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RAPID COMMUNICATION

GeDiPNet: Online resource of curated gene-disease associations for polypharmacological targets discovery

There are numerous online databases dedicated to genes associated with human diseases. The redundancy and lack of consistency of disease terms in these databases pose a significant impediment in high throughput data analysis. To address this, we developed GeDiPNet by compiling data available on gene-disease associations from six popular open access sources namely DisGeNET,[1] ClinGen, ClinVar,[2] HPO,[3] OrphaNet, and PsyGeNET; and curated through several stages including manual curation and merging of disease names to ensure standard vocabulary (Supplementary file 1). GeDiPNet currently includes information on 12,270 genes that have disease association curated from literature records and 20,013 genes have disease association based on text mining.

Comorbid disease prediction using GeDiPNet

The non-redundant, curated data of genes and associated diseases in GeDiPNet can be effectively mined for unraveling shared disease etiologies and novel therapies using algorithms such as enrichment analysis, comorbidity risk prediction and polypharmacological target prediction that are integrated in GeDiPNet.

The utility of GeDiPNet for comorbid disease prediction is illustrated using metabolic syndrome (MetS) as a case study. Disease enrichment algorithm allows hypothesis-free identification of comorbid diseases based on probability of genetic and biological processes overlap between the diseases not occurring by chance. The top 20 enriched diseases for MetS genes are displayed in Figure 1. Syndromes related to bilirubin metabolism — Crigler-Najjar syndrome, Lucey-Driscoll syndrome and Gilbert disease are amongst the top most enriched diseases based on genetic overlap (Fig. 1A). Comorbid conditions of MetS such as

hyperinsulinemia, leptin deficiency syndrome, hypercholesterolemia, obesity, hypertension and diabetes are most significantly enriched based on functional overlap (Fig. 1B).

The outcome of the disease enrichment analysis is consistent with our current understanding of MetS. Oxidative stress in MetS is known to be caused due to hyperuricemia and hypobilirubinemia. Therefore, MetS individuals are at higher risk of developing syndromes related to bilirubin metabolism. Individuals with MetS are clinically known to suffer from multimorbidities; primarily linked through obesity and insulin resistance. Hence, it is expected that diseases such as cardiovascular disorders, diabetes, and fatty liver disease are identified to have a higher comorbidity risk with MetS.

Polypharmacological target prediction using GeDiPNet

The importance of managing complex diseases with drugs that act against multiple targets is well known. These polypharmacological targets can be identified based on shared genes amongst the comorbid conditions followed by pathway and network analysis of these genes.

The utility of GeDiPNet in prediction of polypharmacological targets was established using our existing knowledge of four popular polypharmacological drugs and targets. We observed that three of the four known polypharmacological targets, could be correctly identified using GeDiPNet (Supplementary file 2).

The algorithm correctly identified the target gene (*PDE5A*) and the drug Sildenafil for hypertension and erectile dysfunction. The drug methotrexate represses cell division leading to anti-inflammatory action. Therefore, methotrexate is used for the treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis. GeDiPNet correctly predicted the target *ADA* and drug methotrexate for these three diseases. Metformin is a

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Peer review under responsibility of Chongqing Medical University.
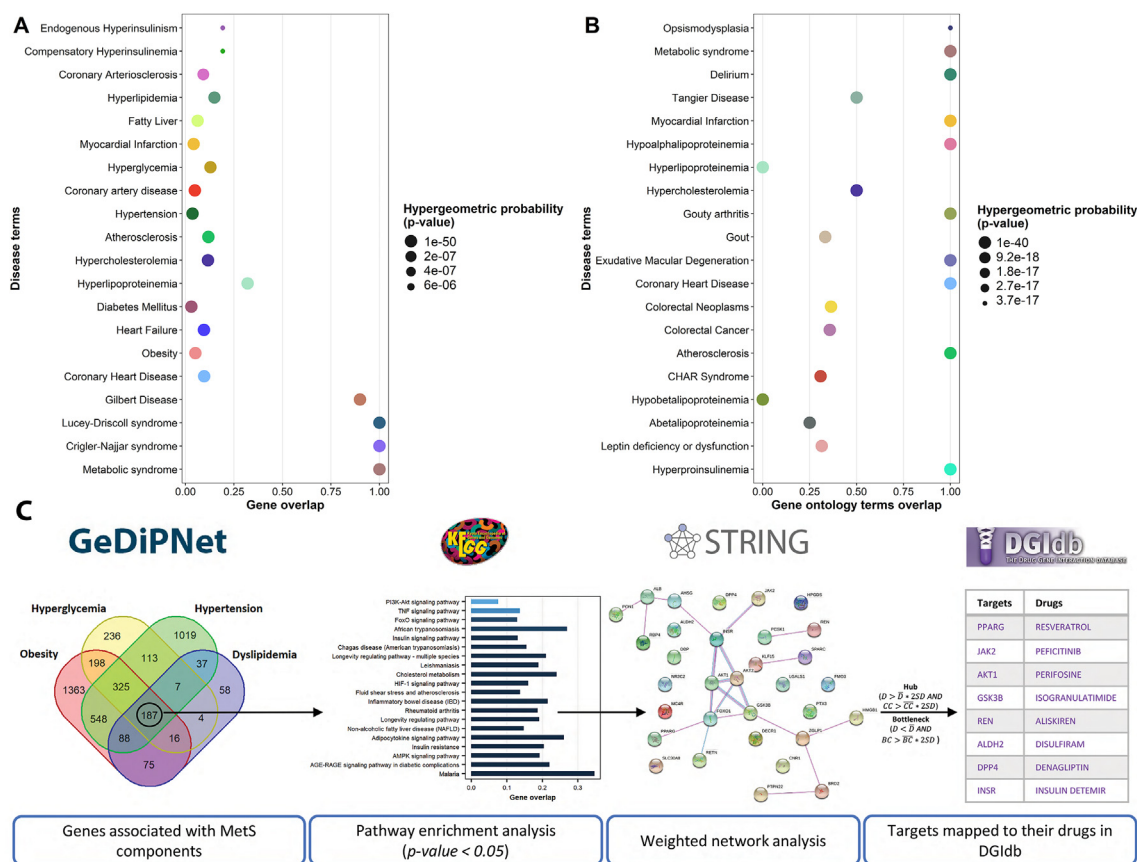
Figure 1 Top 20 enriched diseases (in descending order of significance) identified for MetS based on shared **(A)** genes and **(B)** gene ontology terms associated with MetS. **(C)** Workflow for prediction of potential polypharmacological targets of MetS.

well-known drug for treatment of insulin resistance observed in individuals with type II diabetes and PCOS. It promotes insulin signaling by activating phosphatidylinositol 3-kinase (*PIK3CA*). GeDiPNet, when queried for PCOS and diabetes mellitus correctly identified the target *PIK3CA* and its drug metformin. Dimethyl fumarate is used for treatment of multiple sclerosis and psoriasis. It mediates its anti-oxidant action via decrease in nuclear translocation of *NRF2*. Since *NRF2* is not yet reported as an associated gene for multiple sclerosis or psoriasis in any of the online databases, the algorithm could not predict the polypharmacological drug or the target in this case. Hence, the utility of the tool to predict a polypharmacological target is dependent on the accuracy and completeness of the data captured in gene-disease databases.

Polypharmacological targets for MetS were predicted by querying the tool with MetS components such as obesity, hyperglycemia, hypertension and dyslipidemia (Fig. 1C). The algorithm identified 32 genes (Supplementary file 3) that included *INSR, JAK2, REN, GSK3, DPP4, MAPK, ESR1* and *MC4R* as potential targets. Many of these targets are currently being used in management of components of MetS, for example: i) hyperglycemia is managed using inhibitors of *JAK2* and *GS3K*; as well as agonists of *PPARG* and *INSR*, ii) hypertension is managed using inhibitors of *REN* and *JAK2*, and iii) hypertriglyceride is managed by *PPARG* agonist. In addition to these known targets, few targets identified by the algorithm such as *DECR1*, involved in fatty

acid metabolism and inflammation, and *HPGDS*, involved in renal programming, are worthy of further validation as therapeutic targets for MetS. GeDiPNet also maps the identified targets to their known drugs from DGIdb[4] (Supplementary file 3).

The enhanced utility of GeDiPNet as compared to similar online resources has been demonstrated below using few examples.

1. *Disease pathway enrichment analysis:* Ocular albinism is a genetic condition, characterized by reduced pigmentation in the retina and visual acuity. It is majorly caused due to dysfunctional G protein coupled receptor 143 (*GPR143*) and tyrosinase enzymes, that are critical for melanin production. The disease is annotated as "ocular albinism" and "albinism, ocular" in HPO and DisGeNET respectively. Pathway enrichment analysis using Enrichr of 22 genes associated with ocular albinism from HPO identified tyrosine metabolism, nicotine addiction and lysine degradation pathways; whereas analysis of four disease-associated genes from DisGeNET identified renin secretion, and GABAergic synapse, as most significant. Enrichment analysis using GeDiPNet identified melanogenesis pathway to be most enriched followed by GABAergic synapse and tyrosine metabolism. Melanin synthesis pathways play a crucial role in ocular albinism, which is identified only by GeDiPNet.

2. *Comorbidity risk prediction:* Nicolaides Baraitser Syndrome (NBS) is a neuro-developmental disorder with intellectual disability, seizures and short stature. Prediction of comorbid diseases for NBS, using GeDiPNet, identified *coffin*-siris syndrome and retinoschisis as most significantly enriched. Coffin-siris syndrome is known to be comorbid and phenotypically very similar to NBS. A case report in 2019 documented association of ocular disorders in a girl with NBS. Retinoschisis is predicted to be comorbid with NBS because of *SMARCA2*, *RS1* and *CDKL5* genes commonly associated with the two diseases. The disease association of *SMARCA2* is documented in HPO, OrphaNet and curated subset of DisGeNET. ClinVar has cataloged the association of *RS1* and *CDLK5* genes. The comorbid diseases could be identified by GeDiPNet due to the manually merged data from multiple sources.

3. *Drug-target prediction:* Behcet syndrome (BS) is a multisystemic inflammatory disorder characterized by oral and genital ulcers, retinal vasculitis and deep vein thrombosis. The pathogenesis of BS is complex and the role of inflammatory cytokines such as TNF-α and IFN-γ is well known. Cyclophosphamide is one of the drugs used in the management of arterial aneurysms in BS. GeDiPNet identified tumor necrosis factor receptor 1 (*TNFRSF1A*) and cyclophosphamide as a potential target and drug respectively for BS. It is to be noted that the association of *TNFRSF1A* with BS is only documented in ClinVar database.

The comparative statistics of the data available in GeDiPNet and the other popular online resources are provided in Supplementary file 4. GeDiPNet will be maintained and updated yearly, and can be freely accessed at http://gedipnet.bicnirrh.res.in.

Ethics declaration

Exemption from ethics review was approved by the ICMR-NIRRCH Ethics Committee for Clinical Studies (ICEC/Sci-160/165/2020).

Author contributions

S.I-T planned, designed, and supervised the study. M.S and I.K curated and annotated the data. R.S.B, I.K, and K.P developed the interface and algorithms for analysis. I.K., M.S and S.I-T wrote the manuscript. All authors approved the manuscript.

Conflict of interests

The authors declare that they have no conflict of interests.

Data availability

Data download is available in browse pages in http://gedipnet.bicnirrh.res.in.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.05.034.

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17 February 2022
Available online 13 June 2022