Genomic Risk Prediction of Aromatase Inhibitor-Related Arthralgia In Breast Cancer Patients Using A Novel Analytical Algorithm

The James

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Introduction

Aromatase inhibitors (AIs) are a critical component in the management of post-menopausal women with hormone receptor-positive breast cancer. Whether administered as monotherapy, sequenced therapy or extended therapy, AIs favorably impact disease free survival. However, AIs are also associated with a number of toxicities of which arthralgia is among the most common and significant. AI-induced arthralgias (AIAs) frequently result in non-compliance or discontinuation of treatment, both of which may adversely impact recurrence risk.

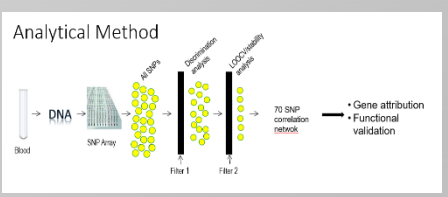
While a genomic basis for AIA has been reported, there is little agreement between studies as to the specific genetic culprit. Results of candidate gene studies to identify AIA risk are limited in scope. In this case controlled study, we evaluated the potential of a novel analytical algorithm (NAA) to predict AIA using germline single nucleotide polymorphism (SNP) data obtained prior to treatment initiation.

Patient Characteristics & Methods

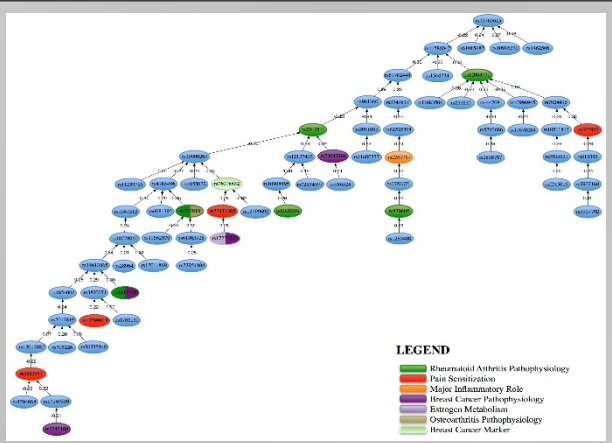
- Systematic chart review of 700 AI treated patients with early stage breast cancer between 2003-2012
- Identified asymptomatic patients (n= 39) and those with clinically significant AIA resulting in AI termination or therapy switch (n= 123)

	Controls (n = 39)	Cases (n = 123)
Stage I	22 (56%)	55 (45%)
Stage II	14 (36%)	54 (44%)
Stage III	3 (8%)	14 (11%)
ER or PR positive / HER2 negative	33 (85%)	104 (85%)
ER or PR positive / HER2 positive	6 (15%)	19 (15%)

- Germline DNA was obtained from peripheral blood mononuclear cells and SNP genotyping performed using the Affymetrix UK BioBank Axiom Array to yield 695,277 SNPs
- The identity of the cluster of SNPs that most closely defined AIA risk was discovered using an NAA that sequentially combined statistical filtering and a machine learning algorithm
- NCBI PhenGenI and Ensemble databases were used to define gene attribution of the 200 most discriminating SNPs. Phenotype, pathway, and ontologic analyses assessed functional and mechanistic validity



Results



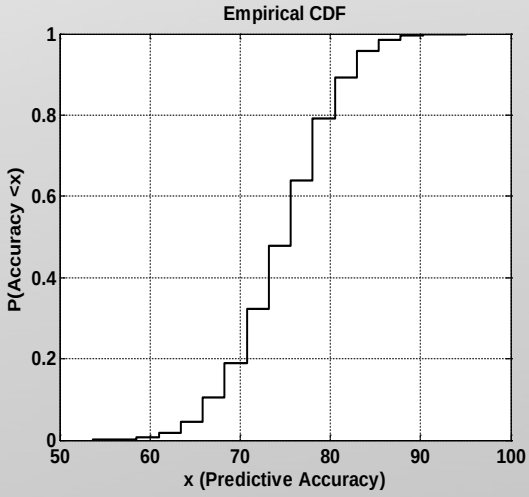
Pain Sensitiza-tion	Osteoarthritis Pathphys.	Rheumatoid Arthritis Pathophys.	Breast Cancer Pathophys.	Estrogen Metabolism	Major Inflammatory Role	Breast Cancer Biomarker
rs322960	rs797818		rs17270243		rs2269767	rs76098632
rs77413365		rs1012629				
rs17599018		rs12004732	rs73042968			
rs2883917		rs8028334	rs3743160			
		rs879605				
		rs2243511				

Color visualization delineating the relationship of the 70 predictive SNPs and their functional relevance

Correlation tree of the most discriminatory SNPs. This tree is built using the minimum spanning tree algorithm using the Pearson correlation coefficient. The algorithm looks for the maximum absolute values of the Pearson correlation coefficient (positive and negative correlations) within the set of most discriminatory SNPs.

The hierarchical figure describes the strength of relationships between SNPs and how each SNP relates to the others in the cluster. Associated phenotypes include similar phenotypes (RA, pain, inflammation and those associated with the tumor diagnosis).

Results (cont.)



Stability analysis of the small scale signature of the 70 SNPs which were identified as being most predictive of AIA risk

The figure shows the cumulative distribution function of the predictive accuracy obtained after 5000 random 75/25 hold out simulations. It can be observed that the median accuracy (percentile 50) is around 75%, being the lower and upper-quartiles 71% and 78%. The minimum and maximum accuracies achieved were 54% and 100%.

Gene Ontology Biological Processes
1. Regulation of RAC1 Activity
2. Vitamin A and Carotenoid Metabolism
3. Signaling By Retinoic Acid
4. Amplification of Signal From Unattached Kinetochores Via A MAD2 Inhibitory Signal
5. EPHA Forward Signaling
6. TRP Channels
7. Regulation of CDC42 Activity
8. G-protein Signaling Regulation of CDC42 Activity
9. EPH-Ephrin Signaling
10. NGF Processing
11. Neuroscience
12. Aldosterone-regulated Sodium Reabsorption
13. NF-KappaB Family Pathway
14. All-trans-Retinoic Acid Mediated Apoptosis
15. G-protein Signaling Regulation of RAC1 Activity
16. Amb2 Integrin Signaling
17. Nuclear Receptor Transcription Pathway
18. PDGFR-beta Signaling Pathway
19. Calcineurin-regulated NFAT-dependent Transcription in Lymphocytes
20. G12-G13 in Cellular Signaling

Identification of biological pathways associated with the 70 SNP predictive cluster

To assess the potential impact of the 57 genes associated with the risk determinant SNPs, we queried GeneAnalytics, which identified 14 pathways with medium score matches. Particularly related to the study cohorts were pathways associated with tumor-related mechanisms (RAC1, Retinoic signaling, CDC42) and those having mechanistic relationships with inflammatory and pain outcomes (EPHA, EPH-Eprin, TRP channels, NF-κB and PDGFR-beta signaling).

Conclusions

- Using a novel analytical algorithm, we identified a 70 SNP cluster that predicted AIA risk with fair accuracy
- Phenotype, functional, and pathway analysis of attributed genes was consistent with clinical phenotypes
- This study is the first to link a specific SNP cluster to AIA risk independent of candidate gene bias. An ongoing prospective companion study will be used to validate and to expand upon results

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