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Research paper

VitiVar: A locus specific database of vitiligo associated genes and variations

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ABSTRACT

Vitiligo is the most common skin pigmentation disorder which affects around 1% of the population worldwide. The disease has complex pathogenesis and is of multifactorial etiology, that finally culminates in patchy depigmentation of skin. Genetic contribution to the disease is well studied, however the information about multiple associated genes and contributing variations are scattered across the literature. To address this complex disorder affecting the skin, we systematically cataloged the genes and variations by creating a Locus Specific Database for vitiligo called, "VitiVar". This comprehensive resource houses manually curated 322 genes and 254 variations, from 202 articles indexed in PubMed. We applied an integrative approach to stratify genes and variations to facilitate dissection of vitiligo pathogenesis by layering it with expression status in specific constituent cell types of skin and in-house vitiligo expression data. Finally, we were able to demonstrate the utility of VitiVar by generating a vitiligo interactome using GeneMANIA and overlaying the vitiligo and cell type specific information. This interaction network yielded 20 new genes (apart from 322 VitiVar genes) of which we were able to prioritize *IFI27* and *IFI6* for further validation. This, thereby makes VitiVar a comprehensive integrative platform in unravelling disease biology by providing meaningful leads for functional interrogation. VitiVar is freely accessible to the research community for prioritizing and validating the candidate genes and variations (http://vitivar.igib.res.in/).

1. Introduction

Complex disorders disproportionately share today's healthcare burden. An interplay of genetic factors along with environment contributes to disease pathogenesis, making it difficult to dissect the etiology. Hence, these complex disorders are of world-wide interest among healthcare professionals, researchers, and patients alike. Understanding these diseases necessitates consolidation of existing information to facilitate integrated evaluation (Motulsky, 2006).

Vitiligo is one such complex disorder manifested by the progressive loss of melanocyte that leads to a white patchy appearance of the skin. Owing to its striking visibility, vitiligo has a severe psycho-social impact and hence is a leading cause of the decline in quality of life among patients. Prevalence of 0.2–1% in different populations around the world is observed for vitiligo, with rates as high as 5–8% in certain local populations (Richmond et al., 2018; Singh et al., 2018). Autoimmunity is attributed to be the cause of melanocyte cell death whereas factors such as redox imbalance, an aberration in melanogenesis and loss of cell adhesion contributes to the disease progression (Dwivedi et al., 2015; Lotti and D'Erme, 2014; Picardo et al., 2015). Several genetic markers have been identified for vitiligo through candidate gene variations and association signals in vitiligo versus normal healthy individuals in Genome-wide association studies (GWAS) (Dey-Rao and Sinha, 2017; Jin et al., 2016; Xu et al., 2018). More recently whole-genome microarray study for expression changes has mapped alterations in whole skin and epidermis of vitiligo subjects (Singh et al., 2017). With the availability of disease implicated genes and variations from various study types a disease centric resource portal would pave path for new hypothesis and in identifying key genes through gene prioritization.

Therefore, this study catalogues all possible research work carried out on the genetics of vitiligo along with relevant information to understand the disease etiology in vitiligo development. The static information of genetic variations needs to be comprehended in the context of genome dynamics brought about by transcription. Thus, we have

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compiled the status of expression from public resources (GTEx, (Reemann et al., 2014)) in different skin cells and blood (healthy individual), to aid in understanding the disease map relevant to the affected and effected cell types. Since aberrations in the expression pattern of skin cells and blood are observed in vitiligo, we have also included our in-house microarray data from the epidermis of 15 vitiligo patients (GSE75819). Furthermore, we have employed a network based approach to illustrate the utility of VitiVar. A vitiligo interactome was created by using the 322 genes from VitiVar. Overlaying cell type specific information and the expression status in vitiligo (epidermis) we were able to prioritize two novel candidate genes (*IFI27* & *IFI6*) for further functional study.

To summarize, VitiVar is the first vitiligo centric database which not only provides a compendium of manually curated genetic information associated with vitiligo, it also provides a platform for users in formulating and validating a hypothesis by using cell type-specific expression changes in skin cells and blood tissue. Incorporation of in-house experimental data in VitiVar makes it a robust platform which can be utilized in the prioritization of key disease candidates from the bulk data generated through genome-wide experiments. Both the experimental and public data in VitiVar can be used in studying the vitiligo comorbidities with other diseases (like thyroid). VitiVar database is freely accessible at http://vitivar.igib.res.in/.

2. Data sources & database content

2.1. Compilation of genes and Variations from extensive literature search

Towards creating a compendium of genes and variants associated with vitiligo (called “VitiVar”) a PubMed search was carried out with an initial search term of “Genetics of Vitiligo”. > 1000 articles were screened to collate the vitiligo associated genetic information. An extended search with 31 other search terms was performed in order to ensure the completeness of our catalogue (Supplementary Table 1). The details of the data collection along with various inclusion and exclusion criteria is depicted in, Supplementary Fig. S1.

After the application of various inclusion and exclusion criteria, 202 articles were selected for manual curation to incorporate the associated genes, variations and other relevant details (Supplementary Table 2 and Supplementary Fig. S1). In total VitiVar encompass 322 genes and 254 variations from the genetic studies of vitiligo.

2.2. Computation of differential gene expression in Vitiligo

To incorporate skin specific changes in gene expression as a consequence of vitiligo, pairwise Differential Gene Expression (DGE) was computed by comparing expression differences between the lesional depigmented whole epidermis and non-lesional uninvolved vitiligo epidermis from 15 vitiligo subjects (Dataset 1; Institutional Human ethics committees of Ram Manohar Lohia Hospital, New Delhi and National institute of Immunology, New Delhi, approved this study, which is in agreement with Declaration of Helsinki principles).

The background corrected probe intensity values from the microarray experiment were average normalized and the *p*-value calculation was done using paired *t*-test (was computed by Matlab). Finally, a score was calculated for the probes by multiplying –log10(p-value) and flag (Computation of flag and method details is illustrated in Supplementary Fig. S2; Supplementary Table 3). For this dataset, the inclusion and exclusion criteria, choice of patients, type of vitiligo and the stability of the patches were taken into account (GSE75819; (Singh et al., 2017)); (Demographic details have been provided in Supplementary Table 7). These expression values have been colour coded as green, red or grey for upregulation, downregulation or not differentially expressed respectively and is depicted in gene expression meta-analysis page (link provided in gene summary page).

2.3. Expression enrichment in different skin cell types and blood

Vitiligo manifestation involves cell autonomous changes that would be recapitulated in melanocytes. These changes in melanocyte niche might involve keratinocytes and fibroblasts and the autoimmune effects would be manifested in the infiltrating blood derived cells. To study this, we included data from the recently published work by RNA sequencing from cultured primary human melanocytes, keratinocytes, fibroblasts, as well as the whole skin (Dataset 2). To integrate the autoimmune effects in blood, gene expression datasets were retrieved from GTEx (245 healthy individuals; Dataset 3) (Carithers and Moore, 2015; GTEx Consortium, 2013). We compared the expression of VitiVar genes (genes collated from literature) in different skin cells and tissue types – fibroblasts, keratinocytes, melanocytes, whole skin, and blood. Dataset 2 and 3 were RNA-Seq based studies and were pre-processed according to the criteria/guidelines mentioned in their respective studies. RNA-Seq expression values were normalized by z-score for comparative analysis. These z-score values were then colour coded and is depicted in gene expression meta-analysis page (same as above). Details of samples, data processing and analysis are provided in Supplementary Fig. S2 and Supplementary Table 4.

Thus, for all the genes in the compendium, we provide a summary of gene expression status in skin cells, vitiligo epidermis, as well as blood. This page can be accessed by clicking the hyperlink provided in the gene summary page. Overall, the comparative analysis of cell type-specific information is crucial for understanding disease pathogenesis and would help in the selection of appropriate cells for functional studies.

3. Database implementation

VitiVar Locus Specific Database (LSDB) was created using the Leiden Open Variation Database (LOVDv.3.0) framework (Fokkema et al., 2005). It houses 322 genes and 254 variations from different studies in standardized formats of LSDB. Multiple layers of information were incorporated to aid the user in making useful interpretations. (See Fig. 1.)

Variants were mapped to hg19 build and were converted into Variant Calling Format (VCF) to upload in LSDB. The variants adhere to Human Genome Variation Society (HGVS) nomenclature and were automatically mapped to genes by LOVD. Categorization of variants based on the type of study, mapping risk allele and description of the population in which study was conducted were included. The variants were mapped to genes by LOVD, intergenic variants tagged to adjacent genes by cognate studies are also included. Appropriate links are provided to the National Centre for Biotechnology Information (NCBI) database for the gene, transcript, and protein sequence information. We also provide the global risk allele frequency of 1000 genome data, gnomAD,ExAC and the Indian Genome Variation (IGV) database (http://www.igvdb.res.in/), for comparing the frequency of the variation among different populations (1000 Genomes Project Consortium et al., 2015; Consortium, 2010, 2012; Indian Genome Variation Consortium, 2008; Karczewski et al., 2019; Lek et al., 2016; Narang et al., 2010). The genes reported exclusively from the expression based study of vitiligo were added separately. Since HLA alleles do not adhere to standard nomenclature schema, it is kept as a separate tab (in the form of a flat file) in VitiVar. In future, this data would prove useful in formulating strategies for the assessment of population-specific risk for this disorder. The database is available at: http://vitivar.igib.res.in (Fig. 2).

4. Data browsing

VitiVar provides a user-friendly platform for browsing and searching data in order to retrieve the genetic information on vitiligo. Users can access the complete list of manually curated genes from

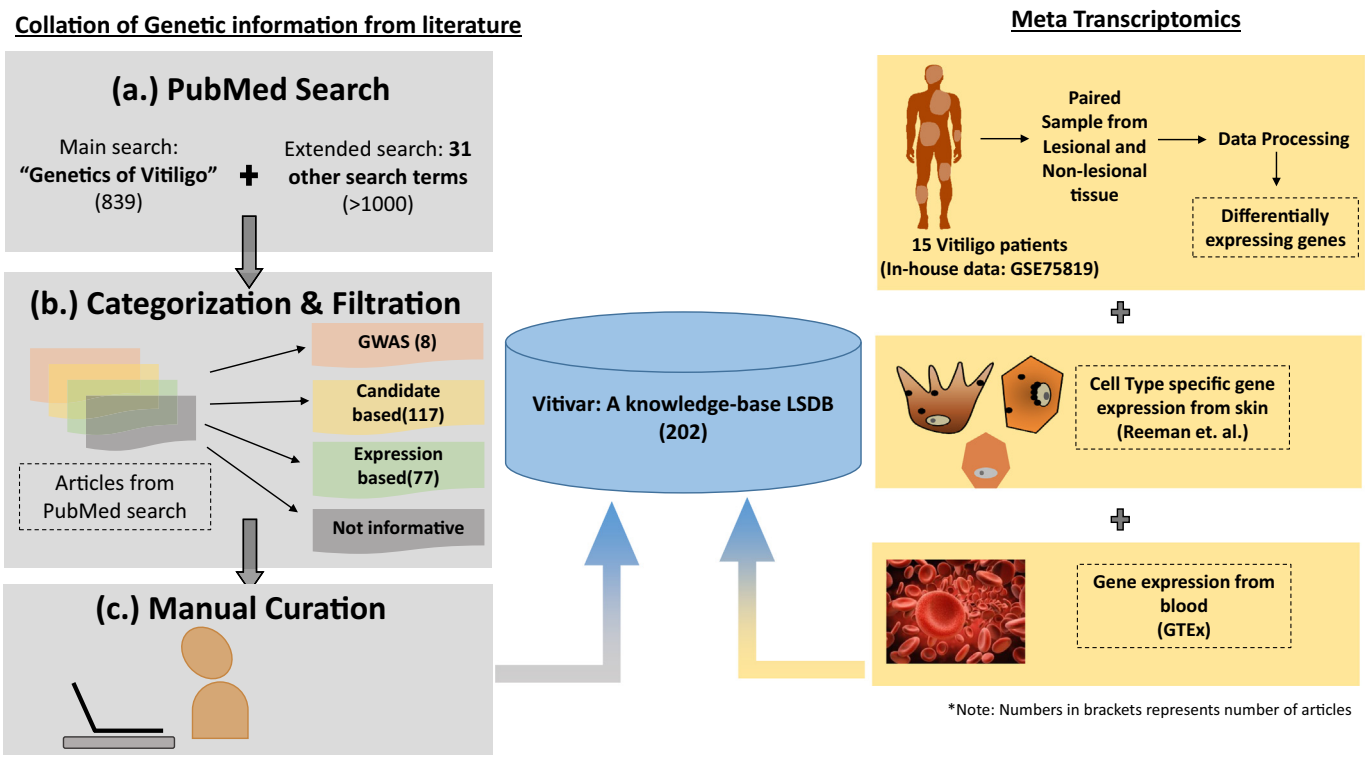

Fig. 1. Workflow for data collation and integrative analysis of VitiVar.
VitiVar is knowledgebase which harbours 202 Vitiligo articles and their associated relevant information. The information content in VitiVar compendium has been divided into mainly two sections: 1) Data collation from literature and 2) Meta transcriptomics of cell type specific data, Blood and Vitiligo in-house dataset.

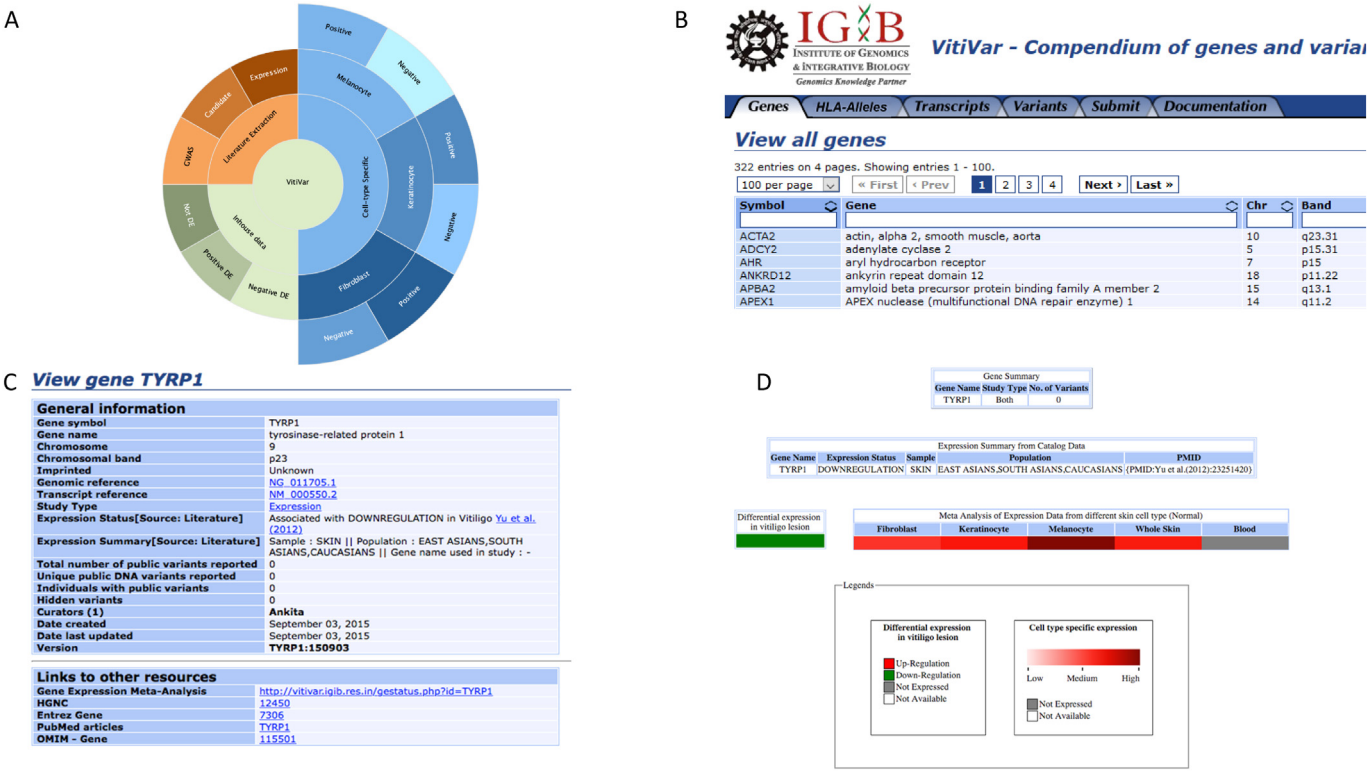

Fig. 2. VitiVar: A Compendium of information on the association of genes and variants in vitiligo.
A. Quick access to the data in VitiVar. B. Vitivar Database has been compiled based on > 1000 publications in various research articles on vitiligo and houses 322 manually curated genes and 254 unique variations derived from various GWAS, candidate and expression based studies. These are cataloged along with the relevant information such as reference to the article, the population where it was studied and genotype of the risk allele. Snapshot depicts the Vitivar layout. C. Gene page of specific variant is depicted. D. Gene expression meta-analysis through Heat map depiction from the database for a representative candidate gene TYRP1.

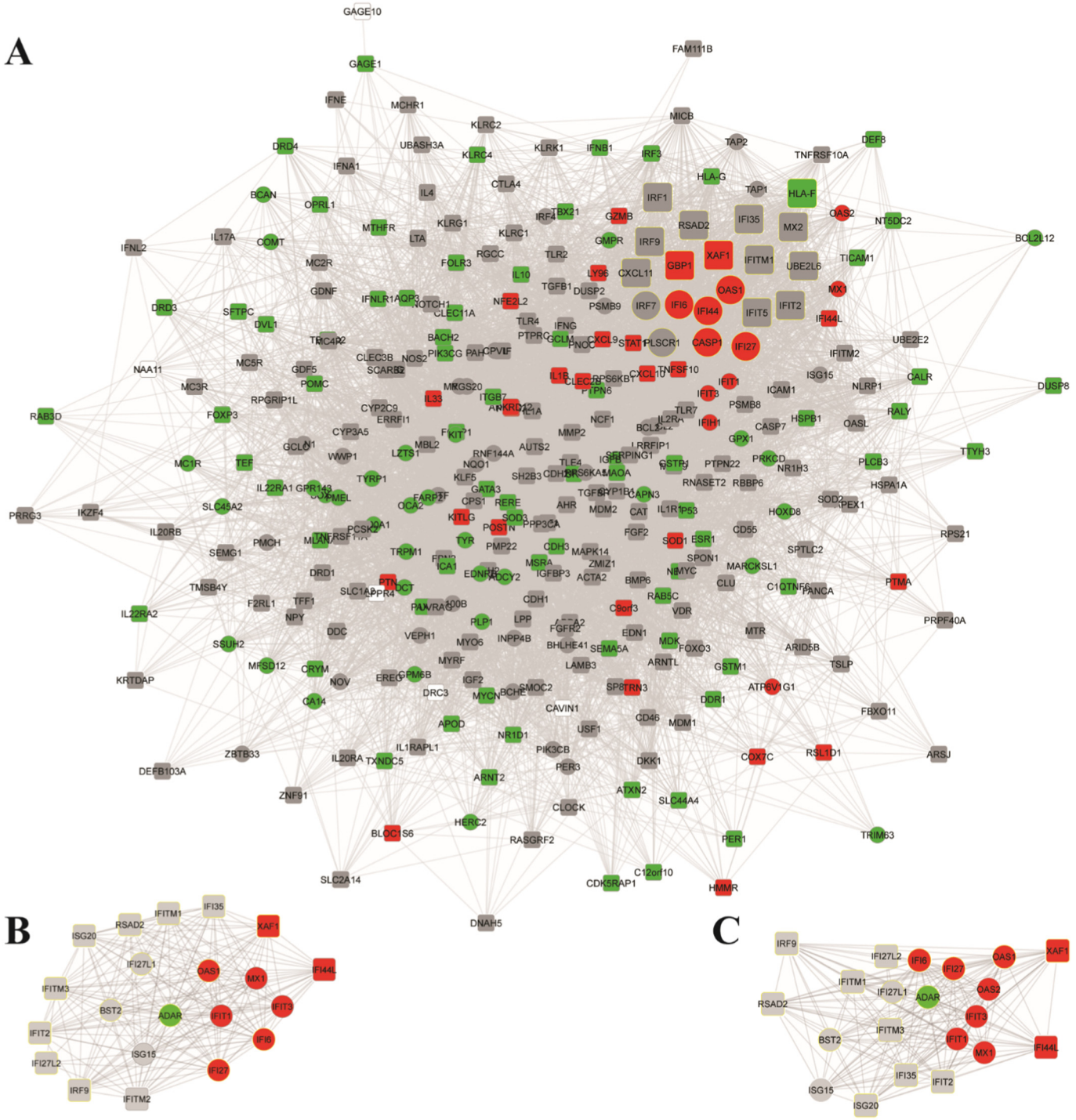

Fig. 3. Cell type specific analysis in vitiligo reveals underlying immunopathology.
Protein interaction network of the genes was retrieved from GeneMania and visualization was done using CytoScape. Colour of the nodes represent their status in in-house Vitiligo dataset; Red for upregulation, Green for downregulation, grey for not differentially regulated and white for no information content. The round shape representing melanocyte specific genes. Yellow order colour of the nodes represent whether the gene is novel or is already present in Vitivar gene list. A) Complete interaction network of 322 genes in VitiVar. B) & C) Interacting partners of *IFI6* and *IFI27* gene. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

literature along with their associated information in the browse database tab (by default it displays the genes page). By going to the genes page users can now select their gene of interest to display its details such as: gene name, chromosome, study type from which it was collated, its expression status in vitiligo (as reported in literature along with reference), type of tissue sample, population and other relevant details. The lower panel of the gene page provides a hyperlink which opens a PHP page and displays the expression status of that gene in various skin cells, blood and in vitiligo (in-house data). This has been briefly described in the previous section. Similar to the genes page there is a variants page which displays the list of vitiligo associated variations, its frequency in the Indian population, link to 1000 genome, the population in which it was studied, PubMed reference, also other range of useful information like, study type from which the variant was

reported and its reported risk allele.

As mentioned earlier, HLA alleles do not adhere to standard nomenclature schema hence they were kept as a separate tab which can be accessed from the page as that of genes and variants.

For searching single/multiple genes search gene tab have been provided where users can enter the gene list to be searched in database. Also, to access the other datasets of cell type specificity and in-house vitiligo expression a separate tab for the same has been provided.

5. Applicability and future directions of VitiVar

5.1. Comparative expression analysis in different skin cell types and blood

To understand the cell type specific effects in vitiligo *Z*-score normalized values from three different skin cell types – Melanocyte, Keratinocyte and Fibroblast (Dataset 2) were used to compare cell type-expression. To compare the expression difference between gene i for cell type j (G_{ij}) and other two cell types, we first calculated mean and standard deviation for other two cell types. Under assumptions of normal distribution, we evaluated where the gene lies in the distribution. To find signature gene (S_{ij}) in a cell type that lies in the extremes of the distribution (gene should have either very high/low expression than other two cell types or uniquely expressed), we used the following formula –

$$S_{ij} = (\mu - 2\sigma) > G_{ij} > (\mu + 2\sigma), \text{ if } G_{ij} \neq 0$$

($G_{ij} = 0$ means the gene i is not-expressed in the cell type j)where, μ is the mean and σ is the standard deviation. Gene expression within two standard deviations of the distribution (genes that have intermediate expression in any of the cell type) should fulfil the following criteria -

$$(\mu - 2\sigma) < G_{ij} < (\mu + 2\sigma), \text{ if } G_{ij} \neq S_{ij} \text{ and } G_{ij} \neq 0$$

The set of signature genes were ascertained to be cell specific as their cumulative contribution in the other two cell types was negligible but was found to be significant in the third cell type and whole skin. Thereby a set of cell type specific gene expression signatures were derived for the three skin cell types namely melanocytes, keratinocytes and fibroblasts (Natarajan et al., 2012). We cross validated our results by utilizing information available in literature. For example, TYR, a known pigmentation gene was also found to be melanocyte specific by our analysis. Apart from known genes we were also able to identify several novel genes as melanocyte specific which can later be functionally validated (Supplementary Table 5)

5.2. Utilizing network based approach to establish the utility of VitiVar

Disease could be visualized as an outcome of malfunctioning modules in multiple interacting gene networks. Application of network based approach to a well-curated genetic data would help in the identification of disease modules, and novel interactants which were not reported earlier. We therefore, generated the vitiligo interactome with 322 VitiVar genes by using GeneMANIA. In total, we had 13,644 interactions from 322 set of input genes. We created the network using Cytoscape, which is the most frequently used tool for visualizing interaction in genes/proteins (Shannon et al., 2003). To understand how these genes, behave in vitiliginous skin we overlaid the transcriptomic information from in-house Vitiligo microarray dataset. The differential gene expression (DGE) was calculated by comparing lesional to non-lesional epidermis from 15 vitiligo subjects (Supplementary Fig. 2; Dataset 1; GSE75819; Represented by colour of the node). Generic networks are limited owing to the lack of cell-type specific mapping of genes and their interactions. Therefore, we mapped the information melanocyte specific genes onto the complete vitiligo interactome (Represented by the shape of the node) (Fig. 3). 20 new interactants were found from the network of which 10 were completely novel genes i.e., not reported earlier by any study type in context of Vitiligo. As expected, several melanocyte specific genes were downregulated (which were mainly the pigmentation related genes like TYR, DCT, PMEL etc.). However, 11 genes were found to be upregulated in vitiligo lesions and are also melanocyte specific; out of which two genes Interferon Alpha Inducible Protein 27 (*IFI27*) and Interferon Alpha Inducible Protein 6 (*IFI6*) have not been reported earlier and are novel. These genes are likely to be relevant in immunological aspect of vitiligo especially in Interferon signalling as their common pathways being Interferon gamma signalling and innate immune system. In future, *IFI27, IFI6* genes could be functionally validated in melanocytes as well as in lesional skin of vitiligo to elucidate their role in underlying disease pathogenesis. Also, VitiVar compendium provides a robust platform for vitiligo specific genetic information along with cell type specific information. This can later be utilized in prioritizing the high throughput sequencing data like that from Exome/RNA sequencing.

6. Discussion

Vitiligo is a multifactorial disorder with an undeniable genetic basis. Several GWAS and candidate-based studies indicate the role of variants and expression changes in vitiligo pathogenesis (Shen et al., 2016). However, this information is scattered in literature and a comprehensive understanding of genetic variations would prove useful for the research on vitiligo. Designing an effective intervention for a disorder often begins with the elucidation of underlying patho-mechanisms that contribute to the disease phenotype and necessitates integration of data from diverse studies. In most of the common complex disorders such as vitiligo, multiple loci with minor effects are implicated and replication studies often show low concordance across populations. Understanding the functional basis of variations and its relevance in vitiligo requires a comprehensive analysis of the available data. Here, we provide the most extensive catalogue of manually curated genes and variations in vitiligo. Interpretation of the observations by the overlay of data from relevant cell types and currently available information from varied genomic resources further enhance prioritization of candidates for pursuing further. Resources such as GWAS central and NHGRI-GWAS provide genes and variants that are significantly associated with disease, whereas our disease-centric approach incorporates additional information from candidate gene-based studies and expression studies to maximize the data in the compendium (A brief comparison of VitiVar with above-mentioned databases can be found in Supplementary Table 6) (Beck et al., 2014; Welter et al., 2014). Community-driven curation of the data additionally helps in controlling the quality of the input data. Hence, VitiVar is a unique resource not just for dermatological conditions but also as an initiative towards understanding complex diseases using a systems medicine approach. We built this resource by retrieving data using a combination of search terms to maximize completeness of information and circumvent nomenclature ambiguities in gene and variation identifiers. For example, several alleles within the *HLA* loci are often associated with vitiligo, however ambiguities in nomenclature combined with their incompatibility with the currently accepted norms, often complicate interpretations (Cavalli et al., 2016; Yang et al., 2018). To circumvent this, known alleles of *HLA* loci associated with vitiligo are compiled independently in the VitiVar. Additionally, we were able to establish the usefulness of VitiVar through one such network analysis from which two novel genes (*IFI27* & *IFI6*; Not mentioned in the context of Vitiligo earlier) were selected for further investigation for their role in the disease pathology.

In summary, this compendium provides the necessary information to understand the genetic landscape of vitiligo across the human genome. This can be used to prioritize candidate genes for disease risk and to generate hypotheses regarding the functions of specific genes and variants. Some of the future applications to emanate from VitiVar include predictions on the comorbidity of vitiligo with diseases or skin phenotypes. Additionally, this can be integrated to find the core vitiligo specific networks as well as shared modules or networks common

among different diseases.

Declaration of Competing Interest

The authors declare no conflict of interest.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gene.2019.100018.

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