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Gene Network Analysis of Small Molecules with Autoimmune Disease Associated Genes Predicts a Novel Strategy for Drug Efficacy

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Abstract

Numerous genes/SNPs in autoimmune diseases (ADs) are identified through genome-wide association studies (GWAS) and likely to contribute in developing autoimmune phenotypes. Constructions of biologically meaningful pathways are necessary to determine how these genes interact each other and with other small molecules to develop various complex ADs phenotypes prior to beginning time-consuming rigorous experimentation. We have constructed biological pathways with genetically identified genes leading to shared ADs phenotypes. Various environmental and endogenous factors interact with these ADs associated genes suggesting their critical role in developing diseases and further association studies could be designed for assessing the role of these factors with risk allele in a specific gene. Additionally, existing drugs that have been used long before the identification of these genetically associated genes also interact with these newly associated genes. Thus advanced therapeutic strategies could be designed by grouping patients with risk allele(s) in particular genes that directly or closely interact with the specified drugs. This drug-susceptible gene network will not only increase our understanding about the additional molecular basis for effectiveness against these diseases but also which drug could be more effective for those patients carrying risk allele(s) in that gene. Additionally, we have also identified several interlinking genes in the pathways that could be used for designing future association studies.

Introduction

Autoimmune diseases (ADs) are a group of diseases that occur when the body's immune system turns against the body itself, attacking as if it were a foreign pathogen. They comprise more than 50 distinct diseases and syndromes, and affect about 5% of the population in Europe and North America, with two thirds of the patients being female [1]. Some of the major debilitating, life-threatening ADs are systemic lupus erythematosus (SLE), type 1 diabetes (T1D), rheumatoid arthritis (RA), Crohn's disease/inflammatory bowel syndrome (CHD/IBD), celiac disease (CD), multiple sclerosis (MS), ulcerative colitis (UC), Sjögren's syndrome (SS), Psoriasis (Pso) and Ankylosing spondylitis (ANS). Although many of these diseases have distinct clinical phenotypes, genetic susceptibility of

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multiple organ specific ADs often share underlying commonalities [2–4]. Past six years GWAS on several ADs have identified numerous genes and recently accumulated evidence indicating that common SNPs, such as rs7574865 (*STAT4*), rs6920220 and rs10499194 (*TNFAIP3* region) are associated with multiple ADs including RA, SLE, and T1D [5–8]. In a similar manner, shared autoimmunity with multiple autoimmune disorders, including T1D, RA, and SLE have been observed for C1858T mutation of PTPN22 (rs2476601) [9–11] and for multiple polymorphisms (SNPs) of IRF5 [12, 13]. Non-synonymous (Gly307Ser) coding variant, rs763361 of *CD226* gene has also been shown to be associated with multiple autoimmune phenotypes such as T1D, MS, CD, RA, Wegener's granulomatosis (WG), and autoimmune thyroid disease (AITD)[14–16]. ERAP1 and ERAP2 are also shown to be associated with multiple ADs including T1D, CHD/IBD, MS and ANS[17].

Common SNPs in these genes produce altered protein structures or differences in expression level capable of changing normal molecular functions to activate alternative signaling pathways in the cell. However, in these complex diseases, some healthy people also bear risk alleles but do not develop disease phenotypes. Genotype-phenotype correlation is complex and several factors play critical roles in developing complex disease phenotypes. Interactions of endogenous (estrogen, progesterone, vitamin D, cytokines and chemokines, etc.) and environmental factors such as smoking, nutrition, and Reactive Oxygen Species (ROS) in conjunction with the risk allele immensely contribute to the development of disease phenotypes. Thus building suitable network with the genetically associated genes in ADs would provide excellent hypothesis for future experimentation to tract the molecular pathways of developing disease phenotypes. It would also provide the interacting environmental factors with a risk allele carrying associated genes that could be used for testing associations for disease phenotypes.

Several software are available for identifying protein-protein (gene/gene) interaction such as, KEGG (Kyoto Encyclopedia of Genes and Genomes, www.genome.jp/kegg); Genomatix (www.genomatix.de), DAPPLE (www.broadinstitute.org/mpg/dapple), JMP genomics (www.jmp.com/software/genomic). Large databases for protein-small molecule interactions were developed by Kuhn et al. [18] and also independently compiled by IPA analysis (www.ingenuity.com). IPA is one of the widely cited protein-protein/protein-small molecule interacting software and has more flexibilities in respect to user friendly, interacting and with vast information.

Using current knowledge-based biological networking with Ingenuity Pathway Analysis (IPA), we demonstrate that gene-environment and gene-drug interactions could provide an excellent hypothesis prior to rigorous experimentation and drug design. We also identify connector 'missing interacting genes' between two risk genes that could be further tested for association studies. As it is evident that ADs susceptible genes share common pathways, therefore it would be important to see whether a common drug or a group of common drugs could be effective for risk allele carrying patients and whether this information would improve future therapies.

Materials and Methods

Associated genes in ADs

Genes used in these studies are extracted from published reports of GWAS and are associated with at least one autoimmune disease at the genome level significance ($p < 10^{-8}$). However, very few of them are suggestively linked using either family based genetic studies or associated in multiple populations [Table 1]. For SLE, 50 primary genes are identified and all are used in network except WDFY4, which has no known function and could not be integrated in the network. 20 genes are interconnecting genes (proposed by IPA). For T1D,

15 genes are identified and except CLEC16A, all are included in the network. Six genes and 11 miRNAs (Mir) are interconnecting. For RA, 32 genes are known to be associated and included in the network with the exception of 2 genes (TAGAP, LCE3B). Seven genes and 12 miRNAs are interconnecting. Nineteen associated genes are included in the IBD network excluding MUC19. Two genes and 12 miRNAs are interconnecting. For MS, ULC and CD, individual networks are not constructed due to a limited number of identified genes.

However, several genes are associated in multiple ADs and are included in the shared network and the small molecule network. In shared and gene-small molecule/drug interactions, each gene is shown only once in the pathway although some of them are associated in multiple diseases and interconnected through the whole network, implying that any gene could be associated in any of the autoimmune phenotypes, but not yet explored extensively in association studies. In the shared and drug-gene network, all 128 associated genes were used to construct the basic network but 5 genes are not integrated into the network. However, 42 genes are interacting and could be extremely useful for designing future association studies.

IPA analysis

All networks are constructed using IPA (Ingenuity Pathway Analysis); IPA analyzes two types of data. From large scale gene expression data, it takes input as gene names and constructs a network based on expression level, thus also calculates statistical power of interactions. However, in absence of expression data, for knowledge based interaction, it connects any two given molecules (gene/protein/drug/small molecule) based on existing literatures. This is extremely powerful as because without such interactive databases it would be impossible to know every possible interactions of a molecule existed in scientific literatures. In brief, after giving the names of genes/molecules, it is to enquire IPA whether there are any known interactions exists for these two molecules in the literature. Generally IPA gives two types of connections: a solid line and a dotted line. Solid lines represent confirmed, established interactions and are validated with multiple techniques. Thus, any connections represented by solid lines automatically warrant that direct interactions are experimentally verified. However, dotted lines represent hypothetical connections meaning they are connected through intermediate genes or some physical interactions that are reported but not well established. Here IPA connections used are literature based interactions, primarily in the gene/protein and small molecule level.

“Missing interacting genes” refers to those genes which were not identified through GWAS or genetically but are necessary to construct the shortest pathway between two associated genes. When two associated genes do not interact directly, it gives a common gene that both of these genes are known to interact with biochemically. “Close interacting genes” here refer to shortest pathways by which two genes interact to construct the pathway without involving many interlinking genes. For example, ITGAM interacts with other SLE risk genes directly or indirectly with one or two intermediate genes but does not need 20 unknown genes (biochemically relevant) to connect other associated genes [Fig 1].

Selection of small molecules and drugs

Small molecules are common molecules that play important roles in physiological processes, such as nicotine, vitamin D, progesterone, beta-estradiol, lipopolysaccharides, reactive oxygen species (ROS), etc. The information for prescribed drugs generally used for ADs were obtained from a clinical rheumatologist scientist. Some cancer drug information was obtained from literature and used in this study.

Results

SLE-associated genes interact each other leading to common molecular pathways

In SLE, more than 50 genes have been identified [Table 1] through genome wide association studies (GWAS) and candidate gene analysis. Although these genes could be connected to known biochemically interacting genes and pathways, it would be valuable/worthwhile to investigate whether these genes interact each other without prior known biochemically interacting genes or pathways. In such cases, new pathways would be generated and provide an experimental basis for developing disease phenotypes. In addition, to connect two genetically identified SLE genes, IPA could identify novel genes that would be tested for further association studies.

ITGAM (CD11b) is an integrin that is expressed in neutrophil, monocytes, macrophages and its role in phagocytosis, aggregation, leukocyte adhesion and cellular signaling are well established [19, 20]. GWAS showed that it is strongly associated with SLE, specifically with renal manifestation [21, 22]. Although shared genetic loci are often involved in many ADs, this gene is not associated with any other ADs [3]. When a pathway is constructed [Fig 1], ITGAM surprisingly shows close interactions with other SLE associated genes that have been identified through GWAS studies [23–27] and shares common molecular pathways. However, these biological pathways are not exhaustive and may exclude other genes/pathways as this network is constructed with the shortest possible interacting pathways and a minimal input of nonassociated genes known as biochemically interacting genes (proteins). For example, ITGAM is not known to biochemically interact with IFNG and CD226 while all these three genes are associated with SLE [16, 21, 28]. However indirect interaction suggests that potential biochemical interaction could be explored for these proteins. Thus the network provides the basis for interacting genetically susceptible genes in SLE and has future potential for biochemical characterization of SNP specific functions. This network also identifies interlinking genes such as ERBB2, STK16, IL4, IL1B, HNF4A, BCL2, HDAC1, PKC and PPARG that are not studied or reported to be associated with any ADs but these are potential genes to include in designing further future association studies. Among interlinking genes, STAT3, RELA, TGFB1 and IL12 are not reported to be associated with SLE but they are associated with T1D, RA, RA and MS respectively and could be assessed for potential association with SLE.

T1D associated genes interact each other mainly through miRNA

GWAS and candidate gene analysis identified [Table 1] several genes in T1D [14, 16, 29] but their molecular etiologies relating to T1D pathogenesis have not been investigated. Although these genes could be in the known biochemical pathways but it is not known whether they themselves can interact each other or can be regulated. However, we find that these T1D associated genetically identified genes are mostly interconnected through miRNAs thus could bypass earlier known biochemical interactions. [Fig 2]. It also appears that miRNAs are a necessary link to construct biological pathways interlinking T1D associated genes and identification of miRNA in ADs [30, 31] greatly enhance the construction of such a pathway. As miRNAs are earlier not known and their roles are not been investigated earlier extensively, they are integral part of the T1D interconnecting pathways and could play important role in developing T1D pathogenesis. The effect of these miRNAs could be tested biochemically to define how these miRNAs modulate the expression of these genes, contribute to develop disease phenotypes, and could be efficient targets for associated gene specific molecular therapy [32]. It is also interesting that three of the five interlinking genes PRDM1, IL2 and LYN are shown to be associated with SLE and RA.[28, 33–35], thus could have tremendous potential to look at for future T1D association

studies. Nevertheless, the SNPs in these interconnecting miRNA sequences also could be associated with T1D.

RA associated genes interact each other suggesting they are important components of common molecular pathways

Most of the rheumatoid arthritis associated genes identified [Table 1] through GWAS [29, 33, 36] have very different cellular functions. For example, CD40, CD83, CD244, TRAF1, IL12B, TNFRSF14, CCL21, CCR6, etc. are associated with RA and have a distinct role in modulating the immune system. Again, many genes are not known to have immune functions such as CDK6 (cyclin dependent kinase 6), KIF5A (kinesin family member 5A), IKZF3, ZNF365 (Zinc finger transcription factor), ZFP36L1 (EGF responsive factor) and TGFBI (transforming growth factor) but they have distinct cellular growth or transcription function. However, among many transcription factor or cellular growth factor, these genes are discretely associated with RA but their closely known biochemically interacting genes (such as CDK family) on cellular growth or transcription factors are not reported to be associated with RA. This suggests that except their known distinct biochemical functions, these genes could function in multiple ways in multiple pathways. However, these genes are mostly connected to each other through miRNAs suggesting a need for rigorous biochemical experimentation is necessary for defining their role in RA pathogenesis. Additionally, these miRNAs could be important regulator of these genes. Thus genes having unknown immune functions are well connected in the network [Fig 3] and provide an excellent molecular basis to explore their novel role in autoimmune phenotypes, especially to RA phenotypes. Among interconnecting genes, IL2 is associated with IBD and could be tested for association studies in other ADs. However, other interlinking genes such as IL4, RNF2, MYC and PLD could be a potential target for designing future association studies.

IBD/CHD associated genes form a network of common molecular pathways

GWAS identified numerous genes in IBD/CHD [29, 37] [Table 1] but little is known about their molecular interactions leading to development of disease phenotypes. Similar to RA associated genes, IBD associated genes are also involved in diverse cellular functions and most of them are not linked with known immune function. Only with two interconnecting genes, IBD associated genes could form a network suggesting that these genes have distinct molecular pathway that was not known earlier. Also, among 2 interconnecting genes, IFNG is shown to be associated with SLE and thus its association with IBD could also be tested in future investigations. However, gene networking [Fig 4] indicates that these genes are mainly connected through small molecules or miRNAs suggesting that these molecules [32, 38] could be important regulators of these associated genes and could contribute effectively to develop disease phenotypes. Thus, modulation of expression of these genes through small molecules in a defined cellular or animal system could be attempted as a first step towards developing chemotherapy for IBD/CHD [32].

Interaction of genetically identified autoimmune genes could provide pathways leading to shared autoimmune phenotypes

In ADs, numerous genes are associated through GWAS studies [Table 1] [14, 16, 23, 24, 29, 33, 36, 37, 39–41] and some/most of them share various clinical phenotypes and are implicated in more than one disease [4, 23] (designated by star in Fig. 5). Thus this networking has three importances whether 1) shared genes could make a single network comprising common molecular pathways leading to any disease phenotype 2) nonshared genes could also be associated with other ADs and 3) interlinking genes could also be associated with any ADs.

Five genes (WDFY4 (SLE), TAGAP (RA, CD), LCE3B (RA, Pso), CLEC16A (T1D, MS), and MUC19 (IBD)) have no known functions and thus could not be connected in the network. Apart from that, each gene interacts directly or indirectly with each other suggesting a major part of molecular pathways are similar in ADs. To obtain a common ADs network, 42 interconnecting genes between associated genes are essential and these interlinking genes may be useful to consider for future association studies. These are mainly TERT, CDKN1B, IL18, EEF1A1, YWHAG, IRF4, XBP1, NMNAT, HNF4A, HDAC4, TRAF2, IRS1, ZNF217, KIF21B, AGT, CD28, APP and IL1B [Fig 5]. However biochemically interacting genes are not always susceptible for disease phenotypes. For example ITGAM (CD11b) is strongly associated with SLE but its heterodimeric protein partner ITGB2, (CD18) is associated with LAD (*Leukocyte Adhesion Deficiency* [42] not with SLE. GWAS statistics consider significance of a gene/SNP at the population level whereas biochemically interacting genes may not always give significant associations at the population level but could be a integral part of disease developing biochemical pathways.

These pathways also include many prominent multifunctional genes such as NF-KB1, ERK, ERBB2, TGFBI, APP and JNK, although SNPs from these genes are yet to be identified as statistically significantly associated at the genome level. This indicates that either these genes are not studied extensively in association studies or any mutations in these genes are lethal to the individual, thus eliminated from population. For example, the NF-KB1, an important transcription factor regulates multiple pathways in living cells leading to inflammation but is not associated with any ADs. However its interacting partner RELA is shown to be associated with rheumatoid arthritis[43].

Interactions of small molecules, drugs and environmental modifiers with genetically identified autoimmune disease genes

In complex diseases, the role of environmental factors are extremely important because they interact with the gene leading to disease phenotypes[44]. In fact a major part of the effort of the association studies are directed towards identifying the environmental factor that interacts with the risk polymorphism of an SNP. Polymorphic changes in a gene could alter its own expression or produce an altered protein that exhibits a differential binding affinity with its interacting proteins or small molecules and modulates downstream pathway genes. However, these small molecules could be of two types--environmental (nicotine, various nutritional agents, seasonal changes, etc.) or endogenous (hormones, cytokines, chemokines).

In this network, we show that various small molecules such as beta-estradiol, vitamin D, progesterone, nicotine and ROS interact with these ADs associated genes and could be major modulators of ADs pathways [Fig 6]. Although some of these small molecules are known to affect ADs [45], their interactions with genetically identified genes were not worked out earlier and their interactions with these genes are not extensively studied in developing ADs phenotypes. This network provides the basis for experimentation with these factors to understand their effect on susceptible genes in both biochemical and genetic association studies.

Similarly, the interaction of the existing drugs with the ADs associated genes has not been studied earlier due to the fact that these drugs were developed to inhibit specific molecular pathways and during these process of drug development, the informations or identifications of association with ADs were not known. Various drugs have long being used to treat ADs but none of them completely reverse disease processes, although they may suppress or delay disease progression. These drugs were developed on the basis of their ability to act mainly as immunosuppressors (azathioprine, celcept, cyclophosphamide), TNF inhibitors (infliximab, etanercept) or DNA synthesis inhibitors (methotrexate, cyclophosphamide). It is

fascinating to work out whether these existing drugs also interact with these newly identified GWAS genes that was not known earlier as a part of existing biochemical pathways.

Surprisingly, most of these drugs interact with these genes directly or indirectly suggesting that these genes could be clinically useful targets for these existing drugs. This implies that the efficacy of these existing drugs could be improved by categorizing patients based on their genotypes, specifically with the risk SNPs carrying genes. For example, an existing drug that interacts with an SLE associated gene or with its closely interacting genes could be more effective for those patients carrying the risk allele in those genes.

In our drug-gene network, we observe adalimumab and golimumab interact with TNF, methotrexate with TGFB1, phenethyl isothiocyanate with ERK, and can modulate ADs pathway genes. Similarly, infliximab interacts only with IFNG and IRS1. Pelargonidin chloride mainly acts as an antioxidant and modulates many redox regulatory molecules. Cyclophosphamide interacts through IFNG, ERBB2 and IL12B. Decitabine, camptothecin, and bucladesine interact with many genes and may act through common autoimmune pathways [Fig. 6]. A modular views are shown for closely interacting drugs and associated genes [Fig. 7]. However, etanercept interacts with many genes including ICAM1, IL12B, IL1B, RELA (ICAM1 is associated with SLE, IL12B is susceptible for MS, RELA is a susceptible gene for RA (Fig 6, 7d); cyclophosphamide acts with IL12B and IFNG (IFNG is a susceptible gene for SLE, IL12B is a susceptible gene for MS), while geldanamycine interacts with JAK2 and LRRK2 (both are susceptible for IBD (Fig 6, 7a). Similarly, diethyl nitrosamine interacts with ITLN1 (susceptible gene for ULC) and tetrachlorodibenzodioxin with SLC2275, CCL21, RELA and IL2 (CCL21, RELA, IL2 are associated with several ADs). It would be interesting to see whether etanercept works better with the patients carrying the risk allele of ICAM1 or RELA or IL12B and diethyl nitrosamine with the patients carrying risk allele of ITLN1. Similarly, Abatacept is a fusion protein of IGG and CTLA4 that is used to treat RA and interacts with many genes such as IFNG, CD80, CD86, PDCD1, etc. Except for IFNG and PDCD1 which are susceptible genes for SLE, none of these directly interacting genes are associated with any ADs (Fig. 6.). However, among these closely interacting genes, CD86 and CD80 directly interact [Fig. 7b, d] with RELA, which is susceptible gene for RA, thus, abatacept could be more effective on patients having risk allele of RELA or IFNG or ICAM1. Similarly, rituximab interacts with IL10 and STAT3 indicating that patients with the risk SNP in either of these two genes or in their closely interacting genes could benefit most from this treatment.

Drugs that are developed for other diseases, such as cancer, may also be useful in treating ADs (e.g rituximab was developed primarily for cancer and is being used successfully in ADs). We tested some of these cancer drugs to see whether they also interact with ADs genes. Many drugs such as cycloheximide interact with TNIP1 and TNFIP3 (susceptible for SLE and RA respectively), camptothecin interacts with SH2B3 (susceptible for MS and T1D), rotenone interacts with NMAT2 and MMEL1 (susceptible for SLE and RA respectively) through AGT, thus indicating their potential as therapeutic drugs in ADs. Several small molecules not yet tested for drug development, such as Lipopolyscharides (LPS), PMA, forskolin, and PD98059 interact with multiple genes in ADs pathways and could be considered as potentially important molecules for future drug design and therapy.

Discussion

Expression of genes are cell type specific and cell type specific biological pathways are abundant in the literature[23, 24, 46]. However, what is not known is how the risk SNPs in these genes cause disease phenotypes. The cell type specific expression has not been discussed here solely to emphasize shortest route of gene-gene/protein-protein interactions

of genetically identified disease associated genes beyond their barrier of cell specific expressions. In fact, in ADs, most of these gene products act on other cells (carried by blood) from the cells where they are primarily produced such as (cell surface molecules or receptors, CD series such as CD11b, CD83, CD226, etc., or chemokines, such as interferon, interleukins, etc.). For example, CD11b is strongly associated with SLE. Consequently it could indirectly signal for autoantibody production from B cells which is a hallmark of SLE pathogenesis although CD11b is not expressed in naive B cells [47, 48].

The genetic interaction of small molecules has not been studied extensively in the population level, yet it is known that estrogen and progesterone levels and ATP generation play a critical biochemical role in ADs phenotype [49, 50]. These factors are well integrated in ADs gene network and could be a major modulator of genetically susceptible genes. They could have a substantial impact in the outcome of various phenotypes. The environmental factor that was most studied was smoking behavior with IBD/CHD (Crohn's disease) phenotype. By studying 310 patients with smoking behavior and 976 controls, van der Heide (2010) [51] showed that PTPN2 (rs2542151) was only associated in the smoking CHD cohort ($P=0.041$) and not in the entire ($P=0.23$) population or only in the non-smoking CHD cohort ($P=0.80$). Risk polymorphism specific drug efficacy for TNF alpha blocker has also been reported [52]. In another AD, pemphigoid (Pg), computer assisted mechanism explains the production of four different antibodies from a single HLA allele for four different antigens that result in four subset of disease with different prognosis and clinical profiles [53]. However, large cohorts with adequate lifestyle information are often necessary for identification of such interactions of environmental factors with genetically susceptible genes to be significant at the genome level.

The network building leading to molecular interactions of currently used medicines or drugs with genetically identified susceptible genes has multiple potential for biological and clinical applications. All drugs were developed on the basis of their biochemical functions or interactions prior to the knowledge of identified associated genes/SNPs. Despite these facts, it is evident that these commonly used drugs could modulate the molecular function of associated genes and could have substantial impact in curing or delaying diseases.

The outcome of these approaches could be tested experimentally by several ways. Primarily, if large cohort of patients with genotyping data and data of prescribed drug use are available, patients' recovery rate or drug efficacy could be statistically analyzed directly with the genotype (for a risk SNP) of the patients. In other words, RA patients who were given a spectrum of drugs including methotrexate, the data could be analyzed statistically for methotrexate used patients with ZFP36L1 risk SNP (Fig 7) to assess whether ZFP36L1 risk SNP carrying patients were better recovered with methotrexate. However, as ADs patients are generally given multiple drugs, it would be difficult to analyze for the effect of single drug. But if data of large cohorts is available, by subtracting each drug and by condition analysis, the effect of single drug would theoretically be possible. Another approach would be to design clinical trials based on these criteria. Patients with a risk SNP in a gene could be prescribed the specific drug that interacts with that gene. Some of these patients carrying same genotype could be treated with other drugs using conventional criteria. The first group of patients (risk gene interacting drug treated group) would be expected to have better recovery than the second group (other drug users). In the future, we foresee patient grouping could be possible on the basis of interactions of particular medicine with patients carrying risk SNP(s) in certain genes. Thus, existing drugs could be used for developing personalized medicine based on patient genotypes. We have also shown interactions of ADs associated genes with some potential small molecules or drugs that are being used or developed to treat other diseases such as cancer. Such drugs as rituximab, cyclophosphamide, and methotrexate are being used for both cancer and ADs. Therefore other cancer drugs that are

not being currently used, such as geldanamine or sulfanilamine could be evaluated for ADs on the basis of their interactions with autoimmune susceptible genes and be expected to be much more effective for ADs patients carrying genetically susceptible risk allele. Again, in ADs and auto inflammatory diseases (AIDs), the chronic activation of immune system are common, thus ADs drugs could also be useful to treat AIDs. FMF (Familial Mediterranean Fever) and other 11 genes are identified in AIDs [54] and interaction studies with these genes and drugs or therapeutic peptides (domain) that are used for ADs could also be tested for their efficacy for treating AIDs.

Drug dependent gene expression is well documented and it changes the expression of its directly interacting or downstream pathway genes. The information available based on drug dependant gene expression are of two types- tissue specific global gene expression with large scale techniques, such as microarray, CHIPseq, etc and risk allele specific gene expression in patient samples. However, the tissue specific expression with large genomic techniques are not useful to obtain risk allele specific added information, thus it would be worthwhile to consider risk allele specific expression in patients. Although discrete reports are available for some specific genes, vast databases are not available and it is important to address to develop such databases. The proposed model of susceptibility genes and drug interaction would be very useful when the risk allele specific gene expression data is available. Nevertheless, it is often observed that risk allele carrying susceptibility genes have impact on its own gene expression. For example, TNFSF4 and BLK, both are associated with SLE and the risk allele at their own promoter region increases[1] and decreases[55] their expression respectively. Thus, if a drug interacts with these proteins such as camptothecin that interacts with BLK [Fig. 6], would definitely have major impact in drug efficacy. More specifically, risk allele specific interaction with the drug could have been the reason for drug efficacy compared to nonrisk allele.

Beside these drugs, numerous peptides are also used as drugs in ADs and are developed based on their biochemical functions. This could be efficiently performed using the specific peptide (used as drug) which is generally a part of a domain of a protein molecule and *in silico* interaction with the ADs associated genes could open up a new area of modern day treatment of ADs [56]. Thus an associated gene -peptide interaction map could be developed similar to gene-drug network and could be tested similarly for a risk allele specific treatment by classifying these patients based on their risk allele carrying genes.

In summary, a number of GWAS have identified numerous genes associated with ADs and our in-depth comprehensive network analyses demonstrate that interactions of these genetically susceptible genes provide a distinctive molecular basis of developing ADs. Nevertheless, interactions with small molecules such as beta-estradiol, progesterone, ROS, vitamin D, oxygen, ATP, nicotine and lipopolysaccharides are implicated to modulate these genetically associated genes and contribute extensively to the development of disease phenotypes. Moreover, existing drugs and other small molecules that interact with AD genes may provide the molecular basis of their mechanism of actions. In addition, some conventional drugs are attractive candidates for gene specific drug design for those patients carrying specific risk allele(s) leading to the development of personalized medicine using the patient's genotype.

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References

- Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. *J Autoimmun.* 2009; 33(3–4):197–207. [PubMed: 19819109]
- Lettre G, Rioux JD. Autoimmune diseases: insights from genome-wide association studies. *Human molecular genetics.* 2008; 17(R2):R116–121. [PubMed: 18852199]
- Ramos PS, Criswell LA, Moser KL, Comeau ME, Williams AH, Pajewski NM, Chung SA, Graham RR, Zidovetzki R, Kelly JA, et al. A comprehensive analysis of shared loci between systemic lupus erythematosus (SLE) and sixteen autoimmune diseases reveals limited genetic overlap. *PLoS Genet.* 2011; 7(12):e1002406. [PubMed: 22174698]
- Cotsapas C, Voight BF, Rossin E, Lage K, Neale BM, Wallace C, Abecasis GR, Barrett JC, Behrens T, Cho J, et al. Pervasive sharing of genetic effects in autoimmune disease. *PLoS Genet.* 2011; 7(8):e1002254. [PubMed: 21852963]
- Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, de Bakker PI, Le JM, Lee HS, Batliwalla F, et al. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med.* 2007; 357(10):977–986. [PubMed: 17804842]
- Graham RR, Cotsapas C, Davies L, Hackett R, Lessard CJ, Leon JM, Burt NP, Guiducci C, Parkin M, Gates C, et al. Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. *Nat Genet.* 2008; 40(9):1059–1061. [PubMed: 19165918]
- Plenge RM, Cotsapas C, Davies L, Price AL, de Bakker PI, Maller J, Pe'er I, Burt NP, Blumenstiel B, DeFelice M, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. *Nat Genet.* 2007; 39(12):1477–1482. [PubMed: 17982456]
- Musone SL, Taylor KE, Lu TT, Nititham J, Ferreira RC, Ortmann W, Shifrin N, Petri MA, Kamboh MI, Manzi S, et al. Multiple polymorphisms in the TNFAIP3 region are independently associated with systemic lupus erythematosus. *Nat Genet.* 2008; 40 (9):1062–1064. [PubMed: 19165919]
- Begovich AB, Caillier SJ, Alexander HC, Penko JM, Hauser SL, Barcellos LF, Oksenberg JR. The R620W polymorphism of the protein tyrosine phosphatase PTPN22 is not associated with multiple sclerosis. *Am J Hum Genet.* 2005; 76(1):184–187. [PubMed: 15580548]
- Plenge RM, Padyukov L, Remmers EF, Purcell S, Lee AT, Karlson EW, Wolfe F, Kastner DL, Alfredsson L, Altshuler D, et al. Replication of putative candidate-gene associations with rheumatoid arthritis in >4,000 samples from North America and Sweden: association of susceptibility with PTPN22, CTLA4, and PADI4. *Am J Hum Genet.* 2005; 77(6):1044–1060. [PubMed: 16380915]
- Lee YH, Rho YH, Choi SJ, Ji JD, Song GG, Nath SK, Harley JB. The PTPN22 C1858T functional polymorphism and autoimmune diseases--a meta-analysis. *Rheumatology (Oxford).* 2007; 46 (1): 49–56. [PubMed: 16760194]
- Graham RR, Kozyrev SV, Baechler EC, Reddy MV, Plenge RM, Bauer JW, Ortmann WA, Koeuth T, Gonzalez Escribano MF, Pons-Estel B, et al. A common haplotype of interferon regulatory factor 5 (IRF5) regulates splicing and expression and is associated with increased risk of systemic lupus erythematosus. *Nat Genet.* 2006; 38(5):550–555. [PubMed: 16642019]
- Santana-de Anda K, Gomez-Martin D, Diaz-Zamudio M, Alcocer-Varela J. Interferon regulatory factors: beyond the antiviral response and their link to the development of autoimmune pathology. *Autoimmun Rev.* 2011; 11(2):98–103. [PubMed: 21872684]
- Todd JA, Walker NM, Cooper JD, Smyth DJ, Downes K, Plagnol V, Bailey R, Nejentsev S, Field SF, Payne F, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. *Nat Genet.* 2007; 39(7):857–864. [PubMed: 17554260]
- Smyth DJ, Plagnol V, Walker NM, Cooper JD, Downes K, Yang JH, Howson JM, Stevens H, McManus R, Wijmenga C, et al. Shared and distinct genetic variants in type 1 diabetes and celiac disease. *N Engl J Med.* 2008; 359(26):2767–2777. [PubMed: 19073967]
- Maiti AK, Kim-Howard X, Viswanathan P, Guillen L, Qian X, Rojas-Villarraga A, Sun C, Canas C, Tobon GJ, Matsuda K, et al. Non-synonymous variant (Gly307Ser) in CD226 is associated with susceptibility to multiple autoimmune diseases. *Rheumatology (Oxford).* 2010; 49 (7):1239–1244. [PubMed: 20338887]

17. Fierabracci A, Milillo A, Locatelli F, Fruci D. The putative role of endoplasmic reticulum aminopeptidases in autoimmunity: Insights from genomic-wide association studies. *Autoimmun Rev.* 2012
18. Kuhn M, Szklarczyk D, Franceschini A, von Mering C, Jensen LJ, Bork P. STITCH 3: zooming in on protein-chemical interactions. *Nucleic Acids Res.* 2012; 40(Database issue):D876–880. [PubMed: 22075997]
19. Springer TA. Folding of the N-terminal, ligand-binding region of integrin alpha-subunits into a beta-propeller domain. *Proc Natl Acad Sci U S A.* 1997; 94(1):65–72. [PubMed: 8990162]
20. Corbi AL, Kishimoto TK, Miller LJ, Springer TA. The human leukocyte adhesion glycoprotein Mac-1 (complement receptor type 3, CD11b) alpha subunit. Cloning, primary structure, and relation to the integrins, von Willebrand factor and factor B. *J Biol Chem.* 1988; 263(25):12403–12411. [PubMed: 2457584]
21. Nath SK, Han S, Kim-Howard X, Kelly JA, Viswanathan P, Gilkeson GS, Chen W, Zhu C, McEver RP, Kimberly RP, et al. A nonsynonymous functional variant in integrin-alpha(M) (encoded by ITGAM) is associated with systemic lupus erythematosus. *Nat Genet.* 2008; 40 (2): 152–154. [PubMed: 18204448]
22. Kim-Howard X, Maiti AK, Anaya JM, Bruner GR, Brown E, Merrill JT, Edberg JC, Petri MA, Reveille JD, Ramsey-Goldman R, et al. ITGAM coding variant (rs1143679) influences the risk of renal disease, discoid rash, and immunologic manifestations in lupus patients with European ancestry. *Ann Rheum Dis.* 2009
23. Zhernakova A, van Diemen CC, Wijmenga C. Detecting shared pathogenesis from the shared genetics of immune-related diseases. *Nat Rev Genet.* 2009; 10(1):43–55. [PubMed: 19092835]
24. Harley IT, Kaufman KM, Langefeld CD, Harley JB, Kelly JA. Genetic susceptibility to SLE: new insights from fine mapping and genome-wide association studies. *Nat Rev Genet.* 2009; 10(5): 285–290. [PubMed: 19337289]
25. Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, Ortmann W, Kosoy R, Ferreira RC, Nordmark G, et al. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. *Nat Genet.* 2009; 41 (11): 1228–1233. [PubMed: 19838195]
26. Yang W, Shen N, Ye DQ, Liu Q, Zhang Y, Qian XX, Hirankarn N, Ying D, Pan HF, Mok CC, et al. Genome-wide association study in Asian populations identifies variants in ETS1 and WDFY4 associated with systemic lupus erythematosus. *PLoS Genet.* 2010; 6(2):e1000841. [PubMed: 20169177]
27. Harley JB, Alarcon-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, Tsao BP, Vyse TJ, Langefeld CD, Nath SK, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXX, KIAA1542 and other loci. *Nat Genet.* 2008; 40(2):204–210. [PubMed: 18204446]
28. Kim K, Cho SK, Sestak A, Namjou B, Kang C, Bae SC. Interferon-gamma gene polymorphisms associated with susceptibility to systemic lupus erythematosus. *Ann Rheum Dis.* 2010; 69(6): 1247–1250. [PubMed: 19919944]
29. Noomen CG, Hommes DW, Fidder HH. Update on genetics in inflammatory disease. *Best Pract Res Clin Gastroenterol.* 2009; 23(2):233–243. [PubMed: 19414149]
30. Dai R, Ahmed SA. MicroRNA, a new paradigm for understanding immunoregulation, inflammation, and autoimmune diseases. *Transl Res.* 2011; 157(4):163–179. [PubMed: 21420027]
31. Bang-Berthelsen CH, Pedersen L, Floyel T, Hagedorn PH, Gylvin T, Pociot F. Independent component and pathway-based analysis of miRNA-regulated gene expression in a model of type 1 diabetes. *BMC Genomics.* 2011; 12:97. [PubMed: 21294859]
32. Lundstrom K. Micro-RNA in Disease and Gene Therapy. *Curr Drug Discov Technol.* 2011
33. Raychaudhuri S, Remmers EF, Lee AT, Hackett R, Guiducci C, Burt NP, Gianniny L, Korman BD, Padyukov L, Kurreeman FA, et al. Common variants at CD40 and other loci confer risk of rheumatoid arthritis. *Nat Genet.* 2008; 40(10):1216–1223. [PubMed: 18794853]
34. Maiti AK, Kim-Howard X, Viswanathan P, Guillen L, Rojas-Villarraga A, Deshmukh H, Direskeneli H, Saruhan-Direskeneli G, Canas C, Tobon GJ, et al. Confirmation of an association

- between rs6822844 at the IL2-IL21 region and multiple autoimmune diseases: evidence of a general susceptibility locus. *Arthritis Rheum.* 2010; 62(2):323–329. [PubMed: 20112382]
35. Lu R, Vidal GS, Kelly JA, Delgado-Vega AM, Howard XK, Macwana SR, Dominguez N, Klein W, Burrell C, Harley IT, et al. Genetic associations of LYN with systemic lupus erythematosus. *Genes Immun.* 2009; 10(5):397–403. [PubMed: 19369946]
 36. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, Li Y, Kurreeman FA, Zhernakova A, Hinks A, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet.* 2010; 42(6):508–514. [PubMed: 20453842]
 37. Franke A, Fischer A, Nothnagel M, Becker C, Grabe N, Till A, Lu T, Muller-Quernheim J, Wittig M, Hermann A, et al. Genome-wide association analysis in sarcoidosis and Crohn's disease unravels a common susceptibility locus on 10p12. *Gastroenterology.* 2008; 135(4):1207–1215. [PubMed: 18723019]
 38. Dalal SR, Kwon JH. The Role of MicroRNA in Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y).* 2010; 6(11):714–722. [PubMed: 21437020]
 39. Criswell LA. Gene discovery in rheumatoid arthritis highlights the CD40/NF-kappaB signaling pathway in disease pathogenesis. *Immunol Rev.* 2010; 233(1):55–61. [PubMed: 20192992]
 40. Zhernakova A, Stahl EA, Trynka G, Raychaudhuri S, Festen EA, Franke L, Westra HJ, Fehrmann RS, Kurreeman FA, Thomson B, et al. Meta-analysis of genome-wide association studies in celiac disease and rheumatoid arthritis identifies fourteen non-HLA shared loci. *PLoS Genet.* 2011; 7(2):e1002004. [PubMed: 21383967]
 41. Hoffjan S, Akkad DA. The genetics of multiple sclerosis: an update 2010. *Mol Cell Probes.* 2010; 24(5):237–243. [PubMed: 20450971]
 42. Kuijpers TW, Van Lier RA, Hamann D, de Boer M, Thung LY, Weening RS, Verhoeven AJ, Roos D. Leukocyte adhesion deficiency type 1 (LAD-1)/variant. A novel immunodeficiency syndrome characterized by dysfunctional beta2 integrins. *J Clin Invest.* 1997; 100(7):1725–1733. [PubMed: 9312170]
 43. Gregersen PK, Amos CI, Lee AT, Lu Y, Remmers EF, Kastner DL, Seldin MF, Criswell LA, Plenge RM, Holers VM, et al. REL, encoding a member of the NF-kappaB family of transcription factors, is a newly defined risk locus for rheumatoid arthritis. *Nat Genet.* 2009; 41(7):820–823. [PubMed: 19503088]
 44. Costenbader KH, Gay S, Alarcon-Riquelme ME, Iaccarino L, Doria A. Genes, epigenetic regulation and environmental factors: which is the most relevant in developing autoimmune diseases? *Autoimmun Rev.* 2012; 11(8):604–609. [PubMed: 22041580]
 45. Pender MP. CD8+ T-Cell Deficiency, Epstein-Barr Virus Infection, Vitamin D Deficiency, and Steps to Autoimmunity: A Unifying Hypothesis. *Autoimmune Dis.* 2012; 2012:189096. [PubMed: 22312480]
 46. Singh RP, Waldron RT, Hahn BH. Genes, tolerance and systemic autoimmunity. *Autoimmun Rev.* 2012; 11(9):664–669. [PubMed: 22155015]
 47. Kawai K, Tsuno NH, Matsushashi M, Kitayama J, Osada T, Yamada J, Tsuchiya T, Yoneyama S, Watanabe T, Takahashi K, et al. CD11b-mediated migratory property of peripheral blood B cells. *J Allergy Clin Immunol.* 2005; 116(1):192–197. [PubMed: 15990794]
 48. Arnold LW, Pennell CA, McCray SK, Clarke SH. Development of B-1 cells: segregation of phosphatidyl choline-specific B cells to the B-1 population occurs after immunoglobulin gene expression. *J Exp Med.* 1994; 179(5):1585–1595. [PubMed: 8163938]
 49. Cutolo M, Sulli A, Capellino S, Villaggio B, Montagna P, Seriolo B, Straub RH. Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity. *Lupus.* 2004; 13(9): 635–638. [PubMed: 15485092]
 50. Walker SE. Estrogen and autoimmune disease. *Clin Rev Allergy Immunol.* 2011; 40(1):60–65. [PubMed: 20182819]
 51. Wada T, Furuichi K, Sakai N, Iwata Y, Yoshimoto K, Shimizu M, Takeda SI, Takasawa K, Yoshimura M, Kida H, et al. Up-regulation of monocyte chemoattractant protein-1 in tubulointerstitial lesions of human diabetic nephropathy. *Kidney Int.* 2000; 58(4):1492–1499. [PubMed: 11012884]

52. Ingegnoli F, Favalli EG, Meroni PL. Does polymorphism of genes coding for pro-inflammatory mediators predict the clinical response to tnf alpha blocking agents? A review analysis of the literature. *Autoimmun Rev.* 2011; 10(8):460–463. [PubMed: 21296193]
53. Zakka LR, Reche P, Ahmed AR. Role of MHC Class II genes in the pathogenesis of pemphigoid. *Autoimmun Rev.* 2011; 11(1):40–47. [PubMed: 21782980]
54. Touitou I. New genetic interpretation of old diseases. *Autoimmun Rev.* 2012
55. Hom G, Graham RR, Modrek B, Taylor KE, Ortmann W, Garnier S, Lee AT, Chung SA, Ferreira RC, Pant PV, et al. Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX. *N Engl J Med.* 2008; 358(9):900–909. [PubMed: 18204098]
56. Shoenfeld Y. The future of autoimmunity. *Clin Rev Allergy Immunol.* 2012; 42(2):113–120. [PubMed: 22203433]
57. Lu R, Vidal GS, Kelly JA, Delgado-Vega AM, Howard XK, Macwana SR, Dominguez N, Klein W, Burrell C, Harley IT, et al. Genetic associations of LYN with systemic lupus erythematosus. *Genes Immun.* 2009
58. Kozyrev SV, Abelson AK, Wojcik J, Zaghlool A, Linga Reddy MP, Sanchez E, Gunnarsson I, Svenungsson E, Sturfelt G, Jonsen A, et al. Corrigendum: Functional variants in the B-cell gene BANK1 are associated with systemic lupus erythematosus. *Nat Genet.* 2008; 40 (4):484. [PubMed: 18368128]
59. Lofgren SE, Frostegard J, Truedsson L, Pons-Estel BA, D'Alfonso S, Witte T, Lauwerys BR, Endreffy E, Kovacs L, Vasconcelos C, et al. Genetic association of miRNA-146a with systemic lupus erythematosus in Europeans through decreased expression of the gene. *Genes Immun.* 2012; 13(3):268–274. [PubMed: 22218224]
60. Jacob CO, Reiff A, Armstrong DL, Myones BL, Silverman E, Klein-Gitelman M, McCurdy D, Wagner-Weiner L, Nocton JJ, Solomon A, et al. Identification of novel susceptibility genes in childhood-onset systemic lupus erythematosus using a uniquely designed candidate gene pathway platform. *Arthritis Rheum.* 2007; 56(12):4164–4173. [PubMed: 18050247]
61. Sawalha AH, Webb R, Han S, Kelly JA, Kaufman KM, Kimberly RP, Alarcon-Riquelme ME, James JA, Vyse TJ, Gilkeson GS, et al. Common variants within MECP2 confer risk of systemic lupus erythematosus. *PLoS One.* 2008; 3(3):e1727. [PubMed: 18320046]
62. Smyth DJ, Howson JM, Payne F, Maier LM, Bailey R, Holland K, Lowe CE, Cooper JD, Hulme JS, Vella A, et al. Analysis of polymorphisms in 16 genes in type 1 diabetes that have been associated with other immune-mediated diseases. *BMC Med Genet.* 2006; 7:20. [PubMed: 16519819]
63. Graham DS, Akil M, Vyse TJ. Association of polymorphisms across the tyrosine kinase gene, TYK2 in UK SLE families. *Rheumatology (Oxford).* 2007; 46(6):927–930. [PubMed: 17384181]
64. Siminovitch KA. PTPN22 and autoimmune disease. *Nat Genet.* 2004; 36(12):1248–1249. [PubMed: 15565104]
65. Bottini N, Musumeci L, Alonso A, Rahmouni S, Nika K, Rostamkhani M, MacMurray J, Meloni GF, Lucarelli P, Pellecchia M, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet.* 2004; 36(4):337–338. [PubMed: 15004560]
66. Alarcon GS, McGwin G Jr, Petri M, Ramsey-Goldman R, Fessler BJ, Vila LM, Edberg JC, Reveille JD, Kimberly RP. Time to renal disease and end-stage renal disease in PROFILE: a multiethnic lupus cohort. *PLoS Med.* 2006; 3(10):e396. [PubMed: 17076550]
67. Cooper JD, Smyth DJ, Smiles AM, Plagnol V, Walker NM, Allen JE, Downes K, Barrett JC, Healy BC, Mychaleckyj JC, et al. Meta-analysis of genome-wide association study data identifies additional type 1 diabetes risk loci. *Nat Genet.* 2008; 40(12):1399–1401. [PubMed: 18978792]
68. Jacob CO, Zhu J, Armstrong DL, Yan M, Han J, Zhou XJ, Thomas JA, Reiff A, Myones BL, Ojwang JO, et al. Identification of IRAK1 as a risk gene with critical role in the pathogenesis of systemic lupus erythematosus. *Proc Natl Acad Sci U S A.* 2009; 106(15):6256–6261. [PubMed: 19329491]
69. Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Hu Z, Xu JH, Cai ZM, Huang W, Zhao GP, et al. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. *Nat Genet.* 2009; 41(11):1234–1237. [PubMed: 19838193]

70. Oishi T, Iida A, Otsubo S, Kamatani Y, Usami M, Takei T, Uchida K, Tsuchiya K, Saito S, Ohnisi Y, et al. A functional SNP in the NKX2-5-binding site of ITPR3 promoter is associated with susceptibility to systemic lupus erythematosus in Japanese population. *J Hum Genet.* 2008; 53(2): 151–162. [PubMed: 18219441]
71. Nusinow SR, Zuraw BL, Curd JG. The hereditary and acquired deficiencies of complement. *Med Clin North Am.* 1985; 69(3):487–504. [PubMed: 3892188]
72. Budarf ML, Goyette P, Boucher G, Lian J, Graham RR, Claudio JO, Hudson T, Gladman D, Clarke AE, Pope JE, et al. A targeted association study in systemic lupus erythematosus identifies multiple susceptibility alleles. *Genes Immun.* 2011; 12(1):51–58. [PubMed: 20962850]
73. Vazgiourakis VM, Zervou MI, Choulaki C, Bertsias G, Melissourgaki M, Yilmaz N, Sidiropoulos P, Plant D, Trouw LA, Toes RE, et al. A common SNP in the CD40 region is associated with systemic lupus erythematosus and correlates with altered CD40 expression: implications for the pathogenesis. *Ann Rheum Dis.* 2011; 70(12):2184–2190. [PubMed: 21914625]
74. Hong CH, Lee JS, Lee HS, Bae SC, Yoo DH. The association between fcgammaRIIIB polymorphisms and systemic lupus erythematosus in Korea. *Lupus.* 2005; 14(5):346–350. [PubMed: 15934433]
75. Prokunina L, Castillejo-Lopez C, Oberg F, Gunnarsson I, Berg L, Magnusson V, Brookes AJ, Tentler D, Kristjansdottir H, Grondal G, et al. A regulatory polymorphism in PDCD1 is associated with susceptibility to systemic lupus erythematosus in humans. *Nat Genet.* 2002; 32(4):666–669. [PubMed: 12402038]
76. Reveille JD, Moulds JM, Ahn C, Friedman AW, Baethge B, Roseman J, Straaton KV, Alarcon GS. Systemic lupus erythematosus in three ethnic groups: I. The effects of HLA class II, C4, and CR1 alleles, socioeconomic factors, and ethnicity at disease onset. LUMINA Study Group. *Lupus in minority populations, nature versus nurture. Arthritis Rheum.* 1998; 41 (7):1161–1172. [PubMed: 9663471]
77. Sadovnick AD. Genetic background of multiple sclerosis. *Autoimmun Rev.* 2012; 11 (3):163–166. [PubMed: 21619948]
78. Moser KL, Neas BR, Salmon JE, Yu H, Gray-McGuire C, Asundi N, Bruner GR, Fox J, Kelly J, Henshall S, et al. Genome scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1q in African-American pedigrees. *Proc Natl Acad Sci U S A.* 1998; 95(25):14869–14874. [PubMed: 9843982]
79. Raychaudhuri S, Thomson BP, Remmers EF, Eyre S, Hinks A, Guiducci C, Catanese JJ, Xie G, Stahl EA, Chen R, et al. Genetic variants at CD28, PRDM1 and CD2/CD58 are associated with rheumatoid arthritis risk. *Nat Genet.* 2009; 41(12):1313–1318. [PubMed: 19898481]
80. Furnrohr BG, Wach S, Kelly JA, Haslbeck M, Weber CK, Stach CM, Hueber AJ, Graef D, Spriewald BM, Manger K, et al. Polymorphisms in the Hsp70 gene locus are genetically associated with systemic lupus erythematosus. *Ann Rheum Dis.* 2010; 69(11):1983–1989. [PubMed: 20498198]
81. Al-Mayouf SM, Sunker A, Abdwani R, Abrawi SA, Almurshedi F, Alhashmi N, Al Sonbul A, Sewairi W, Qari A, Abdallah E, et al. Loss-of-function variant in DNASE1L3 causes a familial form of systemic lupus erythematosus. *Nat Genet.* 2011; 43(12):1186–1188. [PubMed: 22019780]
82. Yasutomo K, Horiuchi T, Kagami S, Tsukamoto H, Hashimura C, Urushihara M, Kuroda Y. Mutation of DNASE1 in people with systemic lupus erythematosus. *Nat Genet.* 2001; 28 (4):313–314. [PubMed: 11479590]
83. Kim K, Brown EE, Choi CB, Alarcon-Riquelme ME, Kelly JA, Glenn SB, Ojwang JO, Adler A, Lee HS, Boackle SA, et al. Variation in the ICAM1-ICAM4-ICAM5 locus is associated with systemic lupus erythematosus susceptibility in multiple ancestries. *Ann Rheum Dis.* 2012
84. Hakonarson H, Grant SF, Bradfield JP, Marchand L, Kim CE, Glessner JT, Grabs R, Casalunovo T, Taback SP, Frackelton EC, et al. A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. *Nature.* 2007; 448(7153):591–594. [PubMed: 17632545]
85. Awata T, Kawasaki E, Tanaka S, Ikegami H, Maruyama T, Shimada A, Nakanishi K, Kobayashi T, Iizuka H, Uga M, et al. Association of type 1 diabetes with two Loci on 12q13 and 16p13 and the influence coexisting thyroid autoimmunity in Japanese. *J Clin Endocrinol Metab.* 2009; 94(1): 231–235. [PubMed: 18940880]

86. Cooper JD, Walker NM, Healy BC, Smyth DJ, Downes K, Todd JA. Analysis of 55 autoimmune disease and type II diabetes loci: further confirmation of chromosomes 4q27, 12q13.2 and 12q24.13 as type I diabetes loci, and support for a new locus, 12q13.3–q14. 1. *Genes Immun.* 2009; 10 (Suppl 1):S95–120. [PubMed: 19956108]
87. Barratt BJ, Payne F, Lowe CE, Hermann R, Healy BC, Harold D, Concannon P, Gharani N, McCarthy MI, Olavesen MG, et al. Remapping the insulin gene/IDDM2 locus in type 1 diabetes. *Diabetes.* 2004; 53(7):1884–1889. [PubMed: 15220214]
88. Espino-Paisan L, de la Calle H, Fernandez-Arquero M, Figueredo MA, de la Concha EG, Urcelay E, Santiago JL. A polymorphism in PTPN2 gene is associated with an earlier onset of type 1 diabetes. *Immunogenetics.* 2011; 63(4):255–258. [PubMed: 21246196]
89. Freudenberg J, Lee HS, Han BG, Shin HD, Kang YM, Sung YK, Shim SC, Choi CB, Lee AT, Gregersen PK, et al. Genome-wide association study of rheumatoid arthritis in Koreans: population-specific loci as well as overlap with European susceptibility loci. *Arthritis Rheum.* 2011; 63(4):884–893. [PubMed: 21452313]
90. Ueda H, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, Rainbow DB, Hunter KM, Smith AN, Di Genova G, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature.* 2003; 423(6939):506–511. [PubMed: 12724780]
91. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet.* 2010; 42(12):1118–1125. [PubMed: 21102463]
92. Perdignes N, Vigo AG, Lamas JR, Martinez A, Balsa A, Pascual-Salcedo D, de la Concha EG, Fernandez-Gutierrez B, Urcelay E. Evidence of epistasis between TNFRSF14 and TNFRSF6B polymorphisms in patients with rheumatoid arthritis. *Arthritis Rheum.* 2010; 62 (3):705–710. [PubMed: 20187130]
93. Wagner J, Sim WH, Ellis JA, Ong EK, Catto-Smith AG, Cameron DJ, Bishop RF, Kirkwood CD. Interaction of Crohn's disease susceptibility genes in an Australian paediatric cohort. *PLoS One.* 2010; 5(11):e15376. [PubMed: 21079743]
94. Ho P, Bruce IN, Silman A, Symmons D, Newman B, Young H, Griffiths CE, John S, Worthington J, Barton A. Evidence for common genetic control in pathways of inflammation for Crohn's disease and psoriatic arthritis. *Arthritis Rheum.* 2005; 52(11):3596–3602. [PubMed: 16255050]
95. McGovern DP, Hysi P, Ahmad T, van Heel DA, Moffatt MF, Carey A, Cookson WO, Jewell DP. Association between a complex insertion/deletion polymorphism in NOD1 (CARD4) and susceptibility to inflammatory bowel disease. *Human molecular genetics.* 2005; 14 (10):1245–1250. [PubMed: 15790594]
96. Hugot JP, Chamaillard M, Zouali H, Lesage S, Cezard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature.* 2001; 411(6837):599–603. [PubMed: 11385576]
97. Orozco G, Gonzalez-Gay MA, Paco L, Lopez-Nevot MA, Guzman M, Pascual-Salcedo D, Balsa A, Martin J. Interleukin 12 (IL12B) and interleukin 12 receptor (IL12RB1) gene polymorphisms in rheumatoid arthritis. *Hum Immunol.* 2005; 66(6):710–715. [PubMed: 15993716]
98. Cargill M, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callis KP, Matsunami N, Ardlie KG, Civello D, Catanese JJ, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet.* 2007; 80 (2):273–290. [PubMed: 17236132]
99. Plenge RM, Seielstad M, Padyukov L, Lee AT, Remmers EF, Ding B, Liew A, Khalili H, Chandrasekaran A, Davies LR, et al. TRAF1-C5 as a risk locus for rheumatoid arthritis--a genomewide study. *N Engl J Med.* 2007; 357(12):1199–1209. [PubMed: 17804836]
100. Hunt KA, Zhernakova A, Turner G, Heap GA, Franke L, Bruinenberg M, Romanos J, Dinesen LC, Ryan AW, Panesar D, et al. Newly identified genetic risk variants for celiac disease related to the immune response. *Nat Genet.* 2008; 40(4):395–402. [PubMed: 18311140]
101. Coenen MJ, Trynka G, Heskamp S, Franke B, van Diemen CC, Smolonska J, van Leeuwen M, Brouwer E, Boezen MH, Postma DS, et al. Common and different genetic background for rheumatoid arthritis and coeliac disease. *Human molecular genetics.* 2009; 18(21):4195–4203. [PubMed: 19648290]

102. Suzuki A, Yamada R, Kochi Y, Sawada T, Okada Y, Matsuda K, Kamatani Y, Mori M, Shimane K, Hirabayashi Y, et al. Functional SNPs in CD244 increase the risk of rheumatoid arthritis in a Japanese population. *Nat Genet.* 2008; 40(10):1224–1229. [PubMed: 18794858]
103. Matthey DL, Nixon N, Dawes PT, Kerr J. Association of polymorphism in the transforming growth factor {beta}1 gene with disease outcome and mortality in rheumatoid arthritis. *Ann Rheum Dis.* 2005; 64(8):1190–1194. [PubMed: 15695537]
104. Barton A, Eyre S, Ke X, Hinks A, Bowes J, Flynn E, Martin P, Wilson AG, Morgan AW, Emery P, et al. Identification of AF4/FMR2 family, member 3 (AFF3) as a novel rheumatoid arthritis susceptibility locus and confirmation of two further pan-autoimmune susceptibility genes. *Human molecular genetics.* 2009; 18(13):2518–2522. [PubMed: 19359276]
105. Okada Y, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, Kawaguchi T, Stahl EA, Kurreeman FA, Nishida N, et al. Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. *Nat Genet.* 2012
106. Docampo E, Rabionet R, Riveira-Munoz E, Escaramis G, Julia A, Marsal S, Martin JE, Gonzalez-Gay MA, Balsa A, Raya E, et al. Deletion of the late cornified envelope genes, LCE3C and LCE3B, is associated with rheumatoid arthritis. *Arthritis Rheum.* 2010; 62(5):1246–1251. [PubMed: 20213803]
107. Rivas MA, Beaudoin M, Gardet A, Stevens C, Sharma Y, Zhang CK, Boucher G, Ripke S, Ellinghaus D, Burt N, et al. Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. *Nat Genet.* 2011; 43(11):1066–1073. [PubMed: 21983784]
108. Anderson CA, Massey DC, Barrett JC, Prescott NJ, Tremelling M, Fisher SA, Gwilliam R, Jacob J, Nimmo ER, Drummond H, et al. Investigation of Crohn's disease risk loci in ulcerative colitis further defines their molecular relationship. *Gastroenterology.* 2009; 136(2):523–529. e523. [PubMed: 19068216]
109. Amre DK, Mack DR, Morgan K, Israel D, Deslandres C, Seidman EG, Lambrette P, Costea I, Krupoves A, Fegury H, et al. Susceptibility loci reported in genome-wide association studies are associated with Crohn's disease in Canadian children. *Aliment Pharmacol Ther.* 2010; 31(11):1186–1191. [PubMed: 20222910]
110. Hampe J, Franke A, Rosenstiel P, Till A, Teuber M, Huse K, Albrecht M, Mayr G, De La Vega FM, Briggs J, et al. A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet.* 2007; 39(2):207–211. [PubMed: 17200669]
111. Wang K, Zhang H, Kugathasan S, Annese V, Bradfield JP, Russell RK, Sleiman PM, Imielinski M, Glessner J, Hou C, et al. Diverse genome-wide association studies associate the IL12/IL23 pathway with Crohn Disease. *Am J Hum Genet.* 2009; 84(3):399–405. [PubMed: 19249008]
112. Danoy P, Pryce K, Hadler J, Bradbury LA, Farrar C, Pointon J, Ward M, Weisman M, Reveille JD, Wordsworth BP, et al. Association of variants at 1q32 and STAT3 with ankylosing spondylitis suggests genetic overlap with Crohn's disease. *PLoS Genet.* 2010; 6(12):e1001195. [PubMed: 21152001]
113. Hauser F, Deyle C, Berard D, Neukirch C, Glowacki C, Bickmann JK, Wenzel JJ, Lackner KJ, Rossmann H. Macrophage-stimulating protein polymorphism rs3197999 is associated with a gain of function: implications for inflammatory bowel disease. *Genes Immun.* 2012
114. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet.* 2008; 40(8):955–962. [PubMed: 18587394]
115. van der Heide F, Nolte IM, Kleibeuker JH, Wijmenga C, Dijkstra G, Weersma RK. Differences in genetic background between active smokers, passive smokers, and non-smokers with Crohn's disease. *Am J Gastroenterol.* 2010; 105(5):1165–1172. [PubMed: 19953089]
116. Aithal GP, Craggs A, Day CP, Welfare M, Daly AK, Mansfield JC, Hudson M. Role of polymorphisms in the interleukin-10 gene in determining disease susceptibility and phenotype in inflammatory bowel disease. *Dig Dis Sci.* 2001; 46(7):1520–1525. [PubMed: 11478505]
117. Koutroubakis IE, Theodoropoulou A, Xidakis C, Sfiridaki A, Notas G, Kolios G, Kouroumalis EA. Association between enhanced soluble CD40 ligand and prothrombotic state in

- inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2004; 16(11):1147–1152. [PubMed: 15489574]
118. Weersma RK, Stokkers PC, Cleynen I, Wolfkamp SC, Henckaerts L, Schreiber S, Dijkstra G, Franke A, Nolte IM, Rutgeerts P, et al. Confirmation of multiple Crohn's disease susceptibility loci in a large Dutch-Belgian cohort. *Am J Gastroenterol*. 2009; 104(3):630–638. [PubMed: 19174780]
 119. Kugathasan S, Baldassano RN, Bradfield JP, Sleiman PM, Imielinski M, Guthery SL, Cucchiara S, Kim CE, Frackelton EC, Annaiah K, et al. Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet*. 2008; 40(10):1211–1215. [PubMed: 18758464]
 120. McGovern DP, Gardet A, Torkvist L, Goyette P, Essers J, Taylor KD, Neale BM, Ong RT, Lagace C, Li C, et al. Genome-wide association identifies multiple ulcerative colitis susceptibility loci. *Nat Genet*. 2010; 42(4):332–337. [PubMed: 20228799]
 121. Massey DC, Parkes M. Genome-wide association scanning highlights two autophagy genes, ATG16L1 and IRGM, as being significantly associated with Crohn's disease. *Autophagy*. 2007; 3(6):649–651. [PubMed: 17921695]
 122. Leung E, Hong J, Fraser AG, Merriman TR, Vishnu P, Krissansen GW. Polymorphisms in the organic cation transporter genes SLC22A4 and SLC22A5 and Crohn's disease in a New Zealand Caucasian cohort. *Immunol Cell Biol*. 2006; 84(2):233–236. [PubMed: 16519742]
 123. Yamazaki K, McGovern D, Ragoussis J, Paolucci M, Butler H, Jewell D, Cardon L, Takazoe M, Tanaka T, Ichimori T, et al. Single nucleotide polymorphisms in TNFSF15 confer susceptibility to Crohn's disease. *Human molecular genetics*. 2005; 14(22):3499–3506. [PubMed: 16221758]
 124. Weber F, Fontaine B, Cournu-Rebeix I, Kroner A, Knop M, Lutz S, Muller-Sarnowski F, Uhr M, Bettecken T, Kohli M, et al. IL2RA and IL7RA genes confer susceptibility for multiple sclerosis in two independent European populations. *Genes Immun*. 2008; 9(3):259–263. [PubMed: 18354419]
 125. Esposito L. IL12A, MPHOSPH9/CDK2AP1 and RGS1 are novel multiple sclerosis susceptibility loci. *Genes Immun*. 2010; 11(5):397–405. [PubMed: 20555355]
 126. Hasan NM, Kendrick MA, Druckenbrod NR, Huelsmeyer MK, Warner TF, MacDonald MJ. Genetic association of the neuropilin-1 gene with type 1 diabetes in children: Neuropilin-1 expression in pancreatic islets. *Diabetes Res Clin Pract*. 2010; 87(3):e29–32. [PubMed: 20053475]
 127. Booth DR, Arthur AT, Teutsch SM, Bye C, Rubio J, Armati PJ, Pollard JD, Heard RN, Stewart GJ. Gene expression and genotyping studies implicate the interleukin 7 receptor in the pathogenesis of primary progressive multiple sclerosis. *J Mol Med (Berl)*. 2005; 83 (10):822–830. [PubMed: 16075257]
 128. Guerini FR, Cagliani R, Forni D, Agliardi C, Caputo D, Cassinotti A, Galimberti D, Fenoglio C, Biasin M, Asselta R, et al. A functional variant in ERAP1 predisposes to multiple sclerosis. *PLoS One*. 2012; 7(1):e29931. [PubMed: 22253828]
 129. Arnaud-Lopez L, Usala G, Ceresini G, Mitchell BD, Pilia MG, Piras MG, Sestu N, Maschio A, Busonero F, Albai G, et al. Phosphodiesterase 8B gene variants are associated with serum TSH levels and thyroid function. *Am J Hum Genet*. 2008; 82(6):1270–1280. [PubMed: 18514160]
 130. Capon F, Bijlmaers MJ, Wolf N, Quaranta M, Huffmeier U, Allen M, Timms K, Abkevich V, Gutin A, Smith R, et al. Identification of ZNF313/RNF114 as a novel psoriasis susceptibility gene. *Human molecular genetics*. 2008; 17(13):1938–1945. [PubMed: 18364390]
 131. Hollox EJ. Copy number variation of beta-defensins and relevance to disease. *Cytogenet Genome Res*. 2008; 123(1–4):148–155. [PubMed: 19287149]
 132. van Heel DA, Franke L, Hunt KA, Gwilliam R, Zhernakova A, Inouye M, Wapenaar MC, Barnardo MC, Bethel G, Holmes GK, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. *Nat Genet*. 2007; 39 (7):827–829. [PubMed: 17558408]
 133. Fisher SA, Tremelling M, Anderson CA, Gwilliam R, Bumpstead S, Prescott NJ, Nimmo ER, Massey D, Berzuini C, Johnson C, et al. Genetic determinants of ulcerative colitis include the

- ECM1 locus and five loci implicated in Crohn's disease. *Nat Genet.* 2008; 40(6):710–712. [PubMed: 18438406]
134. De Jager PL, Chibnik LB, Cui J, Reischl J, Lehr S, Simon KC, Aubin C, Bauer D, Heubach JF, Sandbrink R, et al. Integration of genetic risk factors into a clinical algorithm for multiple sclerosis susceptibility: a weighted genetic risk score. *Lancet Neurol.* 2009; 8(12):1111–1119. [PubMed: 19879194]
135. Narumi Y, Isomoto H, Shiota M, Sato K, Kondo S, Machida H, Yanagihara K, Mizuta Y, Kohno S, Tsukamoto K. Polymorphisms of PTPN11 coding SHP-2 as biomarkers for ulcerative colitis susceptibility in the Japanese population. *J Clin Immunol.* 2009; 29(3):303–310. [PubMed: 19160029]

Figure 1. Interaction pathways of SLE associated genes

Genetically associated genes (dark blue) interact to form a common network although some of the interlinking genes (sky blue) to complete a biological pathway. Small molecules are red and miRNAs are shown in orange.

Figure 2. Interaction of T1D associated genes

Genetically identified T1D associated genes interact each other mainly through miRNAs suggesting that miRNAs could be important regulator of T1D. Associated genes (dark blue), interconnecting genes (light blue), small molecules and miRNAs (red and orange respectively).

Figure 3. Gene-network analysis of genetically identified RA associated genes
Interaction of RA associated genes leads to common biological pathways. Manipulating miRNAs to modulate RA associated genes could have positive outcome for developing chemotherapy. Associated genes (dark blue), interconnecting genes (light blue), small molecules and miRNAs (red and orange respectively).

Figure 4. IBD/CHD associated genes are connected through small molecules

IBD/CHD associated genes are connected through small molecules and share a common biological pathway. miRNAs or small molecules could be major determinants to regulate IBD/CHD associated genes. Associated genes (dark blue), interconnecting genes (light blue), small molecules and miRNAs (red and boxes respectively).

Figure 5. Genetically identified ADs genes are connected to form a shared autoimmune pathways Genes those are associated with various ADs are interacting each other to form connected biological network that could explain shared autoimmune phenotypes as they are interacting in a network. Associated genes (dark blue), interconnecting genes (light blue), small molecules and miRNAs (red boxes and orange respectively). AITD, autoimmune thyroid disease. ULC, ulcerative colitis. * designates gene shared by multiple ADs.

Figure 6. Interactions of current drugs and various small molecules with shared ADs pathway genes

Various small molecules interact with shared ADs genes suggesting that SNPs in these genes could be modulated through these factors. This networking also demonstrates that current drugs those are used to treat various ADs interact with these newly associated genes. Susceptible gene with risk allele carrying patients could be better benefitted with the specific drug that interacts with that gene. Associated genes (dark blue), interconnecting genes (light blue), small molecules and miRNAs (red and orange respectively).

Figure 7. Individual modules for specific drug-gene interaction

Modules of four selected drugs those are shown here to emphasize the spectrum of specific drug interactions with several genes. Associated genes are shown in dark blue. Nodes represent the existing drugs. In most of the cases, each drug interacts with many genes but associated genes are newly identified and this information could be used for clinical benefit. Associated genes (dark blue), other interacting genes (light blue), small molecules and miRNAs (red).

Table 1

ADs associated genes used in this study with their location and function.

No.	Genes associated with ADs	Accession no (Genebank)	cytogenetic location	Disease	Reference (association with diseases)	Function
1	ITGAM	68563402	1p11.2	SLE	[21]	Complement receptor
2	STAT4	21411474	2q32.2-q33	SLE, RA	[55]	Transcription factor
3	ATG5	CA120313.1	6q21	SLE	[24, 27]	Autophagy
4	LYN	307144	8q13	SLE	[57]	Tyrosine protein kinase
5	BANK1	158563738	4q24	SLE	[58]	B cell specific calcium mobilization
6	PXK	33874042	3p14.3	SLE	[27]	Serine threonine kinase
7	PTTG1	49456331	5q35.1	SLE	[59]	Pituitary tumor transforming gene
8	IFNG	47124535	12q24	SLE	[28]	Macrophage activator
9	SELP	56417670	1q22-q25	SLE	[60]	Mediate interaction with leukocytes
10	MECP2	160707950	Xq28	SLE	[61]	Methyl Cpg binding protein
11	IRF5	1255255	7q32	SLE	[12]	Regulates interferon production
12	IFIH1	27886568	2q24	SLE, T1D,	[25, 62]	Viral binding protein and apoptosis
13	UBE2L3	373432684	22q11.21	RA	[40]	Ubiquitin ligase, protein degradation
14	TYK2	15559784	19p13.2	SLE	[63]	Tyrosine kinase
15	BLK	116284012	8p22-23	SLE, RA	[55]	B lymphocyte kinase
16	IL10	186271	1q31-32	IL10	[25]	Cytokine synthesis inhibition
17	PTPN22	47938186	1p13.2	SLE, RA, T1D	[64, 65]	Lymphoid specific phosphatase
18	FCGR3A	21708067	1q23	SLE	[66]	Fc receptor for CD16
19	IL2	47682793	4q26-q27	T1D, SLE	[34, 67]	T cell growth factor
20	IRAK1	3002590	Xq28	SLE	[68]	IL1 associated kinase
21	TNFSF4	49457019	1q25	SLE	[69]	Adhesion of activated T cell
22	ETS1	49457502	11q23.3	SLE	[26]	Transcription factor
23	TNFAIP3	5454132	6q23	SLE	[6]	TNFA induced transcription factor
24	ITPR3	153945846	6p21	SLE	[70]	Inositol phosphate receptor
25	TNIP1	15559297	5q32-33.1	SLE	[69]	Nuclear shuttling of HIV virus
26	RELA	48775023	2p13-12	RA	[43]	NFKB1 associated transcription factor

No.	Genes associated with ADs	Accession no (Genebank)	cytogenetic location	Disease	Reference (association with diseases)	Function
27	UHRF1	224589810	1p13.3	SLE	[25]	Ubiquitin protein ligase
28	NMNAT2	111 55958921	1q25	SLE, T1D	[27]	NAD biosynthetic pathway
29	C3	1919p13.3 179665	1p13.3	SLE	[71]	Complement component
30	C4B	AAR89095.1	6p21.3	SLE	[71]	Complement component
31	C2	15277207 6p21.3		SLE	[71]	Complement component
32	ICA1	209862841 7p22		SLE	[27, 72]	Islet cell autoantigen
33	C1Q	166235903	1p36.1	SLE	[71]	Complement component
34	CD40LG	4557433	Xq26	SLE, RA	[73]	B cell activating CD40 ligand
35	FCGR2A	18044348 1Q231q1q23	SLE	[27]	Fc receptor and phagocytosis	
36	FCGR3B	348041254	1q23	SLE, RA	[74]	Fc receptor for CD16
37	PDCD1	29124993	2q37.3	SLE	[75]	apoptosis
38	JAZF1	51094968	7p15.2	SLE	[25]	Transcriptional repressor
39	XKR6	71153416	8p23.1	SLE	[27, 72]	blood precursor protein
40	HLA-DRB3	2687823	6p21.3	SLE, RA, M S, Pso	[76, 77]	Histocompatibility antigen
41	HLA-DRA	48146143	6p21.3	SLE, RA, M S, Pso	[77, 78]	Histocompatibility antigen
42	HLA-DRB1	4467831		SLE, RA, M S, Pso	[55, 77]	66 Histocompatibility antigen 6p21.3
43	PRDM1	187761390	6q23	SLE, RA	[25, 79]	B lymphocyte maturation protein
44	CD226	50960061	18q23.1	SLE, T1D	[16]	T lineage specific activated antigen
45	SCUBE1	25992504	22q13	SLE	[27]	Signal transduction in vascular cells
46	HSPA1A	17511780	6p21.3	SLE	[80]	HSP70 molecular chaperone
47	WDFY4 *	22028271	10q11.3	SLE	[26]	WD repeat carrying Transcription factor
48	DNASE1L3	16198371	Xq28	SLE	[81]	Dna damage and repair
49	DNASE1	21361254	16p13.3	SLE	[82]	DNA damage
50	ICAM1	306896	16p11.2	SLE	[83]	chemokine
51	CLEC16A *	86577656	16p13.13	SLE	[84]	C-type lectin
52	ERBB3	12803739	12q13	T1D, SLE	[72, 85, 86]	Viral oncogene
53	INS	386828	11p15.5	T1D	[87]	proinsulin
54	AFF3	223462736	2q11.2	T1D, RA	[36]	Lymphoid development

No.	Genes associated with ADs	Accession no (Genebank)	cytogenetic location	Disease	Reference (association with diseases)	Function
55	CD19	901823	1p11.2	T1D	[36]	B lymphocyte antigen
56	ZEB1	55958385	10p11.2	T1D	[36]	Crystalin enhancer transcription factor
57	SH2B3	223460482	12q24	T1D, celiac	[15]	Lymphocyte specific adaptor
58	IL2RA	57208805	10p15-p14	T1D, RA, celiac	[36]	Interleukin receptor
59	PTPN2	14198363	18p11.3	IBD, T1D, RA	[88, 89]	Tyrosine phosphatase
60	CTLA4(SLC44A4)	15778586	2q33	T1D, RA	[90]	T lymphocyte associated antigen
61	TNSF14	49457019	19p13.3	RA	[33]	Proliferation of T cell
62	CD40	114053977	20q12-q13	RA	[33]	T cell specific antigen
63	KIF5A	45446749	12q13.13	RA	[33]	Intracellular organelle transport
64	ZFP36L1	347659013	14q22-24	IBD, RA	[91]	EGF responsive factor
65	CCL21	47496599	9p13	RA	[36]	Lymphocyte specific chemokine
66	CDK6	223718134	7q21-22	RA	[33]	Cell division kinase 6
67	TNFRSF6B	21706465	20q13.3	RA, IBD	[92, 93]	FAS mediated cell death
68	NOD2	14595638	16q21	IBD, RA	[94-96]	Apoptosis
69	IL12B	24497438	5q31.1	RA, IBD	[97, 98]	Lymphocyte maturation
70	TRAF1	18848177	9q33-q34	RA	[99]	Activation of MAPK
71	IL18RAP	76826845	2q12	CD, RA	[100]	Interleukin accessory protein
72	IL23R	55710298	1p31.3	IBD	[29]	Interleukin receptor
73	BLK	116284012	8p22-23	SLE, IBD, R A	[55]	B lymphocyte maturation
74	PRKCQ	55957459	10p15	RA, CD	[101]	Protein kinase
75	PHF19	115528901	9q33.3	RA	[99]	Transcription factor
76	CD244	19684050	1q23.3	RA	[102]	Glutathione catalyzing protein
77	TGFB1	18490116	19q13.1	RA	[103]	Transforming growth factor
78	IKZF3	21595809	17q21	RA	[36]	Zinc finger transcription factor
79	PIP4K2C	226371743	12q13.3	RA	[33]	Phosphoinositol kinase
80	AFK3	219518204	2q11.2		[104]	Lymphoid transcription factor
81	B3GNT2	44890720	2p15	RA	[105]	Biosynthesis of polyacetyl lactosaminine
82	ANXA3	4826643	4q21.21	RA	[105]	Anticoagulant protein
83	CSF2	109731225	5q31.1	RA	[105]	Macrophage colony stimulating factor

No.	Genes associated with ADs	Accession no (Genebank)	cytogenetic location	Disease	Reference (association with diseases)	Function
84	CD83	48146155	6p23	RA	[105]	B cell activating glycoprotein
85	NFKBIE	71274109	6p21.1	RA	[105]	B cell inhibitor
86	ARID5B	78395052	10q21.1	RA	[105]	Modulation recognition factor
87	PLD4	94681038	14q32.33	RA	[105]	Cholin phosphatase
88	CCR6	37188165	6q27	RA	[36]	Chemokines receptor
89	SPRED2	31872021	2p15	RA	[36]	MAP kinase activator
90	TAGAP *	56202995	6q25.3	RA, CD	[100]	T cell activating protein
91	LCE3B *	30410041	1q21.3	RA, Pso	[106]	Envelope protein
92	MUC19 *	32395928	12q12	IBD	[107]	mucin
93	SBNO2	AAI06022.1	19p13.3	IBD	[108]	Notch signaling factor
94	ZNF365	116284343	10q21.2	IBD,	[109]	Zinc finger transcription factor
95	ATG16L1	148342529	2q37.1	IBD	[110]	autophagy
96	STAT3	21618340	17q21.31	IBD	[111]	Transcriptional activator
97	LRRK2	55740398	12q12	IBD	[91, 112]	Serine threonine protein kinase
98	MST1	1117791	3p21	IBD	[113]	Macrophage stimulating factor
99	ITLN1	48146565	1q21.3	IBD	[114]	Endothelial leukocyte adhesion
100	CCNY	55710051	10p11.21	IBD	[115]	Cyclin box protein
101	CD40LG	4557433		IBD	[117]	
102	NKX2-3	148746211	10q24.2	IBD, CD, U LC	[118]	Homeobox transcription factor
103	JAK2	4826776	9p24	IBD	[114]	Tyrosine protein phosphatase
104	PSMG1	44680114	21q22.3	IBD	[119]	Chaperone function
105	ORMDL3	21165608	17q12	IBD	[120]	Protein degradation
106	IRGM	118764297	5q33.1	IBD	[121]	Immunity related GTPase
107	ICOSLG	40352972	21q22.3	IBD	[114]	T cell, stimulating ligand
108	SLC22A5	4507005	16q12	IBD	[122]	apoptosis
109	TNFSF15	50959659	9q32	IBD	[123]	Endothelial growth factor
110	IL2RA	57208805	10p15	MS	[124]	IL2 receptor
111	MPHOSPHO9/CDK2API	21961207	12q24	MS	[125]	M phase phosphoprotein

No.	Genes associated with ADs	Accession no (Genebank)	cytogenetic location	Disease	Reference (association with diseases)	Function
112	RBPJ	42560227	4p15.2	MS	[36]	VDJ recombination
113	CD6	194018748	11q13	MS	[36]	T cell differentiation antigen
114	IL7R	90403048	5p13	MS	[127]	IL 7 receptor
115	ERAP1	21315078	5q15	MS	[128]	Aminopeptidase inhibitor
116	TSHR	6721136	14q31	ATD	[129]	Thyroid hormone receptor
117	RNF114	15489174	20q13.13	Pso	[130]	Zn finger transcription factor
118	DEFB	4758150	8p23	Pso, IBD	[131]	Inflammation induced peptides
119	IL12B	50960610	5q31.1	Pso, MS	[125]	Interleukin 12b
120	IL12A	24430219	3q25.33	CD	[100]	NK cell stimulatory factor
121	RGS1	12313896	1q31	CD	[100, 125]	B cell specific G protein
122	IL21	46575632	4q26	CD, Pso, RA, SLE, T1D	[132],[34]	Differentiation of B, T and NK cells
123	ECM1	55958999	1q21	UL, IBD	[133]	Extracellular matrix binding
124	CCR1	4502631	3p21	CD, MS	[134]	Chemokines receptor
125	PTPN11	14250501	12q24	ULC	[135]	Tyrosine phosphatase

* -not integrated in the network