

Original article

A network analysis of the single nucleotide polymorphisms in acute allergic diseases

Background: Genetics of acute allergies has focused on identifying single nucleotide polymorphisms (SNPs) within genes relevant in the pathogenesis. In this study, we begin a systems biology analysis of the interconnectivity and biological functions of these genes, their transcripts and their corresponding proteins.

Methods: The literature (Pubmed) was searched for SNPs within genes relevant in acute allergic diseases. The SNP-modified genes were converted to corresponding proteins and their protein–protein interactions were searched from six different databases. This interaction network was analysed with annotated vocabularies (ontologies), such as Gene Ontology, Reactome and Nature pathway interaction database. Time-series transcriptomics was performed with nasal epithelial cells obtained from allergic patients and their healthy control subjects.

Results: A total of 39 genes with SNPs related to acute allergic diseases were found from a literature search. The corresponding proteins were then hooked into a large protein–protein interaction network with the help of various databases. Twenty-five SNP-related proteins had more than one interacting protein and a network contained 95 proteins, and 182 connections could be generated. This network was 10-fold enriched with protein kinases and proteins involved in the host–virus interaction compared with background human proteome. Finally, eight of the 95 nodes on our network displayed nasal epithelial transcriptomal regulation in a time-series analysis collected from birch allergic patients during the spring pollen season.

Conclusions: Signal transduction with special reference to host–virus interactions dominated in the allergy-related protein interaction network. Systems level analysis of allergy-related mutation can provide new insights into pathogenetic mechanisms of the diseases.

**J. Renkonen^{1,2}, P. Mattila³,
V. Parviainen¹, S. Joenväärä^{1,3},
S. Toppila-Salmi⁴, R. Renkonen^{1,2}**

¹Transplantation Laboratory & Infection Biology Research Program, Haartman Institute, University of Helsinki; ²HUSLAB, Helsinki University Central Hospital; ³Medicel Ltd, Helsinki; ⁴Department of Clinical Medicine, University of Tampere and Department of Eye, Ear and Oral diseases, Tampere University Hospital, Tampere, Finland

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R. Renkonen
Transplantation Laboratory
Haartman Institute
PO BOX 21 (Haartmaninkatu 3)
FI- 00014 University of Helsinki
Helsinki
Finland

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The prevalence of allergic diseases has grown rapidly in the Western countries (1–3). This causes significant morbidity and indirect losses of productivity in the society. Although the origin of allergy remains unresolved, it has been hypothesized that living in urban environments deprives people from environmental micro-organisms and other predisposing factors (4). This could prevent natural tolerance and result in hypersensitivity. The current dogma of allergen avoidance is not effective in halting the ‘epidemic’ and thus a national Finnish Allergy Programme 2008–2018 has been launched. It is a comprehensive plan to reduce the burden of allergies within the society (2, 5).

Acute allergic reactions, such as the type I hypersensitivity, are caused by allergens cross-linking with specific anti-IgE molecules bound on mast cells in immunologically sensitized patients (6–8). While the majority of

studies on pollen allergies have focused on aberrant immunoresponses (6, 9, 10), the role of the respiratory epithelium as the first line of defence against allergens has also been emphasized recently (11–14).

The search for genes responsible for a multifactorial disease such as acute allergy has revealed tens of putative polymorphic candidate genes and their corresponding proteins. Typically, these studies concentrate on one gene at a time, and suggest only a small, yet statistically significant, contribution to the development of allergic disease. To begin to learn from these individual observations, a systems level approach, binding all the available information from these genes, transcripts and proteins from numerous databases, needs to be conducted.

To this end, we adopted a new systems biology approach and first identified from the published literature a list of genes proposed to have a mutation, in this study a

single nucleotide polymorphism (SNP). We identified 39 individual genes and their corresponding proteins, which all on their own had been proposed to have an incremental contribution to acute allergic diseases.

To learn how these individual observations would be linked together, we then used various databases to learn more. With the help of an integrated data warehouse and other resources, we pulled together all the genes, their corresponding transcripts, their corresponding proteins and finally all protein–protein interactions and generated a network of these nodes.

A very large protein–protein interaction network with 573 proteins (nodes) and 654 connections (edges) between them was generated with all the 39 proteins coded by genes proposed to have SNPs in allergic patients and all the proteins binding to them. When taking into account only interacting proteins binding to at least two SNP-related proteins, a more stringent data set was drawn. This network contained only 25 SNP-related proteins, 70 other interacting proteins and 182 connections. We conducted further characterization of this subnetwork with various annotated vocabularies (ontologies), such as Gene Ontology (GO), Reactome and Nature pathway interaction database. The basic question in such analyses was whether the observed set of 95 proteins is enriched for some annotation categories, such as ‘protein kinases’ or ‘host–virus interaction’ compared with the over all presence of the same categories within the whole human proteome. Finally, we also tested how this set of proteins is regulated at the transcriptomal level. We obtained nasal epithelial cell swabs from healthy and birch pollen allergic subjects in a weekly time-series manner during the April–May pollen season and performed whole genome transcriptomics.

Material and methods

Literature search

A literature search was carried out in December 2008 in Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed/>) with a search phrase ‘allergy or allergic and SNP’. The list obtained was then manually annotated and the list of SNP modifications in allergic diseases was collected. Even though this list is probably not a complete one, it represents a very good proportion of the found and proposed SNP modifications linked to acute allergic diseases, such as grass allergy, atopy, allergic rhinitis, Stevens–Johnson syndrome, urticaria, hypersensitivity and penicillin allergy. The list of SNPs claimed to be associated with allergic diseases (Table 1) was used for further analyses.

Protein–protein interaction networks

We used a web-based protein interaction network analysis platform (PINA), which integrates the protein–protein interaction data from six databases and provides a network construction by using our polymorphic proteins as the baseline (15). The SwissProt names without the tag ‘_HUMAN’ are used throughout this study if not otherwise stated.

Table 1. A list of genes and their corresponding proteins, where SNP(s) has been found to relate to allergic diseases

Gene	Protein	Disease	Reference
ADRB2	ADRB2	Grass allergy	(20)
ARG1	ARG1	Atopy	(21)
ARG2	ARG2	Atopy	(21)
CCL11	CCL11	Atopic dermatitis	(22)
CCL26	CCL26	Allergic rhinitis	(23)
CCL5	CCL5	Allergic rhinitis	(24)
CCR4	CCR4	Atopic dermatitis	(25)
CMA1	CMA1	Atopic eczema	(26)
CYSLTR1	CLTR1	Atopy	(27)
FASLG	TNFL6	Stevens–Johnson syndrome	(28)
FCER1A	FCERA	Serum IgE level	(29)
FCER1B	FCERB	Urticaria/angio-oedema	(30)
FLG	FILA	Atopic dermatitis	(31)
FOXJ1	FOXJ1	Allergic rhinitis	(32)
GATA3	GATA3	Eczema	(33)
GSTP1	GSTP1	Allergic respiratory diseases	(34)
HCP5	HCP5	Hypersensitivity	(35)
IL1RL1	ILRL1	Atopic dermatitis	(36)
IL4	IL4	Penicillin allergy	(37)
IL4R	IL4RA	Stevens–Johnson syndrome	(38)
IL10	IL10	Penicillin allergy	(37)
IL12B	IL12B	Atopic dermatitis	(39)
IL12RB1	IL12R1	Atopic dermatitis	(39)
IL13	IL13	Eczema	(33)
IL18	IL18	Atopic dermatitis	(40)
ITGB3	ITB3	Allergy	(41)
KDR	VGFR2	Atopy	(42)
KLK7	KLK7	Atopic dermatitis	(31)
LELP1	LELP1	Atopic dermatitis	(43)
MBL2	MBL2	Allergic rhinitis	(44)
NFKB1	NFKB1	Atopic dermatitis	(25)
NLRP4	NALP4	Atopic dermatitis	(45)
RAD50	RAD50	Atopic eczema	(29)
SCGB1A1	UTER	Allergic rhinitis	(46)
SPINK5	ISK5	Atopic dermatitis	(31)
STAT1	STAT1	Atopy	(47)
TLR2	TLR2	Atopic dermatitis	(48)
TLR3	TLR3	Stevens–Johnson syndrome	(49)
TNC	TENA	Allergic diseases	(50)

The proteins displayed on the common pathway as shown in Fig. 1 are marked in bold. The SwissProt names for proteins are used without the tag ‘_HUMAN’ throughout the study.

The GO categories provide a controlled vocabulary to describe the gene and gene product attributes of any organism, in this study human subjects. The enrichment analyses of proteins in the various gene ontology (GO Slim) categories as well as KEGG (<http://www.genome.jp/kegg>), Reactome (<http://www.reactome.org>) and Nature Pathway interaction Database, PID (<http://pid.nci.nih.gov>) pathways were essentially calculated as described elsewhere (11, 12, 16).

When the analysis within these annotated categories was carried out, we searched for enriched categories. The basic question was: is the category ‘protein kinases’ or the keyword ‘host–virus interactions’ enriched within the observed SNP-related network compared with the background set of the whole human proteome. If such enrichment was observed, it would suggest that such categories and keywords could play a role within the SNP-related protein network found in allergic patients.

Medicel integrator platform

The nonredundant objects in the Reference Pathway Model depict data for genes, their transcripts and corresponding proteins integrated from various biological databases to a data warehouse, i.e. the Integrator (Medicel Ltd, Helsinki, Finland). The data analysis was performed using the Medicel Integrator (<http://www.medicel.com>). For the microarray data analysis, the following integrated databases (version number in parentheses) were used for probe annotations and conversions from transcripts to proteins: Illumina human WG-6 v2, NCBI/RefSeq/RNA (05/24/2007), EnsEMBL (45-a), SwissProt (53.2-a) and Medicel Reference Model. In the data analysis and in searching for/finding protein–protein interactions for the differently expressed genes, the following databases were used: KeGG (2006/12/15-1), Intact (2007-07-27), PID (2008-03-05) and Reactome (2008-03-05).

Subjects

This study was performed according to the Declaration of Helsinki, and the study protocol was reviewed and accepted by the Committee on Ethics of both Helsinki University Eye and Ear Hospital, and Tampere University Hospital. Informed consent was obtained from all subjects.

The diagnosis of birch allergic rhinitis was based on a positive history of intermittent allergic rhinitis, a clinical examination and a skin prick test. The selection criteria for patients included in this study were the following: having a positive history of moderate seasonal birch pollen allergic rhinitis without asthma or other allergic symptoms, showing a positive response to birch pollen allergen in a routine skin prick test, showing the symptoms of early-phase allergic response after *in vivo* nasal challenge with birch pollen extract and suffering from no other allergies nor other diseases. All persons included in this study were nonsmokers. All the subjects did not have respiratory or other infections 4 weeks before and during the course of sample collection. The healthy nonsmoking control subjects were negative for all tested antigens and had no history of seasonal allergies. Neither group used any medication during the analyses.

Nasal epithelial cell swab specimens from both birch pollen allergic patients (four females, mean age 24 years, range 21–27 years) and healthy control subjects (three females and one male, mean age 23.8 years, range 22–25 years) were collected first during nonsymptomatic winter season and then four more samples were obtained from the same subjects at weekly intervals, starting at the onset of the spring allergy season in 2007. The collection of time-series specimens was launched at the beginning of the birch pollen season when the patients, but not the healthy subjects, began to generate clinical symptoms in Southern Finland, i.e. in late April to mid-May. Before performing the specimen collection, all subjects filled a visual analogue scale questionnaire weekly for symptoms, such as nasal obstruction, runny nose, sneezing, itchy nose/eyes, loss of smell, postnasal discharge and facial pain/pressure.

For RNA isolations, Rneasy Mini Kit (Qiagen, Helsinki, Finland) was used according to the manufacturer's instructions. Both RNA integrity and concentration were measured with RNA 6000 Nano kit with an Agilent Bioanalyser. The processed RNA samples were hybridized on Illumina human WG-6 v2 chips, in Finnish DNA Microarray Centre (Turku Centre for Biotechnology, Turku, Finland). The *in silico* analysis of the time-series transcriptomics was carried out in a Medicel workflow environment. Instead of using the manufacturer's probe annotations, the probe sequences were blasted (Blastall, NCBI) against the whole integrated transcriptome of EnsEMBL. For normalization, the measurement values were converted to a logarithmic scale before

using the quantile normalization method. The values corresponding to probes were selected for further analysis and the row labels were converted from transcripts to UNIPROT proteins as well as to Medicel (Medicel Ltd.) reference proteins, the nonredundant objects in the reference pathway model.

Results

Study set-up

We first searched the literature published during 2004–2008, on the association of SNPs with allergic diseases. The search produced 231 articles, from which a list of 39 genes and their corresponding proteins linked to an acute allergic disease was compiled (Table 1). Because we focused only on acute allergic reactions, all the literature linked to genes modified in pulmonary asthma were excluded.

We next generated a protein–protein interaction network for these 39 proteins. The interacting proteins for each of these proteins were searched with PINA, which integrates six different protein–protein interaction databanks together (15), as well as with Medicel Integrator, integrating a dozen of different databases with diverse data from genes, mRNA, proteins and metabolites (<http://www.medicel.com>). We first pulled down all the protein interactions of these putatively allergy-related proteins, which resulted in a very large network with 573 proteins (nodes) and 654 connections (edges) between them. To make a more stringent query, we restricted the study to a subset of this network. Only proteins interacting with at least two proteins with allergy-related SNP modifications were accepted for the new smaller network. This more stringent data set contained only 25 SNP-related proteins, 70 interacting proteins and 182 connections between them. The 25 proteins represented the original literature-searched proteins with SNPs (Fig. 1).

We imported this stringent data set to Cytoscape (17) and the network is displayed in Fig. 1. As a positive control for the known players in the allergic reaction, two mast cell Fc Epsilon receptor protein FCER1 and its interacting protein FCER2 are shown in the upper portion of Fig. 1. These receptors also interact with a group of CCL chemokines, such as CCL5, CCL11, CCL17 and CCL26, and their receptors, such as CCR1, CCR2, CCR4, CCR5, CCR6 and CXCR4.

To further utilize and benefit from this allergy-related network, we next manually annotated the database-related information of all the 95 proteins into one document (Table S1). Another way to describe the data set of 95 proteins within the allergy-specific network is to perform the GO enrichment analysis. When the analysis within the GO Slim – biological process categories was performed, a few strongly enriched classes were observed as shown in Fig. 2. Responses to 'stress' and 'external stimulus' were both significantly enriched as were categories entitled 'cell–cell signalling' and 'protein modification process'. As

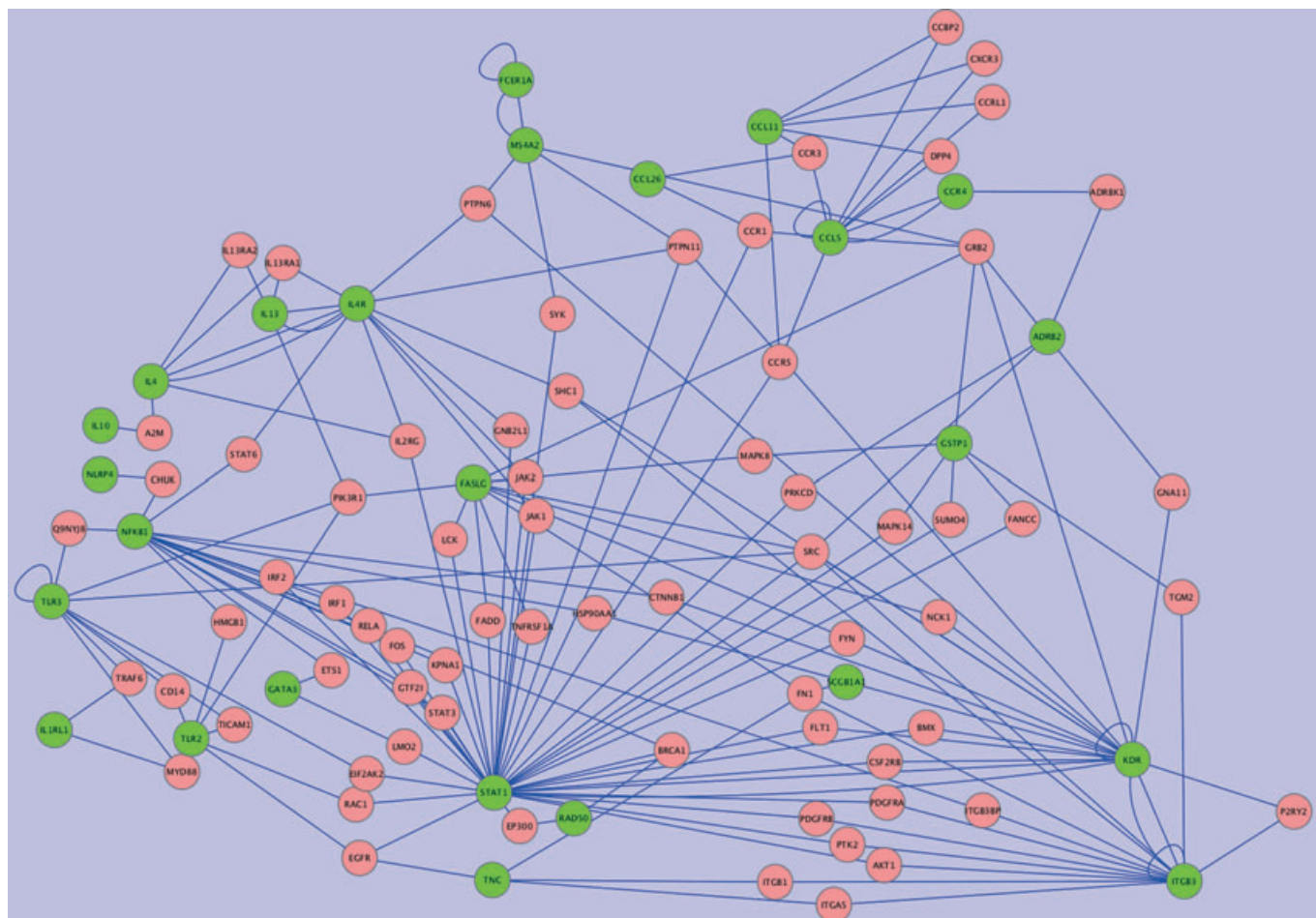


Figure 1. A protein–protein binding network built around the original data set of 25 genes/proteins (yellow nodes), where a single nucleotide polymorphisms (SNP) had been previously found in the literature and their direct interacting proteins found in the integrated PINA database (white nodes), so that each interacting protein binds to at least two (yellow) SNP proteins. A Cytoscape (.cys) file can be loaded from the Online Supporting Information (Table S1). All the proteins are marked with the SwissProt name, but without the tag _HUMAN for clarity (see Table S1).

shown in Table 2, the keyword ‘protein kinase’ was significantly enriched (22/95, 23%) as the proportion of protein kinases in the whole proteome was only 3% ($P < 0.0001$, Table 2). Also, a strikingly strong enrichment of the proteins under the keyword ‘host–virus interactions’ was noted (18/95 proteins, 19%) when compared with the presence of these proteins ($< 1\%$) in the whole proteome ($P < 0.0001$, Table 2).

Next, the Nature Pathway Interaction database and Reactome were integrated to the Medcel Integrator. Table 3 displays six most significant pathways, which putatively play an important role in inducing acute allergic reactions: angiopoietin receptor Tie2-mediated signalling; signalling by VEGFR1 and VEGFR2; BCR signalling pathway; signalling by hepatocyte growth factor receptor (c-Met); EPO signalling pathway and Fc epsilon receptor I (FcεR1) signalling in mast cells. These pathways share some genes/proteins, but each of them

has also unique genes/proteins of their own. The FcεR1 pathway may be considered as ‘a positive control’, because the role of FcεR1 in the binding of the allergen-specific IgE to the mast cell surface has been well established. In this study, it is noteworthy that the genes/proteins depicted in this FcεR1 pathway are all from the list of interacting proteins found with PINA and surprisingly not the ones with known allergy-related SNPs. This observation demonstrates well the power of such a network analysis to define the biologically relevant disease-related subsets of protein networks.

Finally, we also wanted to learn if these 95 genes show any transcriptional regulation related to the allergy status. To this end, we collected nasal epithelial cell swabs from both birch pollen allergic patients and healthy subjects. Samples were collected both during the symptom-free winter season and in a weekly time-series manner during the spring pollen season when allergic

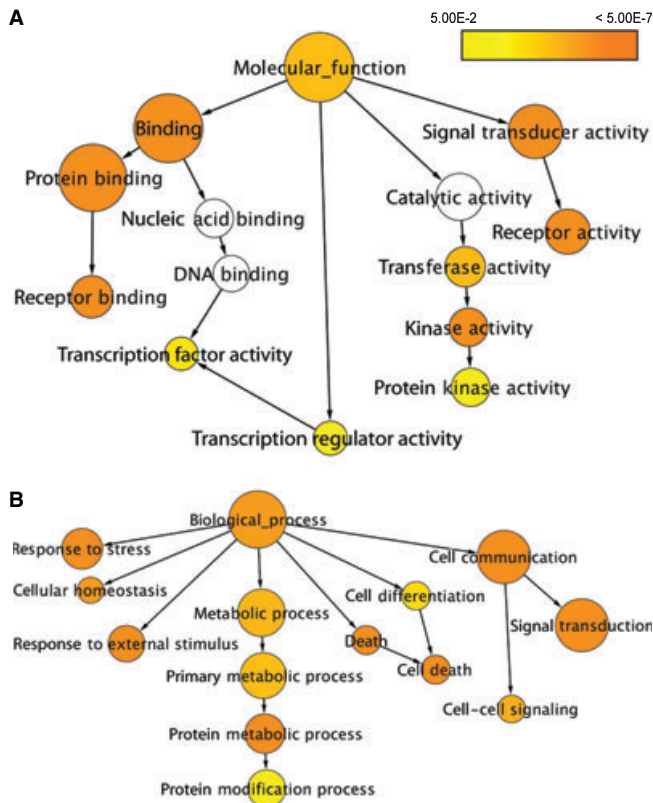


Figure 2. An enrichment analysis of the biological processes (Gene Ontology Slim) of 95 proteins in the network displayed in Fig. 1. The size of the dots reflects the number of proteins within the category and the colour displays the *P*-value of significance compared with background values. (A) molecular function; (B) biological process.

patients showed symptoms. There were 27 nodes in our network displaying transcriptomal regulation during the time-series analysis in the spring season (Fig. 3). Eight of these were found only in allergic patients and it is noteworthy that only two of them had been previously shown to carry SNPs linked to acute allergies (CCL26 and TLR3). All the others, STAT6, TNFR1A, CENPR, NCK1, TGM2 and EGFR, were only binding to proteins previously linked to allergy-related SNP modifications, and have not been shown to carry allergy-specific SNPs.

Discussion

Common allergic diseases heavily burden health care in the Western world. The aetiology of allergies needs to be solved to be able to better prevent the onset of allergic symptoms and treat these patients. Numerous genetic analyses describing SNPs on the coding sequences of several proteins and intergenic, nontranslated regions close to protein coding sequences have been performed. During the last years, dozens of candidate genes harbouring these SNP modifications have been associated

Table 2. A list of protein kinases and proteins involved in the host–virus interaction among the protein–protein network

Protein kinases	Host–virus interactions
AKT1	CCR3
ARBK	CCR5
BMX	CFLAR
E2AK2	E2AK2
EGFR	EP300
FAK1	FYN
FYN	GRB2
IKKA	IL2RG
JAK1	IMA1
JAK2	ITA5
KPCD	ITB1
KSYK	ITB3
LCK	KSYK
MK08	LCK
MK14	P85A
NFKB1	SRC
PGFRA	STAT1
PGFRB	STAT3
SRC	TNR1A
TAB2	VGFR2
VGFR1	
VGFR	

Proteins sharing both protein kinase and host–virus interaction functions are marked in bold. The SwissProt names are used without the tag ‘_HUMAN’ throughout the study

Table 3. Nature Pathway Interaction Database pathways most enriched in the proteins from our allergy-related interaction network from Fig. 1

Nature PID and Reactome pathways	Number of proteins in pathway	Number of observed proteins	Observed proteins
Angiopoietin receptor Tie2-mediated signalling	34	12	AKT1 BMX ETS1 FINC FYN GRB2 MK08 MK14 NCK1 FAK1 PTN11 SHC1
Signalling by VEGFR1 and VEGFR2	44	11	CTNB1 VGFR1 FYN GRB2 HS90A NCK1 FAK1 PTN6 PTN11 RAC1 SRC
BCR signalling pathway	46	10	AKT1 IKKA ETS1 FOS MK08 MK14 PTN6 RAC1 KSYK TRAF6
Signalling by hepatocyte growth factor receptor (c-Met)	44	10	AKT1 CTNB1 GRB2 MK08 NCK1 FAK1 PTN11 SHC1 SRC STAT3
EPO signalling pathway	27	8	GRB2 JAK2 MAPK8 MAPK14 PIK3R1 PTPN6 PTPN11 SHC1
Fc epsilon receptor I signalling in mast cells	45	8	AKT1 CHUK FYN GRB2 MK08 FAK1 PTN11 KSYK

with various allergic diseases. So far no attempts have been made to bind these SNP results together to get a systems level view.

The aim of our study was to begin a systems level analysis of the putative pathogenetic mechanisms involved with allergic reactions. Databases and especially their integrated and merged data warehouses allow a

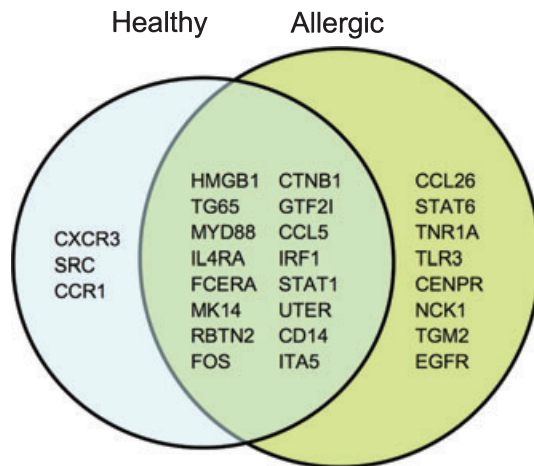


Figure 3. Transcriptionally regulated nasal epithelial nodes on the interaction network displayed in Fig. 1. Samples were collected both during the symptom-free winter season and in a time-series manner during the spring pollen season when allergic patients suffered from symptoms.

rapid and convenient access to the publicly available data. Furthermore, it is possible to place one's own data on top of the publicly available data and thus enhance the level of information. In this study, initiating with 38 SNP modified genes converted to their corresponding proteins obtained from published data, we could identify a protein–protein interaction network of 25 SNP proteins and another 70 proteins binding to at least two of the 25 original proteins.

One of the prominent observations in this network was that 20 of the 95 proteins on the network have previously been linked to a keyword 'host–virus interactions'. This may refer to the nature of the pollen-related allergic reaction, where the epithelium responds to external stimulus. We have recently shown that while the nasal epithelium of healthy subjects responded vigorously to the birch pollen challenge, the allergic patients lacked this ability. This could be one reason why antigens can be rapidly transported through the epithelium in allergic, but not in healthy, subjects. It is noteworthy that concomitantly the healthy subjects do not show any clinical symptoms, while the allergic subjects generate them rapidly. A majority of the structural genetic variations (SNPs) shown to link susceptibility to acute allergic diseases have been found especially in genes coding for proteins involved in immune responses. Thus it is possible that the SNPs associated with the susceptibility of allergic diseases could originate from the lack of this first line immune response against allergens interacting with the epithelium in combination with the aberrantly regulated immunological responses, leading to Th2- and IgE-dominated allergic responses.

Instead of concentrating, in our analysis, only on one or a few altered genes or their corresponding proteins, we attempted to generate larger protein–protein interaction

networks from our data. No single database alone can provide such a connected network; and to understand the new system's levels of diseases, we decided to build an integrated data warehouse, where information from several databases was combined. Thus we can show how the 95 proteins of allergic patients were connected together in a putative network.

The GO enrichment analysis indicates that 'response to stress' and 'responses to various stimuli' are significantly enriched among the proteins of the network. This is in accordance with our observation from manually annotated data, which reveal a significant presence of host–virus interactions within the allergy protein–protein network. Also other GO categories such as 'signal transduction' and 'protein modifications' are significantly enriched in the proteins related to allergic reactivity. In these two categories also various kinases are present. In this study, 22 out of the 95 proteins (23%) within the network were kinases. Protein kinases form one of the largest protein categories in human proteome as 2% of all proteins have one or several protein kinase domain(s) (18). Protein kinases phosphorylate their substrates by modifying their activity in association with other proteins or cellular locations and these events can then mediate the signal transduction phenomena. A large number of protein kinases have been shown to carry a mutation with low frequency and almost 25% of them (120/518) have been suggested to act as cancer genes (19).

The observation that protein kinases are very strongly present in the allergy network is of interest as we have already pointed out in our previous studies the crucial role of lipid rafts and caveolae in the active transport of pollen allergens through the intact epithelium all the way down to the Fc epsilon receptors on mast cells. As the majority of kinases harbour within these lipid rafts and caveolae, this could provide a link to the pathogenesis of allergic reactions in allergic patients. Eight of the proteins in our small allergy-related network showed significant transcriptomic regulation in nasal epithelial cells in the time-series analysis during the birch pollen season in allergic patients, but not in the healthy controls. Once again, the systems level analyses acquiring also other data than just the SNP-modified genes can help us to generate new knowledge of the basic mechanisms in allergy.

Compared with the previous reports where only one gene at a time has been in focus when the pathogenetic mechanisms of multifactorial diseases such as acute allergic reactions were analysed, we now focused on the entire set of 39 genes and their corresponding proteins. Out of these, 25 could be connected to a gene–mRNA–protein and protein interaction network, enriched significantly with protein kinase activity and host–virus interactions. Taken together, we show in this study, with our *in silico* analysis framework and the outside databases, that we can increase the level of knowledge by performing systems level analyses of the previously characterized genes carrying SNPs related to allergic diseases.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. All genes and their corresponding proteins. The original genes, where SNPs were found, and their corresponding proteins are shown in bold.

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Supplement table 1

All genes and their corresponding proteins. The original genes, where SNPs were found and their corresponding proteins are shown in bold.

Genes	Proteins	IL4R	IL4RA_HUMAN
A2M	A2MG_HUMAN	IRF1	IRF1_HUMAN
ADRB2	ADRB2_HUMAN	IRF2	IRF2_HUMAN
ADRBK1	ARBK1_HUMAN	ITGA5	ITA5_HUMAN
AKT1	AKT1_HUMAN	ITGB1	ITB1_HUMAN
BMX	BMX_HUMAN	ITGB3	ITB3_HUMAN
BRCA1	BRCA1_HUMAN	ITGB3BP	CENPR_HUMAN
CCBP2	CCBP2_HUMAN	JAK1	JAK1_HUMAN
CCL11	CCL11_HUMAN	JAK2	JAK2_HUMAN
CCL26	CCL26_HUMAN	KDR	VGFR2_HUMAN
CCL5	CCL5_HUMAN	KPNA1	IMA1_HUMAN
CCR1	CCR1_HUMAN	LCK	LCK_HUMAN
CCR3	CCR3_HUMAN	LMO2	RBTN2_HUMAN
CCR4	CCR4_HUMAN	MAPK14	MK14_HUMAN
CCR5	CCR5_HUMAN	MAPK8	MK08_HUMAN
CCRL1	CCRL1_HUMAN	MS4A2	FCERB_HUMAN
CD14	CD14_HUMAN	MYD88	MYD88_HUMAN
CHUK	IKKA_HUMAN	NCK1	NCK1_HUMAN
CSF2RB	IL3RB_HUMAN	NFKB1	NFKB1_HUMAN
CTNNB1	CTNB1_HUMAN	NLRP4	NALP4_HUMAN
CXCR3	CXCR3_HUMAN	P2RY2	P2RY2_HUMAN
DPP4	DPP4_HUMAN	PDGFRA	PGFRA_HUMAN
EGFR	EGFR_HUMAN	PDGFRB	PGFRB_HUMAN
EIF2AK2	<u>E2AK2_HUMAN</u>	PIK3R1	P85A_HUMAN
EP300	EP300_HUMAN	PRKCD	KPCD_HUMAN
ETS1	ETS1_HUMAN	PTK2	FAK1_HUMAN
FADD	FADD_HUMAN	PTPN11	PTN11_HUMAN
FANCC	FANCC_HUMAN	PTPN6	PTN6_HUMAN
FASLG	TNFL6_HUMAN	Q9NYJ8	TAB2_HUMAN
FCER1A	FCERA_HUMAN	RAC1	RAC1_HUMAN
FLT1	VGFR1_HUMAN	RAD50	RAD50_HUMAN
FN1	FINC_HUMAN	RELA	TF65_HUMAN
FOS	FOS_HUMAN	SCGB1A1	UTER_HUMAN
FYN	FYN_HUMAN	SHC1	SHC1_HUMAN
GATA3	GATA3_HUMAN	SRC	SRC_HUMAN
GNA11	GNA11_HUMAN	STAT1	STAT1_HUMAN
GNB2L1	GBLP_HUMAN	STAT3	STAT3_HUMAN
GRB2	GRB2_HUMAN	STAT6	STAT6_HUMAN
GSTP1	GSTP1_HUMAN	SUMO4	SUMO4_HUMAN
GTF2I	GTF2I_HUMAN	SYK	KSYK_HUMAN
HMGB1	HMGB1_HUMAN	TGM2	TGM2_HUMAN
HSP90AA1	HS90A_HUMAN	TICAM1	TCAM1_HUMAN
IL10	IL10_HUMAN	TLR2	TLR2_HUMAN
IL13	IL13_HUMAN	TLR3	TLR3_HUMAN
IL13RA1	I13R1_HUMAN	TNC	TENA_HUMAN
IL13RA2	I13R2_HUMAN	TNFRSF1A	TNR1A_HUMAN
IL1RL1	ILRL1_HUMAN	TRAF6	TRAF6_HUMAN
IL2RG	IL2RG_HUMAN		
IL4	IL4_HUMAN		