EAACI Fellowship Award (Short-Term Research) – Final Report

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Host Institute: Institute for Environmental Medicine , Karolinska Institute

Fellowship application title: An Integrated Approach For The Genome-Wide Identification Of Allergic Rhinitis-Related Expression Quantitative Trait Loci (AReQTL) In Two Different Allergen Environments

Period of Fellowship – End August to mid-November 2017

Research questions addressed

Comparing gene signatures for allergic rhinitis (AR) between Singapore and Sweden

I wanted to evaluate if genes associated with allergic rhinitis in a perennial environment of Singapore is also replicated in the seasonal AR cohort in Sweden. For this I first used whole genome expression data from the Singapore Chinese population in 111AR cases and 113 controls to identify 23 unique probes differential at a genome wide signficance (**Figure 1**). In addition, Ingenuity Pathway Analysis (IPA) revealed strong immune subsets and functions responsible for allergies (**Table 1**). I was able to replicate 13 out of these candidates in the Swedish BAMSE cohort for association to allergic rhinitis. This reflects a strong set of core genes shared by two different environments. The results of this study are now being prepared for submission to JACI (1).

Determining the impact of genetics (SNPs) on the gene expression between AR cases and controls

Our group has previously published that SNPs control gene expression through transcription factor mediated processes (2,3). Hence we next wanted to evaluate if the interaction of genotype with phenotype affects gene expression signficantly. For this purpose, we used an interaction model of SNP genotype with AR phenotype in determining expression. Interestingly, we found strong pairs of interactions signficantly different between AR cases and controls in the Singapore Chinese cohort. I had a total of 1108 SNPs which were associated as AReQTLs (Allergic Rhinitis expression quantitative trait loci) of which 120 of them were genome-wide significant. I am now working with the data from the BAMSE cohort to validate these findings and also determine other interactions significant.

Future relevance of current findings from the fellowship

I am quite excited by the findings reported here. This is the first time we are comparing tropical environments with European climates in the context of airway allergies. Especially finding a core set of genes shared between seasonal hay fever and perennial allergic rhinitis highlights the importance of specific pathways for disease manifestation. This could identify potential targets that could be targeted for therapeutic purposes and treatment.

Figure 1: Manhattan plot for differentially expressed genes (DEG) for allergic rhinitis

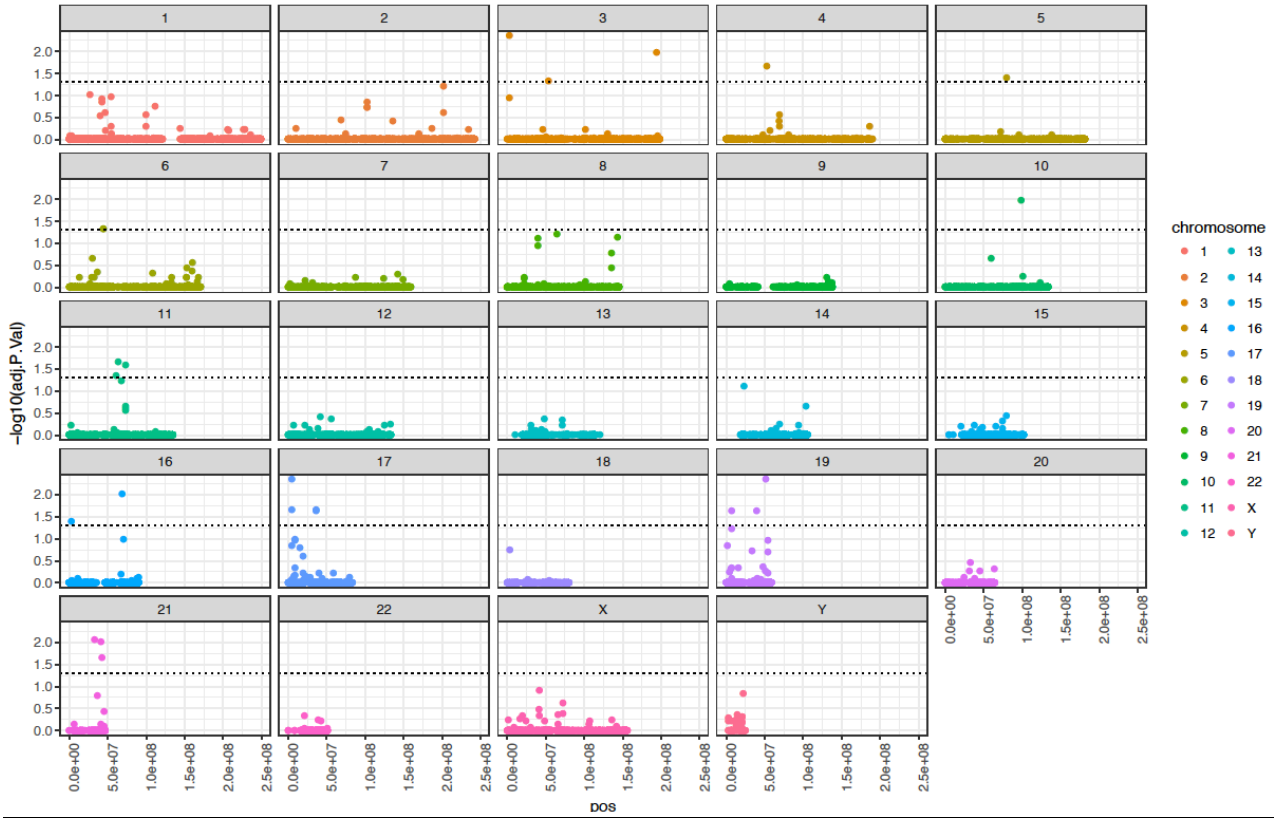

Table 1: Significant terms enriched in the hypersensitivity response as determined by the Ingenuity Pathway Analysis (IPA)

Categories	Diseases/Function	P-value	# Molecules
Cell-to-Cell Signaling	Activation of eosinophils	1.98E-05	IL1RL1, IL5RA, PTGDR2
Hematological system	Quantity of eosinophils	6.25E-05	IL1RL1, IL5RA, PTGDR2, SIGLEC8
Cellular movement	Infiltration by eosinophils	2.68E-04	IL1RL1, PTGDR2, SIGLEC8
Cell-to-Cell Signaling	Response of eosinophils	3.60E-04	IL1RL1, IL5RA
Cellular function and movement	Function of eosinophils	3.72E-03	IL1RL1, SIGLEC8
Cellular function & hematological system	Infiltration by basophils	3.78E-03	IL1RL1, PTGDR2
Hypersensitivity Response	Tolerisation of mast cells	3.78E-03	PTGDR2
Cell-to-Cell Signaling	Inflammation of eosinophils	1.13E-02	IL1RL1

References

1) Anand Andiappan, Bernett Lee, Simon Kebede Merid, Puan Kia Joo, Nurhashikin Yusof, et al. Genome-wide identification of allergic rhinitis-related gene networks using blood transcriptomics in a tropical urban environment. (*In preparation)*
2) Genome-wide analysis of the genetic regulation of gene expression in human neutrophils. Andiappan AK, Melchiotti R, Poh TY, Nah M, Puan KJ, et al. Nat Commun. 2015 Aug 10;6:7971.
3) Cell Specific eQTL Analysis without Sorting Cells. Westra HJ, Arends D, Esko T, Peters MJ, Schurmann C, et al. PLoS Genet. 2015 May 8;11(5):e1005223.

Other Activities during EAACI Research fellowship 20

Research meetings

The fellowship also provided opportunities to attend local and international research meetings pertaining to allergy and clinical immunology.

IgE 50 years symposium – 6 October 2017, Stockholm Sweden

ISMA 2017, International Symposium on Molecular Allergology, 09-11 November Luxembourg

Invited talks

I was also invited to give a talk at Phadia (Thermofisher) at Uppsala, Sweden.
The title was, "Decoding allergies - A tropical perspective"

Personal Reflection

I would first like to thank the EAACI society for the short-term research fellowship. With this opportunity I was able to spend time at the Institute for Environmental medicine at Karolinska Institute. I was trained in the field of epidemiology and clinical research in allergies and asthma. Under the supervision of Dr. Erik Melen I learnt the clinical questions underlying the research and also how to implement various omics and epidemiological data for allergic rhinitis. In addition, I also firsthand experienced how the data was collected at the clinic and also how is integrated into the cohort database. Lastly, I also learnt the bioinformatics pipelines and analysis techniques for the BAMSE cohort, which can also be synchronized with the Singapore data.

On a personal note, this fellowship also provided me exposure to a different work environment in Europe, while most of my research experience was in Asia. Coming from an Immunology institute, I was excited to see how epidemiologists and clinicians address the problem of allergies. In addition, I also learnt from the interdisciplinary approach at Karolinska Institute to biomedical research. Finally, the collegiality at my host institution was excellent. People were open to help and provide support whenever I needed. So that's prepared me better for future research endeavors and collaborative efforts.

Best regards

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