 182 had stage III or IV EOC with either ≤ or > 1 cm of residual disease following pCRS. They had GOG performance status of 0–2, normal blood counts and no baseline neuropathy greater than grade 1. Patients were randomized into 1 of 5 arms each of which included 8 cycles of triplet or sequential doublet chemotherapy and provided a minimum of 4 cycles of carboplatin and paclitaxel IV. OS and PFS were assessed from the date of randomization. The primary endpoint for this study was overall survival

(OS). Details of the treatment arms, modifications, statistical analysis and results are available in the published manuscript. [19]

2.3. Single nucleotide polymorphism analysis

Illumina's Human OMNI1-Quad beadchips (catalog #WG-311-1112) were used. The samples were processed through Illumina's propriety Infinium HD Super Assay using Illumina's propriety reagents. 200 ng of genomic DNA was shipped dried down and then re-suspended, DNA was amplified with standard whole genome amplification. Samples were fragmented and purified with an isopropanol precipitation, re-suspended in Illumina's resuspension buffer, denatured and the fragmented strands were hybridized onto 50-mer oligos attached to the beads on the beadchip overnight. A single-base extension was performed in conjunction with staining in order to determine the base at the position of inquiry. Beadchips were washed and coated with a sealant. The chips were finally scanned individually using Illumina's iScan optical imaging system.

2.4. SNP quality control

93 individuals were classified as genetic outliers and removed. The first three calculated principal components were used to identify genetic outliers. This paper defined the genetic outliers as any sample that was plus or minus 5 standard deviations from the mean of the first three principal components. All subjects self- identified as Caucasian. To obtain the final data set, several quality control checks were performed. Filters for SNPs with call rate >98% and minor allele frequency >5%, sample genotyping rate >98% and Hardy Weinberg equilibrium threshold of $1e^{-08}$ were implemented. In total 636,555 markers and 289 patients passed all filters. After quality analysis and application of filters the final analysis included 289 women, all Caucasian with epithelial ovarian cancer evaluating 636, 555 SNP's.

2.5. Statistical analysis

SNP variables are coded as allelic dosage. All *p*-values reported and displayed in figures are adjusted by the appropriate genomic inflation factor. Survival analyses are based on the proportional hazards regression model, controlling the effect of population stratification by including three principal components in the model. Also included in the survival models were residual disease status (yes/no). The Bonferroni threshold for genome-wide significance is $7.855e^{-08}$.

3. Results

3.1. Overall survival (OS)

Demographic and tumor characteristics for the patients whose samples were included in this analysis are reported in Table 1. The proportional hazards regression model for each SNP included allelic dosage, three principal components representing population substructure and residual disease status. The genomic inflation factor for these analyses was 1.036 and all *p*-values were correspondingly adjusted.

The Manhattan plot for the OS *p*-values is shown in Fig. 1. The horizontal red line at the top of the plot displays the Bonferroni threshold. None of the tests exceed the cutoff, so none attain genome-wide statistical significance.

Supplementary Fig. 1 (supplemental figure) is a quantile-quantile plot comparing the OS test statistics to the values expected under the null distribution. The red line represents the equality of observed and expected values. This plot suggests a slight bump at moderate, non-significant levels, which are possibly effects not discoverable due to low power.

Although none are significant, we list the top ten OS SNP effects which are candidates for inclusion in a higher powered study (Table 2). Ten SNPs were identified for OS; rs295315 ($p = 7.536e^{-07}$) chromosome (Ch) 3, rs17693104 ($p = 7.734e^{-07}$) Ch 10, rs868767 ($p = 1.826e^{-06}$) Ch 3, rs2050203 ($p = 3.904e^{-06}$) Ch20, rs11621975 ($p = 5.186e^{-06}$) Ch 14, rs17548007 ($p = 5.288e^{-06}$) Ch 12, rs202280 ($p = 6.246e^{-06}$) Ch 8, rs1564271 ($p = 8.683e^{-06}$) Ch 10, rs10899426 ($p = 9.003e^{-06}$) Ch 11, rs4618572 ($p = 9.182e^{-06}$) Ch 6. All *p*-values are adjusted for genomic inflation. SNP rs17693104 is located in the SDH2D4B gene and rs1564271 is located in the PDSS1 gene.

3.2. Progression-free survival (PFS)

The proportional hazards regression model for each SNP included allelic dosage, three principal components representing population substructure and residual disease status. The genomic inflation factor for these analyses was 1.102 and all *p*-values were correspondingly adjusted.

The Manhattan plot for the PFS *p*-values is shown in Fig. 2. The horizontal red line at the top of the plot displays the Bonferroni threshold. None of the tests exceed the cutoff, so none attain genome-wide statistical significance.

Supplementary Fig. 2 (supplemental figure) is a quantile-quantile plot comparing the PFS test statistics to the values expected under the null distribution. The red line represents the equality of observed and expected values. This plot suggests a slight bump at moderate, nonsignificant levels, which are possibly effects not discoverable due to low power.

Although none are significant, we list the top ten PFS SNP effects which are candidates for inclusion in a higher powered study (Table 3). The ten SNPS with largest estimated effect on PFS are rs10899426 ($p = 2.144e^{-07}$) Ch 11, rs6256 ($p = 9.774e^{-07}$) Ch 11, rs10832063 ($p = 4.534e^{-06}$) Ch 11, (rs10500780 $p = 4.634e^{-06}$) Ch 11, rs281358 ($p = 1.137e^{-05}$) Ch 17, rs17163580 ($p = 1.173e^{-05}$) Ch 1, rs17011846 ($p = 1.173e^{-05}$) Ch 1, rs227147 ($p = 1.381e^{-05}$), rs11782341 ($p = 2.049e^{-05}$), rs7011443 ($p = 2.142e^{-05.}$). All *p*-values are adjusted for genomic inflation. The genes involved include PTH, BTBD10, DISP1, UTS2, TUSC3, and CSMD1.

4. Discussion

This study combines prospectively collected biospecimens from two randomized phase III front line EOC trials in an effort to evaluate the association of germline SNPs with outcome for advanced EOC. These studies provide a well annotated data set that includes clinical,

pathological, treatment, and patient outcome data. Additionally, pathological review was performed by expert gynecologic pathologists to confirm ovarian cancer diagnosis. Patients whose pathology did not pass pathologic review were not included in this analysis. As stated in the methods, to avoid the genetic heterogeneity associated with ethnicity and histology, this analysis was limited to patients with self- reported Caucasian ethnicity. With the combination of excellent genomic and clinical data, this data set allows for GWAS evaluation of genes associated with PFS and OS in patients with advanced stage EOC.

In this GWAS study we did not identify any SNPs that met the Bonferroni threshold for significance for association with either OS or PFS. We did identify 10 candidate SNP's associated with OS and an additional 10 candidate SNPs associated with PFS in patients with advanced stage serous EOC which may be interesting to reconsider in studies with higher power.

4.1. Overall survival

Among the 10 SNPs with potential association with overall survival, none have definitive association with cancer related outcomes. Two SNPs were located near genes; rs17693104 is located near the SH2 containing domain 4b (SH2D4b) on chromosome 10 and rs1564271 is located near the prenyl (decaprenyl) diphosphate synthase, subunit 1 (PDSS1). SNPs near SH2D4b, specifically rs6586111 and rs7915642 do have possible correlation with sensitivity to capecitabine across multiple cancer cell lines [20]. rs1564271 is located near PDSS1, defects of which cause Coenzyme Q deficiency which is associated with myalgic encephalomyelitis/chronic fatigue syndrome but has no association thus far with outcomes in malignancies [21].

Progression Free Survival: SNP rs6256 is located in Ch11 within the PTH gene and does have a functional association with primary hyper-parathyroid syndrome [22]. SNP rs6256 has been evaluated as a risk factor for colon cancer with the hypothesis being that calcium plays a protective role and activates the tumor suppressor gene E-cadherin in human colonic epithelium. Alteration in calcium homeostasis either through the calcium sensing receptor (CaSR) or through variants in PTH might play a role in colon cancer tumorigenesis. A case control study (350 colon cancer cases and 510 controls) was performed in which rs6256 as well as rs1801725 (a variant of the CaSR gene) were evaluated. There was no difference between the genotype or allelic frequencies between cases and controls [23]. In a meta-analysis of candidate SNPs affecting serum calcium found that rs10500780, a variant of PTH, was not significantly associated with serum calcium levels or associated sequelae such as bone and mineral metabolism and cardiovascular mortality [24]. While it is interesting that two of our most significant SNPs were associated with PTH and calcium homeostasis, the importance to ovarian cancer outcome and risk has not been demonstrated.

SNP rs10500780 has no known functional significance itself but is associated with BTBD10 the protein expression of which is related to motor neuron death and amyotrophic lateral sclerosis [25]. SNPs rs17011846 and rs17163580 are associated with the DISP1 gene and have implicated to be involved in the Hedgehog signaling pathway in cancer. Studies in non-small cell lung cancer tumor microarray data demonstrate a negative association between

PFS and OS and overexpression of DISP1 [26]. This particular SNP has no known clinical association currently.

SNP rs11782441 is in the CSMD1 gene which is a candidate tumor suppressor gene. Loss of CSMD1 expression is associated with high tumor grade and poor survival in invasive ductal breast carcinoma [27] and SNP rs227147 is associated with the gene UTS2 (Urotensin II) the function of which is felt to contribute to angiogenesis and certain polymorphisms (not this one) have been associated with breast cancer risk [28].

Finally, SNP rs7011443 is found within the TUSC3 gene which is another candidate tumor suppressor gene. Epigenetic silencing of this gene has been associated with poor prognosis and is an independent negative prognostic biomarker for PFS and OS in ovarian cancer. The molecular role of TUSC3 in ovarian cancer is not known [29].

Recently, the OCAC reported on a genome wide analysis which included patients with EOC from 13 OCAC studies. Patients included in The Cancer Genome Atlas (TCGA) were used as a validation set. Included patients underwent a cytoreductive surgery and were of European ancestry. 2901 patients made up the main data set with a subset of 1098 who were known to have received ≥4 cycles of paclitaxel and carboplatin chemotherapy. This study evaluated over 2.8 million SNPs for association with EOC outcome and identified SNPs at 5 loci with significance for overall and progression free survival. These SNPs included rs6674079, rs7950311 rs4910232, rs2549714, rs3795247. Three of these SNPs (rs6674079, rs4910232 and rs2549714) were found to be located in long coding RNAs. This is significant in that long coding RNAs are transcripts that have been associated with cancer progression through their impact on regulatory functions including epigenetic control, regulation of chromatin structure, regulation of angiogenesis and others [17]. We attempted to evaluate these 5 SNPs in our dataset. 3 of the SNPs were available and none were significant for PFS or OS. These included PFS (rs6674079; rs7950311 and rs4910232) and OS (rs6674079; rs7950311 and rs4910232) analysis.

In collaboration with the OCAC investigators, the top 10 SNPs identified in the GOG dataset were evaluated in a large dataset with 6160 patients with data on OS and 5596 patients with data on PFS. When the dataset was restricted to those patient who received at least 4 cycles of “standard chemotherapy” this number was 2620 patients. Only Euro-pean samples as determined by principal component analysis were included [30]. Samples underwent analysis via OncoArray which is a custom designed Illumina array consisting of 533,000 variants. 260,660 of these variants comprise the GWAS analysis for this OCAC study [31]. The top 10 SNPs for PFS and OS were evaluated in this data set both in all histologies as well as a high grade serous only subset and none were validated for either PFS or OS [32].

In this GWAS study we did not identify any SNPs that met the Bonferroni threshold for significance in their association with PFS and OS but we did identified 10 candidate SNP’s for both PFS and OS which might be interesting on further evaluation in higher powered studies. It is interesting in that the SNP rs10899426 was found on both lists as possibly associated with PFS and OS and this is worthy of further evaluation in future studies.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2017.08.024.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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32. Analysis and sample information courtesy of the Ovarian Cancer Association Consortium (OCAC).

HIGHLIGHTS

- GWAS may identity single nucleotide polymorphisms (SNPs) associated with survival.
- This GWAS study failed to identify SNPs associated with PFS or OS.
- Larger GWAS analyses may prove more insightful.

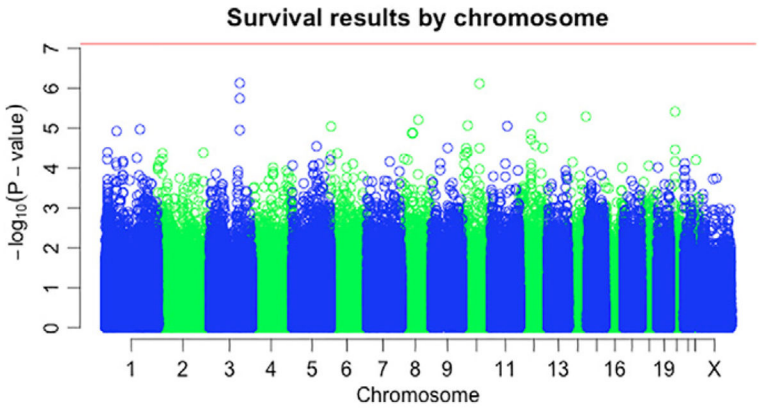

Fig. 1.

Manhattan plot for overall survival. The horizontal red line displays the Bonferroni threshold which was not crossed by any polymorphism indicating lack of statistical significance.

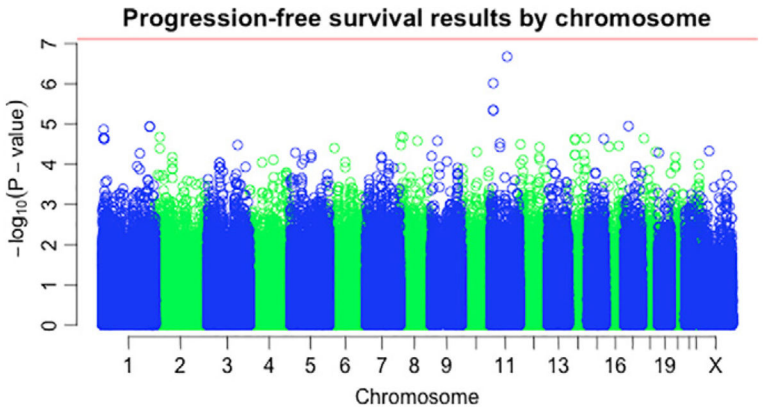

Fig. 2.

Manhattan plot for progression free survival. The horizontal red line displays the Bonferroni threshold which was not crossed by any polymorphism indicating lack of statistical significance.

Table 1

Demographics table.

	Total (*N* = 289)	GOG 172 (*N* = 147)	GOG 182 (*N* = 142)
Age: median (range)	57.79 (30,87)	57.22 (34,83)	59.13 (30,87)
Stage of disease			
III	268	147	121
IV	21	0	21
Size of residual disease			
Microscopic	92	56	36
Gross	197	91	106
Not assessed			
Histologic features			
Serous	220	110 (50%)	110(50%)
Endometrioid	19	8(42%)	11(58%)
Mixed	18	13(72%)	5(28%)
Clear Cell	17	10(59%)	7(41%)
Other	15	6(40%)	9(60%)
Grade			
1	20	9(45%)	11(55%)
2	107	60(56%)	47(44%)
3	157	76(48%)	81(52%)
NA	5	2(40%)	3(60%)
Performance Status			
0	133	64(48%)	69(52%)
1	136	70(51%)	66(49%)
2	20	13(65%)	7(35%)

Table 2

SNPs associated with OS.

SNP	Chromosome	Significance	HR	Associated Gene	Discussion
rs295315	Ch 3	$p = 7.536e^{-07}$	1.82	None	No known clinical significance
rs17693104	Ch 10	$p = 7.734e^{-07}$	1.65	SH2D4B	Associated with capecitabine sensitivity [20]
rs868767	Ch 3	$p = 1.826e^{-06}$	2.12	LOC646730	No known clinical significance
rs2050203	Ch 20	$p = 3.904e^{-06}$	1.78	None	No known clinical significance
rs11621975	Ch 14	$p = 5.186e^{-06}$	2.31	None	No known clinical significance
rs17548007	Ch 12	$p = 5.288e^{-06}$	1.86	None	No known clinical significance
rs202280	Ch 8	$p = 6.246e^{-06}$	0.50	None	No known clinical significance
rs1564271	Ch 10	$p = 8.683e^{-06}$	1.62	PDSS1	Defects in PDSS1 cause coenzyme Q10 deficiency [21]
rs10899426	Ch 11	$p = 9.003e^{-06}$	2.29	None	No known clinical significance
rs4618572	Ch 6	$p = 9.182e^{-06}$	1.86	None	No known clinical significance

Ch = chromosome; SH2D4B = SH2 containing domain 4b; PDSS1 = prenyl (decaprenyl) diphosphate synthase, subunit 1 HR = hazard ratio.

Table 3

SNPs associated with PFS.

SNP	Chromosome	Significance	HR	Associated Gene	Discussion
rs10899426	Ch 11	$p = 2.144e^{-07}$	2.74	None	No known clinical significance
rs6256	Ch 11	$p = 9.774e^{-07}$	1.93	PTH exon 3	Associated with primary hyper-parathyroidism [22]
rs10832063	Ch 11	$p = 4.534e^{-06}$	1.80	None	No known clinical significance
rs10500780	Ch 11	$p = 4.634e^{-06}$	1.79	BTBD10	Reduced expression of BTBD10 is related to motor neuron death and ALS
rs281358	Ch 17	$p = 1.137e^{-05}$	1.67	None	No known clinical significance
rs17163580	Ch 1	$p = 1.173e^{-05}$	2.29	DISP1	The protein product of DISP1 is required for normal Hedgehog (Hh) signaling [26].
rs17011846	Ch1	$p = 1.173e^{-05}$	2.29	DISP1	The protein product of DISP1 is required for normal Hedgehog (Hh) signaling [26].
rs227147	Ch1	$p = 1.381e^{-05}$	0.65	UTS2	Urotensin II may be a significant contributor of angiogenesis and certain polymorphisms have been associated with breast cancer [28]
rs11782341	Ch 8	$p = 2.049e^{-05}$	1.67	CSMD1	Candidate tumor suppressor gene in colon cancer [27]
rs7011443	Ch 8	$p = 2.142e^{-05}$	1.49	TUSC3	Candidate tumor suppressor gene in ovarian cancer xenograph models

Ch = chromosome PTH = parathyroid hormone BTBD10 = BTB (POZ) domain containing 10 ALS = amyotrophic lateral sclerosis DISP1 = dispatched homolog 1 (drosophila) UTS2 = urotensin CSMD1 = CUB and Sushi multiple domains 1 TUSC3 = Tumor Suppressor Candidate 3 HR = hazard ratio.

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