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Original Article

Association analysis of a chemo-response signature identified within The Cancer Genome Atlas aimed at predicting genetic risk for chemo-response in ovarian cancer

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Abstract: Background: A gene signature associated with chemo-response in ovarian cancer was created through integration of biological data in The Cancer Genome Atlas (TCGA) and validated in five independent microarray experiments. Our study aimed to determine if single nucleotide polymorphisms (SNPs) within the 422-gene signature were associated with a genetic predisposition to platinum-based chemotherapy response in serous ovarian cancer. Methods: An association analysis between SNPs within the 422-gene signature and chemo-response in serous ovarian cancer was performed under the log-additive genetic model using the 'SNPassoc' package within the R environment ($p<0.0001$). Subsequent validation of statistically significant SNPs was done in the Ovarian Cancer Association Consortium (OCAC) database. Results: 19 SNPs were found to be associated with chemo-response with statistical significance. None of the SNPs found significant in TCGA were validated within OCAC for the outcome of interest, chemo-response. Conclusions: SNPs associated with chemo-response in ovarian cancer within TGCA database were not validated in a larger database of patients and controls from OCAC. New strategies integrating somatic and germline information may help to characterize genetic predictors for treatment response in ovarian cancer.

Keywords: Ovarian cancer, chemotherapy, genetic risk, single nucleotide polymorphisms, data analysis

Introduction

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer, with serous carcinoma being the most frequent histologic subtype [1]. The standard of care for advanced-stage disease is cytoreductive surgery followed by adjuvant chemotherapy with a platinum-based agent and a taxane [2]. Patients who respond to first-line chemotherapy have an improvement in median survival [3], but those women who do not respond, progress during initial platinum-based therapy (platinum-refractory), or those who recur within 6 months of finishing treatment (platinum-resistant) have a very poor prognosis with a median overall survival of 12-13 months [4].

Recognition of tumor heterogeneity has led to the development of novel systems for screening tumor cells for sensitivity and resistance to chemotherapy agents. It has been shown through genetic instability and epigenic processes that subpopulations of tumor cells can have variations in chemo-response [5]. With the ability to sequence entire genomes in combination with molecular data repositories, chemotherapy development can begin to identify certain molecular signatures as predictors of treatment response.

In a recent published study, a robust genetic signature of 422 genes created from integration of several dimensions of biological data available in The Cancer Genome Atlas (TCGA) was associated with chemo-response in serous ovarian cancer. This association was replicated across independent microarray experiments [6]. Our study aimed to determine if single nucleotide polymorphisms (SNPs) within the 422-gene signature were also associated with genetic predisposition to platinum-based chemotherapy response in serous ovarian cancer patients.

Table 1. Significant SNPs associated with chemo-response in TCGA

SNP	OR	Lower	Upper	*p*-value log-additive	Symbol	Chr	Pos	Alleles
rs1007924	0.56	0.4	0.8	8.91E-04	LRRC23	chr12	6886176	[A/B]=[A/G]
rs2301137	0.55	0.39	0.79	6.97E-04	LRRC23	chr12	6889210	[A/B]=[T/C]
rs1171073	2.18	1.35	3.51	9.59E-04	DCLK1	chr13	35403056	[A/B]=[A/G]
rs1536301	0.55	0.38	0.8	6.93E-04	SUCLA2	chr13	47454680	[A/B]=[A/C]
rs1891670	1.93	1.31	2.82	6.75E-04	DCLK1	chr13	35421209	[A/B]=[A/G]
rs8002322	0.45	0.26	0.77	9.84E-04	SUCLA2	chr13	47447907	[A/B]=[T/G]
rs9595825	0.57	0.4	0.82	8.98E-04	SUCLA2	chr13	47431213	[A/B]=[T/C]
rs12926631	2.85	1.46	5.55	8.54E-04	PLLP	chr16	55878863	[A/B]=[T/C]
rs4785613	2.25	1.39	3.62	6.01E-04	ZNF778	chr16	87813473	[A/B]=[T/C]
rs9931258	2.64	1.51	4.63	3.44E-04	ZNF778	chr16	87815919	[A/B]=[A/G]
rs16988310	3.25	1.63	6.49	8.66E-04	UBOX5	chr20	3058342	[A/B]=[A/G]
rs4820094	0.58	0.42	0.79	2.34E-04	TIMP3	chr22	31491824	[A/B]=[A/G]
rs1425522	1.7	1.25	2.32	6.44E-04	INPP4B	chr4	143712663	[A/B]=[A/G]
rs2659509	1.83	1.28	2.6	7.56E-04	PPP3CA	chr4	102332047	[A/B]=[A/C]
rs2659511	1.88	1.31	2.69	5.01E-04	PPP3CA	chr4	102332104	[A/B]=[T/C]
rs2659534	1.87	1.29	2.71	7.63E-04	PPP3CA	chr4	102349248	[A/B]=[A/C]
rs2850994	2	1.37	2.91	2.31E-04	PPP3CA	chr4	102348322	[A/B]=[T/A]
rs2955262	2.42	1.48	3.95	2.27E-04	MFAP3L	chr4	171111891	[A/B]=[A/G]
rs31226	1.58	1.21	2.08	7.90E-04	ARL15	chr5	53363328	[A/B]=[A/G]

Results of the logistic additive model: OR, *p*-value, chromosomal, genomic locations, and alleles.

Materials and methods

Response to therapy was defined as complete response (CR) when there was complete disappearance of all disease up to 6 months after treatment, N=272. Incomplete response (IR) was defined as disease that either did not respond or progressed during treatment (refractory), or recurred within 6 months of treatment completion (resistant), N=143. These definitions are used in standard clinical practice. A sensitivity statistical power analysis was performed with an 82% power to detect a 15% difference between groups with a *p*-value=0.001.

We included those SNPs genotyped in TCGA with the Affymetrix Genome-Wide SNP Array 6.0 (Affymetrix, Santa Clara, CA) that were contained within the 422-gene signature resulting in a total of 22,007 unique SNPs. The analysis was performed with the 'SNPassoc' package within the R environment [7], and the association between SNPs and chemo-response (phenotype) was done under the log-additive genetic model. Those SNPs with a significant *p*-value ($p<10^{-3}$) were validated within the Ovarian Cancer Association Consortium (OCAC) database.

Results

Chemo-response is the most significant independent clinical factor for survival ($p<10^{15}$) identified in TCGA [6]. The association analysis between the 22,007 SNPs located within the 422-gene signature associated with chemo-response [6] and the outcome of interest, response to chemotherapy, resulted in 19 SNPs with a *p*-value$<10^{-3}$ [**Table 1** and **Figure 1**]. The enrichment pathway analysis with DAVID (http://david.abcc.ncifcrf.gov/) of the SNPs associated with chemo-response showed significant involvement in molecular pathways ($p<0.05$) related to response to amine stimulus, response to organic nitrogen, and developmental growth (Gene Ontology pathways). Validation of the association between chemo-response and these 19 SNPs was performed using the OCAC database. Within the OCAC database, over 2,500 patients with treatment for serous ovarian cancer were identified, but none of the mentioned SNPs were significant for the outcome of interest. This indicates that while individual SNPs may not be significantly associated with the outcome, further analysis of downstream gene expression profiling and pathways are nevertheless potentially useful in a validated predictive algorithm.

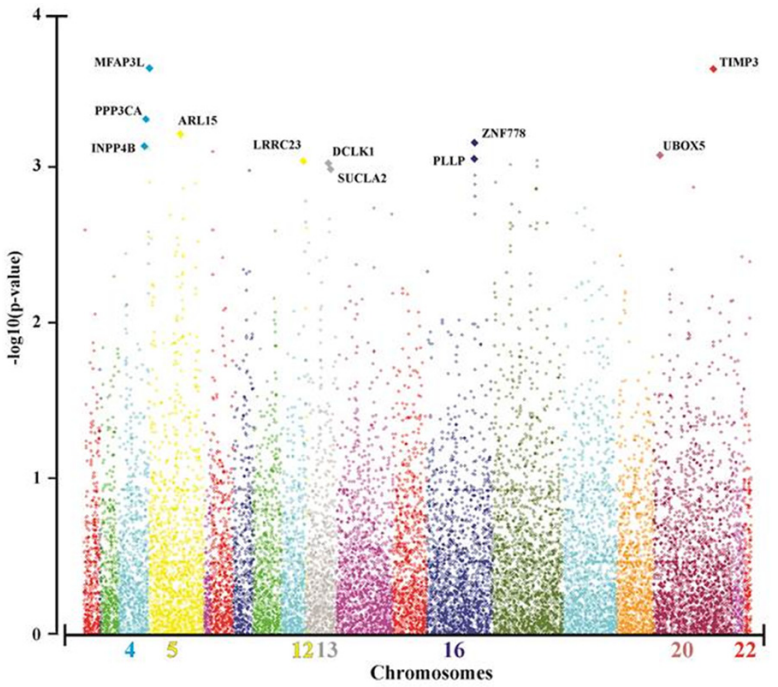

Figure 1. Chemo-response signature from SNPs association analysis with chromosomal and genomic locations.

Discussion

There is a critical need for more individualized treatment and molecular-targeted therapies in ovarian cancer. Targeting molecular signatures as well as signal transduction pathways for tumor sensitivity and resistance is essential for treatment and improving overall survival in ovarian cancer patients. Around 25% of patients will not respond to initial treatment with a poor prognosis [4], yet we do not have an effective way to identify these patients, until they recur. Our line of research is aimed at identifying and diagnosing which patients will not respond to standard treatment, so we can begin designing and implementing new therapies. The TCGA molecular signature associated with chemo-response is an initial approach [6]. The analysis of this signature to therapy response was not validated in a larger, established serous ovarian cancer dataset. Nevertheless, the SNP data pointed the way to novel insights into gene expression patterns and pathways that are predictive. Therefore, integration of genomic data may be a way to not only identify new risk factors, but also discover different associations with molecular pathways or mechanisms of action. Further studies refining phenotypes, cancer classification, and integration of complex data are needed to enhance our search of risk factors to treatment response.

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Disclosure of conflict of interest

None.

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References

[1] Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer Statistics, 2005. CA Cancer J Clin 2005; 55: 10-30.

[2] Harries M, Gore M. Part I: chemotherapy for epithelial ovarian cancer-treatment at first diagnosis. Lancet Oncol 2002; 3: 529-36.

[3] McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Clarke-Pearson DL, Davidson M. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996; 334: 1-6.

[4] Friedlander ML, Stockler MR, Butow P, King MT, McAlpine J, Tinker A, Ledermann JA. Clinical trials of palliative chemotherapy in platinum-resistant or -refractory ovarian cancer: time to think differently? J Clin Oncol 2013; 31: 2362.

[5] Fidler IJ, Kripke ML. Metastasis results from preexisting variant cells within a malignant tumor. Science 1977; 197: 893-895.

[6] Gonzalez-Bosquet J, Marchion DC, Chon H, Lancaster JM, Chanock S. Analysis of chemotherapeutic response in ovarian cancers using publicly available high-throughput data. Cancer Res 2014; 74: 3902-12.

[7] Gonzalez JR, Armengol L, Sole X, Guino E, Mercader JM, Estivill X, Moreno V. SNPassoc: an R package to perform whole genome association studies. Bioinformatics 2007; 23: 644-5.