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A prioritization analysis of disease association by data-mining of functional annotation of human genes

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ABSTRACT

Complex diseases result from contributions of multiple genes that act in concert through pathways. Here we present a method to prioritize novel candidates of disease-susceptibility genes depending on the biological similarities to the known disease-related genes. The extent of disease-susceptibility of a gene is prioritized by analyzing seven features of human genes captured in H-InvDB. Taking rheumatoid arthritis (RA) and prostate cancer (PC) as two examples, we evaluated the efficiency of our method. Highly scored genes obtained included *TNFSF12* and *OSM* as candidate disease genes for RA and PC, respectively. Subsequent characterization of these genes based upon an extensive literature survey reinforced the validity of these highly scored genes as possible disease-susceptibility genes. Our approach, Prioritization ANalysis of Disease Association (PANDA), is an efficient and cost-effective method to narrow down a large set of genes into smaller subsets that are most likely to be involved in the disease pathogenesis.

1. Introduction

Finding disease-causing genes is one of the major issues in the human genome studies. The use of linkage analysis and positional cloning techniques has led to the identification of genes involved in numerous Mendelian genetic disorders [1–4]. However, finding causative genes for complex disorders is more challenging. Multiple genes contribute to the pathogenesis of common disorders and each gene may contribute to a different degree. Therefore, association studies to detect genes contributing to complex diseases are designed by recruiting large numbers of subjects and genotyping many polymorphic markers. The possible susceptible loci identified by association studies usually contain dozens of candidate disease genes. Further studies identifying causative variants and characterizing biological processes of disease-onset mechanism require additional substantial resources, and can be impractical when examining dozens of genes. Even if genome-wide

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association studies (GWAS) are conducted with an enough number of polymorphic markers, a fraction of markers showing statistically significant associations may be false positive. In finding genes involved in the disease pathogenesis, it is not easy to distinguish biological relevance from the false positives in studies with a large number of markers. Thus, a method to prioritize candidate disease genes based on a priori biological knowledge is useful to narrow down candidate genes to identify causative genes of common diseases.

Cataloguing human genes [5–7] and annotations enabled us to analyze biological information of human genes in various ways. One important application has been to prioritize possible candidate genes of disease implication by evaluating similarity or interactions between genes that have not only sequence homology but also share functional information including biological pathways. Recent studies showed that related phenotypes share common genetic basis and susceptibility genes [8–10] because the proteins involved in the pathogenesis are likely to interact together [11,12] in a few biological pathways. Although there are previous studies on prioritizing disease-related genes by use of biological information [13–20], using various kinds of biological information of human genes would be useful. Therefore, we developed a method to prioritize candidate genes for common diseases by utilizing biological information of human genes. Our method depends on two assumptions: (1) genes related to a particular disease often have common inherent structural and functional properties, and (2) known causative genes of a particular disease and novel candidate genes for the disease may share specific biological pathways or subcellular locations of gene products. The analysis starts with collection and curation of known related genes for the target disease. We analyze enrichment of biological functions in known related genes for the target disease, by using biological terms of functional domains from InterPro (www.ebi.ac.uk/interpro/), Enzyme Commission (EC) numbers (www.chem.qmul.ac.uk/iubmb/enzyme/), biological pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) (www.genome.ad.jp/kegg/) [21], and Gene Ontology (GO) (www.geneontology.org/) [22]. Then we examine all the other genes one by one whether a gene is biologically closer to the known related genes for the target disease than to the other genes by a subsequent discriminant analysis. Finally, we obtain a prioritized list of candidate genes for the disease.

We applied our approach to rheumatoid arthritis (RA) and prostate cancer (PC) in order to evaluate its efficiency. RA is the most common disabling autoimmune disease, affecting approximately 0.3–1% of the population [23]. While the etiology and pathogenesis of RA are not completely understood, a previous report has identified candidate genes and loci that may be related to RA [24]. Another common disease, PC, is the most commonly diagnosed male malignancy, and is the second leading cause of male cancer mortality in the world [25]. PC has long been known to cluster in families [26], and both segregation and linkage analyses have identified specific prostate cancer susceptibility loci and candidate genes [27,28]. Thus, both RA and PC represent complex genetic diseases for which the identification of causative disease genes would have a dramatic impact on public health.

This method, which we implemented by a system, Prioritization ANalysis for Disease Association (PANDA), provides prioritized candidates of disease-related genes that are useful for further studies to identify of new causative genes. The resulting output of our approach is a prioritized list of candidate genes for the diseases that represent potential disease biomarkers and perhaps even potential targets for therapies.

2. Results

2.1. Prioritization analysis of candidate genes for RA and PC

Known disease-related genes for RA and PC were retrieved from OMIM database (www.ncbi.nlm.nih.gov/Omim) [29] and subsequently checked in Entrez Gene (www.ncbi.nlm.nih.gov/gene) by using MeSH terms (www.nlm.nih.gov/mesh/) for the two diseases (see Methods and Fig. 1). After manual curation, we selected 139 genes as known RA-related genes and 296 genes as known PC-related genes (Supplemental Tables 1–2). These genes were used as 'training sets' to analyze all other genes in the H1-REFSEQ DB (an in-house database of all human genes containing 14,959 human genes, see Methods) for likeliness of disease susceptibility. Biological information of all human genes was retrieved from H-InvDB, and seven biological features (paralogy, InterPro, EC number, biological pathways from KEGG, and three categories of Gene Ontology, see Methods) of human genes were used to examine biological similarity of a gene to a group of known related genes for the target disease (group 1) or another group of all the other genes (group 2). Then we examined whether a gene tested is closer to the group 1 than to the group 2 by comparing the Mahalanobis distance between a gene and the group 1 (MD1) with another distance between the gene and the group 2 (MD2). We calculated the ratio of MD2 to MD1 (PANDA score) for each gene tested. To narrow down more promising candidate genes for the target diseases, we used a higher threshold; the average values of the PANDA score for the known related genes (21.2 for RA and 14.1 for PC). As a result, 526 genes were detected as candidate genes for RA and 609 genes for PC (Table 1).

2.2. Candidate genes on genomic regions of interest

Although putative susceptible loci for RA and PC have been identified by linkage analysis, association study, comparative genomic hybridization and chromosomal transfer, the actual genes involved in the disease have not been identified yet for many of these genomic regions. Therefore, a localization of a candidate gene on one of these genomic regions of interest (GROI) provides additional support for its potential role in the disease. To select candidate disease genes in GROIs, we searched the GROIs in OMIM for RA and PC, and found nine GROIs for RA and 18 GROIs for PC (listed in Supplemental Tables 3–4). Then we selected the candidate genes that were localized within these GROIs, and obtained 56 candidate genes for RA and 63 for PC.

2.3. Highly scored genes for rheumatoid arthritis

To further narrow down the most plausible candidate genes for RA, we ranked the 56 candidates on the GROIs according to the discriminant analysis with the Mahalanobis distances (Supplemental Table 3). We inspected the highly scored genes, surveyed literature and found that these genes included biologically reasonable candidate genes. For example, tumor necrosis factor ligand superfamily member 12 (*TNFSF12*) showed the third highest score in 17p13 (Table 2A) which is one of the GROIs with RA [24]. The *TNFSF12* gene shares three GO annotations (tumor necrosis factor receptor, immune response and membrane) with other known RA-related genes, including *TNF* (tumor necrosis factor), *HLA-DRB1* (major histocompatibility complex, class II, DR beta 1) and toll-like receptor 2 (*TLR2*) (Table 2B). The *TNFSF12* gene is expressed in macrophages, which infiltrates the synovial membrane to form the inflammatory pannus that is characteristic of RA invading joint cartilage and destroying the underlying bone. TNFSF12 induces activation of matrix metallopeptidase 9 through nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (NFKB1) pathway [30] that controls the incidence of collagen-based arthritis in mice through modulation of inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta (IKBKB) [31,32]. In addition, a molecule in the NFKB1 pathway, encoded by nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1(NFKBIL1), was reported as a candidate RA-susceptibility gene, from an evidence of a di-allelic polymorphism in the promoter region of the gene [33]. Biological annotation of TNFSF12 shows functional similarities with some of the known RA-related genes. Thus, our result suggests that *TNFSF12* may be involved in the pathogenesis of RA.

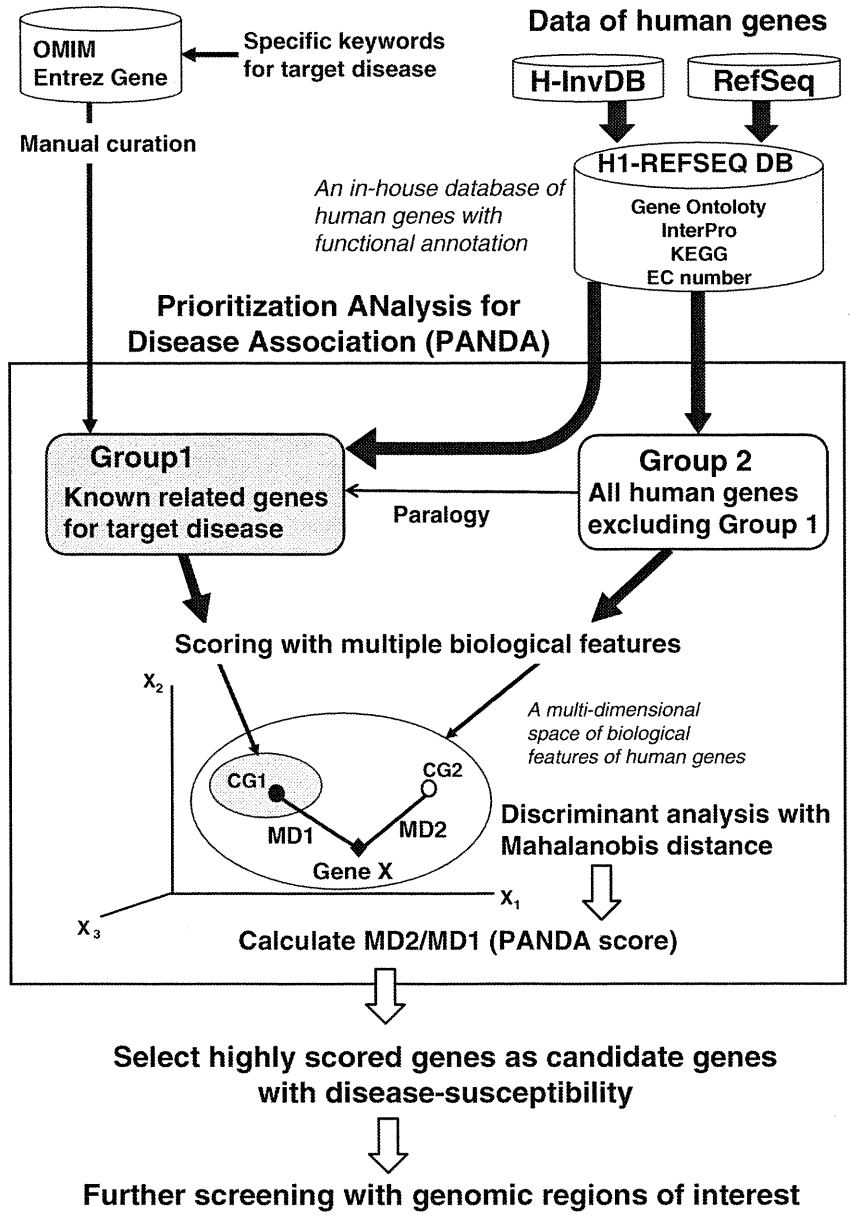

Fig. 1. Analysis pipeline with the Prioritization ANalysis of Disease Association (PANDA) system. Known related genes for the target disease (rheumatoid arthritis and prostate cancer in this study) were retrieved from OMIM and Entrez Gene, manually annotated and used as training set (group 1). We examined the proportion of biological terms in the training set and that in all human genes (H1-REFSEQ DB, see Methods). Based on different proportions of biological functions between the training set and all human genes, scores for multiple parameters were given to the all human genes. Candidate disease-related genes were prioritized by the discriminant analysis with multiple parameters. We calculated the Mahalanobis distances (MD1) between the position of a gene tested (open diamond) and the center of gravity of the group 1 (CG1, open circle) with multiple parameters. Similarly the Mahalanobis distances (MD2) between each gene and the center of gravity of the group 2 (CG2, filled circle) were calculated. Then we calculated the ratio of MD2 to MD1 (PANDA score) for each gene. Using the average value of the PANDA score for the known disease genes as a threshold, we considered any gene to be a candidate gene of disease-susceptibility if the ratio was greater than the threshold.

Table 1
Summary of prioritization analysis of disease-susceptibility genes for RA and PC.

Disease relation	Predicted similarity to known disease genes	RA	PC
Known	–	139	296
Unknown	Yes[a]	526	609
	No	14,294	14,054

Candidate genes with disease-susceptibility for rheumatoid arthritis (RA) and prostate cancer (PC) were prioritized by analyzing biological information of human genes.
We analyzed total 14959 human genes in H1-REFSEQ DB (an in-house database of human genes) including known related genes for the target diseases as the training sets. Each gene was tested one by one whether the gene is more similar to the known disease genes than the others by data-mining and discriminant analysis (see Methods). The numbers of genes for each category are shown.
[a] Genes whose PANDA scores (MD2/MD1) were higher than the threshold (the median in the training set).

2.4. Highly scored genes for prostate cancer

Similarly, we ranked the 63 candidate genes for PC (Supplemental Table 4) that were located in the 18 GROIs. One GROI for PC, 22q12, has been reported to be associated with PC by a combined genome-wide linkage scan [34]. The highly scored genes in 22q12 included Oncostatin M (*OSM*) with the highest PANDA score (30.4, Table 3A). OSM, an interleukin 6 (IL6)-type cytokine, induces activation of the androgen receptor (AR) in the absence of androgen [35]. *OSM* shares four GO annotations (cytokine activity, immune response, regulation of cell growth, extracellular) with known PC-related genes, including *IL6*, *IL8*, *IGFBP3* and *INS* (Table 3B). Interestingly, AR and IL6 have been implicated as relevant molecules for PC, and were present in the known PC-related genes as the training set. Thus, OSM is a candidate

Table 2A
Highly scored genes within 17p13 in relation to RA.

Gene symbol	Gene name	Transcript	PANDA score (MD2/MD1)	No. of GO features[a]	No. of other features[b]
CHRNE	Cholinergic receptor, nicotinic, epsilon polypeptide	NM_000080	85.3	3	0
CHRNB1	Cholinergic receptor, nicotinic, beta polypeptide 1 (muscle)	BC011371	85.3	3	0
TNFSF12	Tumor necrosis factor (ligand) superfamily, member 12	NM_172089	62.1	3	0
NLGN2	Neuroligin 2	AB037787	16.2	2	2
MYH10	Myosin, heavy polypeptide 10, non-muscle	AK026977	14.7	1	2
AURKB	Aurora kinase B	BC000442	13.6	2	3
ALOX12P2	Arachidonate 12-lipoxygenase pseudogene 2	AL832768	11.2	0	2
ALOX15	Arachidonate 15-lipoxygenase	BC029032	11.2	2	3
KIF1C	Kinesin family member 1C	AB014606	10.5	2	2

Highly scored genes were ranked by the PANDA score (MD2/MD1).
[a] Number of GO features of the gene (molecular function, biological process, and cellular component).
[b] Number of non-GO features of the gene for four features (amino acid sequence similarity, InterPro, EC number, and KEGG pathways).

Table 2B
Scores for *TNFSF12* in relation to RA.

Parameter	Functional annotation	ID	Base relevance score	Proportion in gene set		Score to *TNFSF12*[a]
				Training set	All human genes	
GO molecular function	Tumor necrosis factor receptor binding	GO:0005164 (6)[b]	2.5	0.0102	0.0011	134.85
GO biological process	Immune response	GO:0006955 (7)	1.77	0.2342	0.0168	173.16
GO cellular component	Membrane	GO:0016020 (4)	2.03	0.2714	0.2704	8.14

Among the seven parameters, details for the three concepts of GO terms are shown. The score of paralogy was 0 because *TNFSF12* did not have a sequence similarity to any known RA-related gene. The scores of InterPro, EC number and KEGG pathway were also 0.
[a] Scores were calculated by Eqs. (2) and (3).
[b] The level in a nested hierarchical vocabulary is shown in parenthesis.

molecule that is involved in the disease onset of prostate cancer, possibly through its modulation of IL6 related pathways.

2.5. Sensitivity of predicting disease-related genes

In order to evaluate the sensitivity of our approach for predicting disease genes, we examined whether the method correctly detects one of the known related genes for the target disease, which was replaced in a group of genes tested. This is an application of the leave-one-out cross-validation (LOOCV) [36], and we sequentially removed one of the known related genes for the target disease from the training set and placed it in the group of genes to be tested. Then, we calculated a new MD2/MD1 score (PANDA score), and checked whether the PANDA score of the removed gene was greater than 1. As a result, 126 of 139 (90.6%) known RA-related genes had scores greater than 1 (Supplemental Table 5). In the same way, 264 of 296 (89.2%) known PC-related genes showed higher scores than 1 (Supplemental Table 6).

2.6. Contribution of the data type to prioritize candidates of disease gene

We used the seven biological features of human genes to calculate Mahalanobis distance between a gene and a set of genes. However, it is not clear whether larger numbers of parameters increase the power of prediction and what data type is more effective than the other data. To see how the number of parameters affects the prediction power, we examined the sensitivity to identify the known disease genes by the LOOCV with different numbers of parameters in different combinations. First, we examined the sensitivity to find a known disease gene with seven parameters and compared the results with only GO annotations (molecular function, biological process and cellular component). The sensitivities by LOOCV were 74.8% (104 of 139) for the known RA genes and 72.6% (215 of 296) for the known PC genes when only GO annotation was used (Supplemental Tables 5–6). These sensitivities were slightly lower than that with the seven parameters.

We also examined the sensitivities to find known disease genes for RA in all the 120 combinations of using 2–7 parameters (Supplemental Table 5). In identifying the known RA genes, the sensitivity was the highest when all the seven parameters were used. Three combinations of 5–6 parameters had high sensitivities as the seven parameters for the RA genes (Supplemental Table 5) when at least five parameters (InterPro, EC number and three GO concepts) were used.

The sensitivity of identifying the known PC-related genes was examined in all 120 combinations of the parameters in the same way (Supplemental Table 6). The use of all the seven parameters showed the second highest sensitivity for identifying the known PC-related genes. Three combinations of 5–6 parameters were a little more sensitive than the use of the seven parameters, and two combinations of 4 or 6 parameters had the same sensitivity as the seven parameters (Supplemental Table 6). These five combinations had at least four parameters including InterPro, GO molecular function and GO biological process in common. These results suggest that using several features including GO would be effective for prioritization of disease-susceptibility genes.

3. Discussion

In the past several years, several attempts have been made to develop methods for prioritizing potential disease-susceptibility candidates [13–15], and these are based on sequence similarities between genes and functional annotations from Gene Ontology. Perez-Iratxeta et al. developed a method based on the co-appearance of GO terms and MeSH disease terms [16,17]. In contrast, Freudenberg et al. used the clustering method to identify new disease genes [18], while Turner et al. presented prioritization of candidate genes using statistics (POCUS) based on the over-representation of the annotated function for the target disease [15]. Although these methods have been relatively successful, there are two problems in identifying disease-related genes: (1) these methods strongly depend on kind of functional information (i.e., information from GO), and (2) some frequently appearing biological terms in human genes can be "background noise" because

Table 3A
Highly scored genes within 22q12 in relation to PC.

Gene symbol	Gene name	Transcript	PANDA score (MD2/MD1)	No. of GO features[a]	No. of other features[b]
OSM	Oncostatin M	NM_020530	30.4	3	0
KREMEN1	Kringle containing transmembrane protein 1	NM_032045	22.4	0	1
GAS2L1	Growth arrest-specific 2 like 1	NM_006478	20.6	1	1
TIMP3	Tissue inhibitor of metalloproteinase 3	NM_000362	17.5	0	2
LIMK2	LIM domain kinase 2	NM_005569	17.3	2	2
PIK3IP1	HGFL gene	BC011049	16.6	0	1
ADRBK2	Adrenergic, beta, receptor kinase 2	NM_005160	16.4	2	2
CHEK2[c]	CHK2 checkpoint homolog (S. pombe)	NM_007194	15.5	2	2
PLA2G3	Phospholipase A2, group III	NM_015715	14.5	2	2
NF2	Neurofibromin 2	BC020257	11	1	2

The prioritized genes were ranked by the PANDA score (MD2/MD1).
[a] Number of GO features (0–3) of the gene (molecular function, biological process, and cellular component).
[b] Number of non-GO features (0–4) of the gene (amino acid sequence similarity, InterPro, EC number, and KEGG pathways).
[c] This gene was included in the training set in the subsequent analysis with new data.

Table 3B
Scores for *OSM* in relation to PC.

Parameter	Functional annotation	ID	Base relevance score	Proportion in gene set		Score to *OSM*[a]
				Training set	All human genes	
GO molecular function	Cytokine activity	GO:0005125 (5)[b]	2	0.0043	0.0018	23.12
GO biological process	Immune response	GO:0006955 (7)	2	0.0158	0.0168	107.05
	Regulation of cell growth	GO:0001558 (6)	2	0.0158	0.0020	
GO cellular component	Extracellular	GO:0005576 (3)	1.63	0.1348	0.0510	12.95

Among the seven parameters, details for the three concepts of GO terms are shown. The score of paralogy was 0 because *OSM* did not have a sequence similarity to any known PC-related gene. The scores of InterPro, EC number and KEGG pathway were also 0.
[a] Scores were calculated by Eqs. (2) and (3).
[b] The level in a nested hierarchical vocabulary is shown in parenthesis.

they may be common terms frequently found in disease-related genes. For instance, if the training sets include genes encoding proteins that belong to large superfamilies such as immunoglobulin-like domain containing proteins, too many members of the same superfamily may be prioritized as candidate genes for the disease. In order to overcome such possible biases of these methods, we developed a robust method in which we use multiple sources of gene annotation and leverage training sets consisting of known disease genes. Aerts et al. constructed Endeavour which prioritizes disease susceptibility candidate genes [19]. However, the problem of "background noise" in the functional terms was not resolved in their study. Using seven methods for computational prioritization of disease genes, Tiffin et al. (2006) generated a list of nine candidate genes for type 2 diabetes (T2D) common to six of the seven methods [20]. We have also identified three of the nine T2D candidate genes using PANDA system (data not shown), suggesting that our method can pick up reasonable candidate genes for multifactorial diseases.

Here, we have highlighted two examples (*TNFSF12* and *OSM*) that were selected with three GO annotation categories. These two genes, *TNFSF12* and *OSM*, had no positive scores for the other parameters (Tables 2B and 3B). The prioritized genes included another candidate gene for PC, kringle containing transmembrane protein 1 (*KREMEN1*) with the second highest PANDA score in 22q12 (Table 3A). *KREMEN1* has only two InterPro annotations that are shared with known PC-related genes including plasminogen activator urokinase (*PLAU*), plasminogen (*PLG*), hepatocyte growth factor (*HGF*), suppression of tumorigenicity 14 (*ST14*), and neuropilin 1 (*NRP1*) (data not shown). This suggests that a simultaneous usage of various features of human genes with GO annotation is effective for prioritization of disease-related genes.

To ensure that the prioritized genes are likely to be associated with the targeted disease, we surveyed subsequent reports in which a causative link to disease is shown. Interestingly, Godoy-Tundidor et al. reported that IL6 and OSM stimulate proliferation of prostate cancer cells, at least in part, through activation of the phosphatidylinositol 3-kinase signaling pathway [37]. Therefore, *OSM*, one of the predicted candidate genes for PC, may be a reasonable candidate gene. We checked if there is any newly reported gene with susceptibility to RA or PC by searching for the later releases of the public databases (OMIM, Entrez GENE, and PubMed). Then we prepared lists of known related genes for RA and PC again with new data. Between August 2004 and January 2008, 40 genes were newly described as RA-related genes in the OMIM database (Supplemental Table 7). When we conducted PANDA analysis by using this enhanced training set, eight genes of the 40 genes were selected in the training set via Entrez Gene. Three genes (*FLT1*, *IL1RN* and *EBI3*) of the remaining 32 genes were identified as candidate RA-susceptibility genes by our PANDA analysis (PANDA score > 21.2, Supplemental Table 7). However, the *LGALS3* gene encoding galectin-3 was not highly scored although some galectin superfamily members are involved in pathogenesis of RA. This may be because that the gene data for galectin proteins had little functional annotation. One of limitations of our approach is that genes with little annotation are less likely to be prioritized as candidate disease genes. The highly scored genes included *FLT1* (PANDA score = 115.5) whose gene product, FLT1, inhibits vascular endothelial growth factor (VEGF) response. The VEGF response may be involved in the pathogenesis of RA, because De Bandt et al. found that *VEGFA*, *FLT1*, and *KDR* are expressed in synovial cells from arthritic joints, using a transgenic mouse model of RA and antibodies to these three proteins [38]. Another gene prioritized was *IL1RN* (PANDA score = 33.8) whose gene product, IL1RN, inhibits IL1R binding by IL1-alpha and IL1-beta. Because these two cytokines (IL1-alpha and IL1-beta) are involved in both immune response and inflammatory response [39], *IL1RN* may be associated in the pathogenesis for RA. Recently, new susceptible loci for RA have been detected by GWAS [40–43], and many of them are genes involved in immune and inflammatory responses. Thus our analysis may have worked to predict biologically reasonable candidate genes.

We also searched for newly added PC-related genes in the OMIM database between August 2004 and January 2008, and found 57 additional PC-related genes that had not been reported in 2004. Then we conducted PANDA analysis again with the enhanced training set (Supplemental Table 8). Among these 57 genes, 17 genes were selected in the training set via Entrez Gene, and two genes, HNF1 homeobox B (*HNF1B*) and Eph receptor B2 (*EPHB2*), of the remaining 40 genes were identified as candidate genes by our analysis (in which PANDA score was larger than 14.1, a threshold value in this analysis). In particular, *EPHB2* showed the second highest score (PANDA score = 40.4) among the genes that are located at 1p36.1. This gene is of great interest because Huusko et al. identified mutations affecting translation in *EPHB2* in human prostate cancer cells [44]. Although reports of new susceptible loci for PC are increasing by GWAS, analysis of gene expression, and cancer genome sequencing [45–48], results of these studies include false positives. Our approach would be useful to find biologically relevant candidate genes from results by such large-scale analyses.

Although we showed that our approach can predict reasonable candidate disease genes, the approach can be extended in the following ways. First, by including text-mining techniques, we will be able to make enhanced training sets for other complex diseases through automated processes. This will allow researchers to select training sets for PANDA analysis without detailed disease-specific knowledge or manual annotation of literature. Second, an expansion of parameters (e.g. including protein–protein interaction, gene-gene interaction and gene expression) and a customized selection of parameters would increase the flexibility of the analysis and improve the sensitivity in prioritizing disease-related genes that do not have functional similarities with known disease genes or do not have detailed functional annotations. Such developments should further allow researchers to leverage their knowledge base and experience to efficiently prioritize disease-related candidate genes.

This approach, implemented in the PANDA system, is an efficient and cost-effective method to narrow down a large set of genes that are typically identified in microarray or mapping studies, into a smaller subset most likely to be associated with the disease. In addition, the PANDA system would be a useful tool to prioritize biologically relevant candidate genes with result of GWAS, large-scale gene expression data and genome sequencing to find causative variants [49,50].

4. Methods

4.1. Data of human genes

We retrieved data of human genes from the two databases, H-InvDB [6] and RefSeq [5]. H-InvDB (version 1.0, on 15th July 2002) contained 41,118 H-Inv cDNAs, and RefSeq contained a set of 37,488 human mRNA sequences that were available on September 1st, 2003. After merging the two datasets of human genes and removing the genes having no functional information, we created the H1-REFSEQ DB containing a total of 14,959 human genes. We used representative transcripts (one transcript for one gene) instead of all genes in H1-REFSEQ DB to remove the redundancy of cDNAs due to multiple forms of alternative splicing variants. Information of gene structure and functional annotation for the 14,959 human genes was retrieved from the H-InvDB [6].

4.2. Selection and curation of known related genes for the target diseases

Known related genes for the target diseases (RA and PC in this study) were searched from the OMIM database (www.ncbi.nlm.nih.gov/Omim) [29] and Entrez Gene (www.ncbi.nlm.nih.gov/gene), filtered and curated (see below), so that we can use them as the training sets of our prioritization analysis. We used MeSH terms (www.ncbi.nlm.nih.gov/ mesh) associated with the two diseases ('arthritis, rheumatoid', and 'rheumatoid, juvenile arthritis' for RA; 'prostatic neoplasms' and 'prostatic intraepithelial neoplasia' for PC) to scan all abstracts of papers cited in OMIM and Entrez Gene. We obtained 231 genes as possible RA-related genes and 728 genes for possible PC-related genes in August 2004.

Next, the two gene sets were filtered to select genes that have a series of curated references linked by PubMed IDs. We gave scores to these known disease genes based on the associated disease MeSH terms in their PubMed abstracts. The scores (1, 2, or 3) were assigned automatically according to the number of major MeSH topics that an abstract contained; no asterisk (1), asterisk for subheading (2), or asterisk for specific disease term (3). Then we manually annotated each reference whether the relationship between the gene and the target disease was mentioned by checking phenotype-specific terms. Each abstract of the article was reviewed by two or more persons to avoid possible problems by different interpretations and annotations between persons. We did not weight the articles according to approaches, sample numbers or ethnicity when we annotated the disease susceptibilities of genes. The information we collected included some genes whose role in the pathogenesis was examined in mouse models. We did not give scores to the studies without functional validation. Functionally-related genes for RA included those involved in inflammation of synovial membrane, degeneration of synovial joints or immune response. Functionally-related genes for PC included those involved in the proliferation of cells, signal transduction and transcription factors. After discarding genes that were not clearly related to the disease from a list of disease-related genes, we obtained 139 relevant genes for RA and 296 genes for PC (Supplemental Tables 1–2).

The selected known disease-related genes were used as the training set of the prioritization analysis with the relevance scores, which were automatically given and manually checked (mentioned above). Because one known disease gene may have multiple reference articles about susceptibility to the disease, we calculated w_i, the arithmetic mean of all baseline relevance scores for a particular gene i. This w_i was used as a parameter of disease susceptibility for a known related gene for the target disease.

4.3. Analysis of biological information of known related genes for target disease and all human genes

We selected genes that are relevant to the target disease from OMIM and Entrez Gene by querying disease-specific MeSH terms (downloaded on September 5, 2003). We then used these genes as a training set to analyze biological information for prioritization of candidates of disease-related genes. To utilize biological information for the analysis, annotated biological information on human genes from H-InvDB was analyzed with respect to the enrichment of specific biological terms in the known related genes for the target disease. The levels of enrichment of biological terms were converted into scores using several formulae (see below). The paralogy with the known related genes for the target disease was also examined based on similarity of amino acid sequence by using the BLAST program [51]. We gave a higher score for a gene that had sequence similarity to the known related gene for the target disease (see below). In total, we used seven kinds of biological feature of human genes (sequence similarity, InterPro annotation, EC number, three kinds of GO terms, and KEGG pathways).

4.4. Sequence similarity to known related genes for the target disease: the paralogy score

Paralogous genes that result from gene duplications have a similarity in their sequence and may share some related biological features [52]. Therefore, a paralogous gene with known disease gene may be more likely to be involved in the disease than other genes. Based on this concept, we calculated 'paralogy score' so that we give

a higher priority to a gene when the gene has a similarity to any known related gene for the target disease. For this purpose, we searched for genes that have sequence similarity to each known related gene for the target disease. We compared amino acid sequences by using BLAST [51], and 'paralogous' gene pairs were identified with significance cutoff values of *e-100*, *80*, *60* and *40*. When a gene *i* (no previous evidence of linkage to the disease) has a similarity to known disease gene *i'*, the paralogy score $S_{p,i}$ of a gene *i* (no previous evidence of linkage to the disease) has a positive value given by the equation:

$$S_{p,\,i} = -w_{i'}(1-\log_{10}[\text{e-value}])R, \tag{1}$$

where $w_{i'}$ is the baseline relevance score for the known disease gene *i'* with which the gene *i* is similar to. We set the weight *R* ($R_{100}=1$ for the gene pairs whose similarity significance was detected with *e-100*) for the cases that sequence similarity was detected by the lower significance levels (*R* values for *e-80*, *60* and *40* are given in Supplemental Table 9). When gene *i* does not have a similarity to any known related gene for the disease, this score was set to be 0.

4.5. Enrichment of functional terms: disease gene functional score

Genes associated with a disease may be prioritized through their functional similarities to known related genes for the disease or shared physiological pathway with known related genes with the disease. Here, we have made the assumption that certain groups of genes having related functions may be over or under-represented in a group of genes related to a specific disease. To test this assumption, we compared the frequencies of biological terms between the known related genes to the target disease and all the genes in H1-REFSEQ DB. The biological terms from the following resources were analyzed; InterPro identifiers (www.ebi.ac.uk/interpro/), EC numbers (www.chem.qmul.ac.uk/iubmb/enzyme/), KEGG pathways (www.genome.ad.jp/kegg/) [21], and gene ontology (GO) (www.geneontology.org/). For the known PC-related genes, "regulation of transcription, DNA-dependent" was the most frequent among the terms in "biological processes" of GO. However, this term was also frequent in all the cDNAs in H1-REFSEQ DB. From the disease-specific perspective for PC, "synaptic vesicle endocytosis" and "anti-apoptosis", were over-represented in the PC-related genes. As the prostate is an endocrine organ and secretes fluids, vesicle transport is an important component of its function. Apoptosis has also been extensively studied in cancer cells as a survival mechanism. Based on these observations we have extended the analysis to individual genes by quantifying and ranking the potential disease genes based on their levels of association to known disease-related genes through functional similarity or linkage to common physiological pathways. To carry out these comparisons we have utilized functional terms associated with genes, including InterPro identifiers, EC numbers, and KEGG pathway IDs, and expressed the proportion of each term for genes in the disease group compared with the frequencies among all genes in H1-REFSEQ DB. For a given functional term *j* in gene annotation, a score of relevance to the target disease was calculated by using the ratio of the proportion of genes with the term in known disease genes to the proportion of genes with the term in all human genes. This ratio was multiplied by the base score of disease relevance of the term (w_j) based on curation of the known disease genes (see above). Therefore, the score, $S_{f,j}$, was calculate by the equation

$$S_{f,\,j} = w_j \times P_{d,\,j}/P_{a,\,j}, \tag{2}$$

where $P_{d,j}$ is the proportion of genes with the term in known disease genes, and $P_{a,j}$ is the proportion of genes with the term in all human genes. This score was used as an indicator of the specificity of a functional term in known disease genes for the target disease. For a gene whose disease relevance is unknown, the score was calculated by summing $S_{f,j}$ for all the functional terms with the gene.

4.6. Use of biological terms in gene ontology data: GO score

The gene ontology [22] is composed as "a nested hierarchical vocabulary" of biological terms in which 'general' parent terms have nested child terms that are more specific. We have taken advantage of the nested hierarchy present within the GO terminology to provide a scoring system for functional specificity based on the position of GO terms within the hierarchy. For example, cell (GO:0005623), is a first-level GO term under the 'cellular component' category, nucleus (GO:0005634), is a third-level term under the same category of "cellular component". Therefore, we gave a higher weight ($P_{f,j}$) for a GO term *j* in a lower hierarchy. The score of GO term *j*, $S_{go,j}$, was calculated as a product of $P_{h,j}$ and $S_{f,j}$:

$$S_{go,\,j} = P_{h,\,j} \times S_{f,\,j}. \tag{3}$$

The score of GO term for a gene was calculated as the sum of $S_{go,j}$ for all the GO terms for the three concepts (molecular function, biological processes, and cellular components) with the gene.

4.7. Prioritization of candidates of disease-related genes by discriminant analysis

Integration of biological information from human genes allowed us to evaluate similarities between a given gene and multiple sets of genes. Here, there are two groups of genes; the first group is known related genes to the target disease and the second group is all other genes. For a given gene tested, a distance between the gene and the known related genes for the target disease (group 1) was compared with another distance between the gene and all the other genes (group 2). To express the distance between a gene and the center of gravity of a group of genes, the Mahalanobis distance [34] was calculated. For each gene from the group 2, we examined whether the gene is closer to the group 1 than to the group 2 by using Mahalanobis distances and discriminant analysis. The Mahalanobis distance for a given gene *i* and the group 1 (MD1) was calculated as:

$$MD1 = \sqrt{(X_i-\mu_1)'Cov_1^{-1}(X_i-\mu_1)}, \tag{4}$$

where X_i is a vector for gene *i* consisting of scores of multiple parameters (seven parameters in this analysis), μ_1 is a vector of mean values in the group 1, and Cov_1^{-1} is an inverse of the covariance matrix of the observed values of the seven parameters for the group 1. The Mahalanobis distance between a query gene and the group 2 (MD2) was calculated in a same way. Then we judged whether a gene is closer to the group 1 (known related genes for the target disease) than the group 2 (all the other genes). Because we consider a gene showing smaller MD1 than MD2 to be a disease-susceptibility candidate, we calculated the ratio of MD2 to MD1 (PANDA score). We also calculated the PANDA score for each of known related genes to the target diseases (the training set) in the same way, and the average score in the training set was calculated. Using the average score for the training set as a threshold, we considered any gene to be a candidate gene of disease-susceptibility if the score was greater than the threshold. Our results obtained by the prioritization analysis of disease association (PANDA) are available at http://www.h-invitational.jp/panda/app.

Supplementary materials related to this article can be found online at doi:10.1016/j.ygeno.2011.10.002.

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