Computational resources associating diseases with genotypes, phenotypes and exposures

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Abstract

The causes of a disease and its therapies are not only related to genotypes, but also associated with other factors, including phenotypes, environmental exposures, drugs and chemical molecules. Distinguishing disease-related factors from many neutral factors is critical as well as difficult. Over the past two decades, bioinformaticians have developed many computational resources to integrate the omics data and discover associations among these factors. However, researchers and clinicians are experiencing difficulties in choosing appropriate resources from hundreds of relevant databases and software tools. Here, in order to assist the researchers and clinicians, we systematically review the public computational resources of human diseases related to genotypes, phenotypes, environment factors, drugs and chemical exposures. We briefly describe the development history of these computational resources, followed by the details of the relevant databases and software tools. We finally conclude with a discussion of current challenges and future opportunities as well as prospects on this topic.

Key words: disease phenotype; genotype; environmental exposure; database; software tool; web platform

Introduction

As the advance of sequencing and other high-throughput technologies are producing big omics data for medical research, how to utilize and analyze these data to understand human diseases has become increasingly challenging. Whole exome sequencing or whole genome sequencing could unravel hundreds of thousands to even millions of variants, of which only a few may

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be disease-causative or related [1–4], thus identifying disease-causing genes and pathogenic variants is critical in human genetics studies. The focus of the genetics field is shifted from the production of genotypic data to the annotation and interpretation of analysis results.

The causes of a disease and its therapies are not only related to genotypes but also associated with other factors, such as phenotypes, environmental exposures, drugs and chemical molecules, etc. Distinguishing disease-related factors from many neutral factors is critical as well as difficult. Misleading assignment of pathogenicity to factors may result in inaccurate disease-risk assessments and diagnoses along with unsuitable treatments. Individual phenotype, broadly defined as any observable characteristics of an individual [5], arises from complex interactions between the above multiple factors. Correct and accurate interpretation of the relationships between these factors is fundamentally important for the investigation of human disease mechanisms.

Over the past two decades, bioinformaticians have developed more than 100 computational resources to integrate the omics data and discover associations among genotypes, phenotypes, environmental exposures, drugs and chemical molecules. These computational resources, including databases such as Online Mendelian Inheritance in Man (OMIM) [6], ClinVar [7] and dbGAP [8–10], software tools such as Polyphen [11], ANNOVAR [12], Eigen [13], DeepSea [14] and PhenIX [15] and web platforms such as Open Targets [16] and DisGeNet [17], offer online and standalone applications to prioritize genotype-phenotype associations (GPAs), phenotype-drug/chemical-target associations and other associations. Undoubtedly, these computational resources have facilitated the research in life sciences and greatly supported the development of precision clinical medicine. However, researchers and clinicians are experiencing difficulties in choosing appropriate resources from hundreds of relevant databases and software tools. Therefore, it is imperative to critically review the disease-related databases and tools, not only for life scientists, but also for medical researchers and clinicians.

Here we systematically review the public computational resources of human diseases related to genotypes, phenotypes, environment factors, drugs and chemical exposures. We begin with the history of development of computational resources for human diseases, followed by the description of the relevant databases and the comparison of their scales of data and scopes of usage. Then we summarize and compare the software tools and the web platforms for the deeper understanding of associations between multiple disease-related factors. Finally, we conclude with a discussion of current challenges and future opportunities as well as prospects on this topic.

Development of the computational resources

Disease-related data, including phenotypes, genotypes, environment factors and drug/chemical exposures, were mainly generated by a range of international projects or research programs and have been stored and integrated in different public computational resources, freely available to the public (Figure 1 and Supplementary S-Table 1).

OMIM is the first established database to provide a catalog of human genes and genetic disorders [6], followed by the starting of the Human Genome Project in 1990. Five years later, the Human Gene Mutation Database (HGMD) was published to handle the data of human gene mutations [18, 19], followed by the construction of dbSNP [20] and Orphanet [21] in the late 1990s to integrate data of single nucleotide polymorphisms (SNPs) and rare diseases based on protein-coding genes. Since the year of 2000, several organism models have been developed and the databases of these model species are available not only for life science studies but also for medical research, e.g. Mouse Genome Database (MGD) [22] and MouseNet [23], Rat Genome Database (RGD) [24] and Zebrafish Model Organism Database (ZFIN) [25]. In 2000s, the databases of drug targets and chemical molecules were established to accelerate the development of molecular drugs, such as PharmGKB [26], DrugBank [27] and PubChem [28]. Since the late 2000s, noncoding RNAs have been found important in the development of diseases [29–33], and thus databases have been constructed to classify relationships between noncoding RNAs and human diseases, for example, NONCODE [34], miR2Disease [35] and LncRNA Disease [36]. At the same time, the international projects and research programs of population genomics, including 1000Genomes [37], TCGA [38, 39], ICGC [40] and UK10K [41], have produced biomedical big data for the communities of life and medical sciences to share, analyze and utilize. Environmental factors (EFs), drugs and chemicals also play critical roles in the development of diseases, such as the Comparative Toxicogenomics Database (CTD) [42], LncEnviroMentDB [43] and ExpoXome-Explorer [44].

With the rapid growth of data in these databases, data mining and analysis have become another challenge. Since 2003, at least 30 tools have been developed to annotate, predict and prioritize functional effects of genomic variants, as well as to identify genetic variants of uncertain significance (Figure 1 and Supplementary S-Table 1), e.g. SIFT [45], PolyPhen [11], ANNOVAR [12], VASSIT [46] and GWAVA [47]. Additionally, several ontology-driven computational tools have been developed to facilitate clinical interpretation of genomic variants based on functional prediction of genomic variants and deep phenotype annotations, such as PhenIX [15] and Phevor [48]. Moreover, machine learning technologies (including deep learning) have recently been implemented to predict variations and their biological effects, for example, CADD [49], Eigen [13], DeepSea [14] and DeepVariant [50]. Furthermore, several web platforms, such as DisGeNET [17], MalaCards [51], Monarch Initiative [52] and Open Targets Platform [16], have been established to comprehensively integrate a variety of disease-related data sources with computational tools, allowing easy and simultaneous data access and analysis.

Databases

Dozens of public databases have been developed to store, retrieve and manage disease-related data. According to scopes and data associations, the databases can be categorized into seven groups (Table 1). The database group for coding genes includes data resources that primarily provide association information between protein-coding genes and phenotypes of human diseases, while the group for ncRNAs contains non-coding RNAs information associated with diseases. The group for genomic variants associates genomic variant information with phenotypes of disease. The group for population genomic data focuses on the worldwide clinical genomic variation and allele frequencies in various populations. The group of genetical organism models stores association information between genotypes and phenotypes/diseases of laboratory organisms. The group of environment exposures offers toxicogenic relationships relevant to exposed factors, genes, proteins, phenotypes or diseases. The treatment group provides information that involves target drugs, drug resistance mutations, disease and their associations. All of these databases offer internet access of data through web browsers, and some of them also
Figure 1. Development history of disease-related computational resources. The development of disease-related databases, software tools and web platforms, is depicted over the timeline. According to scopes and applications, the computational resources are classified into different groups.

offer web Application Programming Interfaces (APIs). Table 1 summarizes the groups according to their scopes and associations. Table 2 states the current status of the databases and Supplementary S-Table 2 states the data standards of nomenclature. The URLs of the databases can also be found in the supplementary file.

Coding genes

Approximately 50 databases provide disease-related phenotype information associated with genotypes. Several of them focus on depicting the association between protein coding gene and phenotypes (Table 1). One of the most widely used databases is OMIM, which is manually collated and integrated from numerous peer-reviewed literature and other medical information, offering broad and powerful compilations of knowledge about human genes, genetic phenotypes and the relationships between them [6]. The latest OMIM database contains 15,919 gene descriptions, 8,670 phenotypes and 3,928 genes with association to 1 or more phenotype(s) [6] (Table 2). Another similar example is Orphanet [53]. Instead of targeting on Mendelian disorders, Orphanet focuses on easy access to accurate and specific recommendations for the management of rare diseases. It establishes the relationships between classification of rare diseases, textual data and the appropriate services for patients and healthcare professionals.

It has been debated that many diseases classically considered monogenic may be better described as more complex inheritance, such as oligogenic mechanisms [101]. Gazzo et al. published the DIDA database as a Nucleic Acids Research breakthrough article in 2016 to offer the first-time detailed information on genes and associated genetic variants involved in digenic disorders, the simplest form of oligogenic inheritance [55]. The current DIDA database includes 213 digenic combination-disease associations involved in 44 digenic diseases (Table 2).
Table 1. Comparison of different disease-related data resources

| Data resource name | Phenotype/Disease | Genotype | Environmental factors | Drugs/chemicals | Association Types | Score |
|--------------------|-------------------|----------|------------------------|-----------------|------------------|-------|
|                    | Mendelian and Rare Complex and Trait Organism model of disorder Coding Non-coding Function annotation of variant | | | | |
| **Coding genes**   |                   |          |                        |                 |                  |       |
| OMIM               | √(M)             | √(F)     | √(M)                   | √(F)            |                  |       |
| Orphanet           | √                 |          | √(M)                   | √(F)            |                  | GPAs  |
| DIDA               | √                 |          |                        |                 |                  |       |
| DiseaseMeth        |                   | (Cancer) |                        |                 |                  |       |
| **Noncoding RNAs** |                   |          |                        |                 |                  |       |
| miR2Disease        |                   |          | √(miR)                 |                 | GPAs             |       |
| HMDD v2.0          |                   |          | √(miR)                 |                 | GPAs             |       |
| NONCODE            |                   |          | √(inc)                 |                 | GPAs             |       |
| LncRNA Disease     |                   | (Cancer) | √(inc)                 |                 | GPAs             |       |
| NSDNA              |                   | (NSDs)   | √(ncR)                 |                 | GPAs             |       |
| circRNA Disease    |                   | (lncR)   | √(lncR)                |                 | GPAs             |       |
| MNDR               |                   | (M)      | √(ncR)                 |                 | GPAs             |       |
| **Genomic variants** |                 |          |                        |                 |                  |       |
| HGMD               | √                 |          | √(M)                   | √(F)            | GPAs             |       |
| ClinVar            | √                 |          | √(M)                   | √(F)            | GPAs             |       |
| VarCards           | √                 |          | √(M)                   | √(F)            | GPAs             |       |
| GWAS Catalog       | √                 |          | √(M)                   | √(F)            | GPAs             |       |
| GWAS Central       | √                 |          | √(M)                   | √(F)            | GPAs             |       |
| GWASdb             | √                 | (M)      | √(M)                   | √(F)            | GPAs             |       |
| COSMIC             |                   | (Cancer) | √(M)                   | √(F)            | GPAs             |       |
| CIVIC              |                   | (Cancer) | √                      |                 | GPAs             |       |
| Denovo-db          |                   | (NSDs)   | √(M)                   | √(F)            | GPAs             |       |
| miRdSNP            |                   |          | √(miR)                 |                 | GPAs             |       |
| LincSNP            |                   |          | √(inc)                 |                 | GPAs             |       |
| LncRNA SNAP        |                   |          | √(lnc)                 |                 | GPAs             |       |
| **Population genomic data** |               |          | √(M)                   | √(F)            | GPAs             |       |
| dbSNP              | √                 |          | √                      |                 | GPAs             |       |
| ESP                | √                 |          | √                      |                 | GPAs             |       |
| ExAC               |                   |          | √                      |                 | GPAs             |       |
| 1000Genome         |                   |          | √                      |                 | GPAs             |       |
| Kaviar             |                   |          | √                      |                 | GPAs             |       |
| FINDbase           |                   |          | √                      |                 | GPAs             |       |
| **Genetical organism models** |               |          | √                      |                 | GPAs             |       |
| MGD                | √                 | (Cancer) | √(Mouse)               |                 | GPAs             |       |
| MTB                |                   | (Cancer) | √(Mouse)               |                 | GPAs             |       |
| RGD                | √                 |          | √(Rat)                 |                 | GPAs             |       |
| ZFIN               | √                 |          | √(zebra fish)          |                 | GPAs             |       |
| **Environmental exposures** |               |          | √                      |                 | GPAs, GEFAs, PEFA |       |
| CTD                | √                 |          | √                      |                 | GPAs, GEFAs, PEFA |       |
| miREnvironment     | √                 |          | √(miR)                 |                 | GEFAs            |       |
| SM2miR             | √                 |          | √(miR)                 |                 | GEFAs            |       |
| LncEnvironmentDB   |                   |          | √(lnc)                 |                 | GEFAs            |       |
| DLREFD             | √                 |          | √(lnc)                 |                 | GEFAs            |       |

Continued
The publication of DIDA may initiate further data annotation and tool development for deciphering more complex inheritance, such as polygenic disorders.

Complex diseases generally involve multiple levels of alterations, such as epigenetics and transcriptomic alterations [102, 103]. The human disease methylation database (DiseaseMeth), first published in 2012 [104], associates aberrant DNA methylation with human diseases, especially various cancers. Data in DiseaseMeth are manually or computationally extracted from experimental studies and high-throughput metmlyome data. The current DiseaseMeth [55] database contains over 679 000 aberrant DNA methylation-disease associations across 88 diseases (Table 2). To identify correlations between DNA methylation and RNA expression, another methylation-related database, called MethHC, provides a large collection of DNA methylation data combined with mRNA/microRNA expression profiles in human cancer [105]. These resources provide coding gene-disease associations that are a great utility in different research and clinical purposes, including the interpretation of clinical significance of dysfunctions in coding genes. Researchers are recommended to use OMIM for studies in Mendelian inheritance, Orphanet for rare disorders, DIDA for digenic disorders and DiseaseMeth for disease-related methylation.

Noncoding RNAs

A large portion of human genome is transcribed into noncoding RNAs (ncRNAs), particularly long noncoding RNAs (lncRNAs), micro RNAs (miRNAs) and circular RNA (circRNA), potentially representing another layer of epigenetic regulation [33, 106]. Accumulative investigations have shown that ncRNAs play critical roles in many important biological processes [32] and its deregulations could be related to a broad spectrum of diseases [29–33]. Evidently, ncRNAs have become a novel class of potential biomarkers and targets for disease diagnosis, therapy and prognosis. Due to their functional and clinical significance, several databases have been established since 2005, including mirbase [107] for miRNAs, NONCODE [57], LNCipedia [108] and lncRNAdb [109] for lncRNAs. These databases connect ncRNA to diseases and also integrate annotation data of sequences, functions, expressions, related targets and cellular locations.

For example, the latest NONCODE [57] has annotated 167 150 human lncRNA sequences, of which 1110 are associated with 284 diseases [56] (Table 2).

Several databases target on the association between ncRNA dysregulation and human diseases (Table 1 and Table 2). For example, miR2Disease [35] and Human MicroRNA Disease Database (HMDD) [58] provide miRNA dysregulation-human disease associations and miRNA-target associations. The current release of HMDD has integrated 10368 associations between 572 miRNAs and 378 diseases. Similarly, LncRNADisease [36] and Lnc2Cancer [59] contain manually curated entries of experimentally supported lncRNA-disease associations and lncRNA-target associations, and the latter focuses on association data for cancer research. Unlike LncRNADisease and Lnc2Cancer, the Nervous System Disease NcRNAome Atlas (NSDNA) [60] aims to offer a comprehensive, quality and special resource of NSD-related ncRNA dysregulation. It manually collects experimentally supported associations between nervous system diseases (NSDs) and different types of ncRNAs, including miRNAs, lncRNAs, piRNAs, siRNAs and snoRNAs. The latest [60] NSDNA contained 26 128 associations between 8736 ncRNAs and 144 NSDs (Table 2). The MNDR database [110] integrates experimentally supported and predicted ncRNA-disease associations from 14 resources such as HMDD [58], Lnc2Cancer [59], NSDNA and LncDisease [111].

Moreover, several databases store predicted circRNA-disease associations such as Circ2Traits [112] and manually curated circRNA-disease associations from peer review papers such as circRNA2Disease [61]. Currently, circRNA2Disease provides 354 curated associations between 330 circRNAs and 48 diseases including cancers, neurodegeneration and cerebrovascular diseases [61]. Each association has comprehensive annotation information such as circRNA name, expression pattern, associated partners, associated diseases, experimental detection techniques and publication reference.

The above resources of ncRNA-disease relationships can be used conjunctively to discover and predict associations between novel ncRNAs and diseases, and to facilitate the interpretation of clinical significance of dysfunctions in ncRNAs. Lnc2Cancer is preferable for studying cancer-related lncRNAs, and NSDNA for NSD-related lncRNAs.
### Table 2. Summary of disease-related databases

| Database                      | Scope and scale                                                                 | Date of statistic       |
|-------------------------------|---------------------------------------------------------------------------------|-------------------------|
| Coding genes                  |                                                                                |                         |
| OMIM [6]                      | 15 919 gene descriptions, 8670 phenotypes and 3928 genes with association to 1 or more phenotype(s) | 22 June 2018<sup>®</sup> |
| Orphanet [53]                 | 6949 associations between genes and rare diseases                               | Aug 2016<sup>®</sup>    |
| Gene2phenotype [54]           | 2285 GPAs in developmental disorders                                           | Oct 2017<sup>®</sup>    |
| DIDA [55]                     | 213 digenic combination-disease associations in 44 digenic diseases             | Oct 2015<sup>®</sup>    |
| DiseaseMeth v2.0 [56]         | 679 602 aberrant DNA methylation-disease associations in 88 diseases, especially in various cancer | Nov 2016<sup>®</sup>    |
| Noncoding RNAs                |                                                                                |                         |
| NONCODE [57]                  | 1110 IncRNAs associated with 284 diseases                                       | Nov 2016<sup>®</sup>    |
| miR2Disease [35]              | 3273 associations between 349 miRNAs and 169 diseases                           | Jun 2018<sup>®</sup>    |
| HMDD v2.0 [58]                | 10 368 associations between 572 miRNAs and 378 diseases                        | Jun 2013<sup>®</sup>    |
| LncRNADisease [36]            | 3000 association between 914 IncRNAs and 329 diseases                            | July 2017<sup>®</sup>   |
| Lnc2Cancer [59]               | 1488 associations between 666 IncRNAs and 97 cancers                            | July 2016<sup>®</sup>   |
| NSDNA [60]                    | 26 128 associations between 8 736 ncRNAs and 144 nervous system diseases        | May 2017<sup>®</sup>    |
| circRNA2Disease [61]          | 354 associations between 330 circRNAs and 48 diseases                           | Apr 2018<sup>®</sup>    |
| MNDR v2.0 [62]                | 8824 IncRNA-disease, 70 381 miRNA-disease, 118 piRNA-disease and 67 snRNA-disease experimental associations across 6 mammals | Nov 2017<sup>®</sup>    |
| Genomic variants and population genomics |                                                                                     |                         |
| Clinvar [7]                   | 428 435 genomic variant-disease associations across 30 181 genes                | Jun 2018<sup>®</sup>    |
| HGMD [63]                     | 224 642 disease related variants on 8 784 genes                                | Jan 2018<sup>®</sup>    |
| Denovo-db [64]                | (July 2016): 32 991 de novo genetic variants in neurodevelopmental disorders   | Oct 2017<sup>®</sup>    |
| VarCards [65]                 | 110 154 363 artificially generated SNVs and 1 223 370-reported indels in coding region and splicing sites | Dec 2015<sup>®</sup> |
| LOVD 2.0 [66]                 | 3 334 104 (2 400 084 unique) variants in 248 807 individuals in 86 LOVD installations | Dec 2015<sup>®</sup> |
| MITOMAP [67]                  | 1746 variants on mitochondrial DNA                                             | Dec 2015<sup>®</sup>    |
| COSMIC [68]                   | 208 368 associations between somatic mutations and cancer                       | Nov 2016<sup>®</sup>    |
| CIVIC [69]                    | 1678 interpretations of clinical relevance for 713 variants affecting 283 genes associated with 209 cancer subtypes and 291 drugs | Feb 2017<sup>®</sup> |
| GWAS Catalog v2 [70]          | ~60 000 associations between SNPs and traits/diseases                          | Apr 2018<sup>®</sup>    |
| GWASdb v2.0 [71]              | 252 530 associations between SNPs and traits/diseases                          | Nov 2015<sup>®</sup>    |
| GWAS Central [72]             | 69 986 326 associations between 2 974 961 SNPs and 829 traits/diseases          | Nov 2017<sup>®</sup>    |
| LincSNP2.0 [73]               | 3 767 647 associations between LncRNA SNPs and diseases, and 1 266 485 Linkage disequilibrium (LD)-SNPs | Oct 2016<sup>®</sup> |
| LncRNASNFP2 [74]              | 697 IncRNA-Disease associations; 602 GWAS-SNPs and 2 859 147 SNPs in LD regions |
| miRdSNP [75]                  | 786 associations between 630 unique disease-associated SNPs and 204 disease types | Oct 217<sup>®</sup> |
| miRNASNP [76]                 | 2257 SNPs in 15 969 human pre-miRNAs; 706 SNPs in miRNA mature regions and 227 SNPs in miRNA seed regions | Jan 2015<sup>®</sup> |
| dbSNP [77]                    | A genomic variation database including 660 773 127 SNPs of Homo sapiens.        | Mar 2018<sup>®</sup>    |
| ExAC [78]                     | Variations from 130 000 subject exome sequencing data from a wide variety of large-scale sequencing projects | Aug 2016<sup>®</sup> |
| ESP [79]                      | 1 788 563 variants of 6700 exome sequencing data from heart-, lung- and blood-related diseases and traits | Oct 2016<sup>®</sup> |
| 1000Genome [80-82]            | Over 88 million variants of 2504 whole genome sequencing data from 26 populations | Oct 2015<sup>®</sup> |
| Kaviar [83]                   | Over 162 million variants from 35 projects encompassing 13 200 genomes and 64 600 exomes | Feb 2016<sup>®</sup> |
| Genetically modified organism models |                                                                                     |                         |
| MGD [84]                      | 5 021 associations between mouse genetic models and human diseases              | Nov 2016<sup>®</sup>    |
| MouseNet v2 [85]              | 7 880 080 functional gene network associations for laboratory mouse and eight other model vertebrates | Nov 2015<sup>®</sup> |
| MTB [86]                      | 6057 associations between mouse genetic models-human cancer; 2288 associations between specific genes-cancers | Oct 2014<sup>®</sup> |
| RGD [87]                      | 2 998 associations between rat genetic models-human diseases                    | Nov 2016<sup>®</sup> |
| ZFIN [88]                     | 11 348 associations between zebrafish genetic models-human diseases            | Nov 2016<sup>®</sup>    |
| Environmental exposures       |                                                                                |                         |
| CTD [89]                      | 1 379 105 chemical-gene associations, 202 085 chemical-disease associations and 33 583 gene-disease associations | Sep 2016<sup>®</sup>    |

Continued
Many genetic and complex diseases are associated with genomic variations and thus many genotype–phenotype databases store and curate genomic coverage of germline and somatic variations in single genes across the majority of genetic diseases, including Mendelian disorders, rare diseases and complex traits (Table 2). HGMD [63] is a representative repository for the clinical annotation of genetic mutations manually curated from more than 2600 peer-reviewed journals. HGMD has two types of version: the public version is freely available to users from academic institutions and non-profit organizations while the subscription version is available to all users from academic institutions under a commercial license provided by QIAGEN Inc. Another representative repository is ClinVar [7], which provides clinical annotation of genomic variation data. Data in ClinVar are submitted by clinical laboratory users and integrated from a variety of curated resources, including HGMD. Compared to HGMD, the freely available database LOVD provides not only the gene-centric collection and web search of nuclear DNA variations, but also the patient-centric data storage and storage of NGs data, even of variants outside of genes [66]. Moreover, MITOMAP reports 1746 human mitochondrial variants associated with diseases [67].

To provide standardization of annotation and improve accessibility of genomic variants, Li et al. developed VarCards to artificially generate all possible human single nucleotide variants (SNVs) in coding regions and splicing sites, and to classify all reported insertions and deletions (indels) [65]. VarCards has annotated variants from more than 60 genomic data sources, including disease-associated knowledge, functional effects, drug–gene interactions, predicted consequences through different in silico algorithms and allele frequencies in different population [65]. VarCards currently maintain over 110 million possible SNVs and more than 1.2 million reported indels (Table 2). Additionally, several other databases also cover genomic variations in genome-wide association studies (GWASs), such as GWAS Catalog [70], GWASdb [71], GWAS Central [72] and somatic variations in cancer, such as Catalogue of Somatic Mutations in Cancer (COSMIC) [68].

During recent years, abundant de novo variants and non-coding variants have been discovered in studies of complex diseases [64]. Novel variants of an individual not presented in either of his/her parents are termed de novo [113]. To facilitate better usages of the data of de novo variants, many databases have been established to integrate, characterize and annotate disease-related human de novo variants, including Denovo-db [64], NPDeNovo [114] and Developmental Brain Disorder [115]. On the other hand, a few other databases focus on the disease/trait-related variants in human ncRNAs, ncRegion or their transcript factor binding sites (TFBSs), e.g. IncRNAsNP [74], SNPR2TFBS [116], miRdSNP [75], miRNAsNP [117] and LincSNP 2.0 [73]. LincSNP specifically integrates and annotates disease-associated SNPs in human IncRNAs and TFBSs [73]. Similarly, miRNAsNP [117] collects polymorphisms altering miRNA target sites, in order to identify miRNA-related SNPs in GWAS SNPs and eQTLs. The current miRNAsNP [76] has integrated multiple filters to prioritize functional SNPs and experimentally supported miRNA-mRNA, as well as provided expression level annotation and correlation of miRNAs and target genes in various tissues.

These above resources often have a limitation that there is no mechanism for rapid improvement of the content and annotation of genomic variants. To address this, Griffith et al. have recently developed the CIViC knowledgebase for biocurators to annotate the clinical interpretation of variants in cancer which involves in the susceptible, diagnostic, therapeutic and prognostic relevance of somatic and germline variants of all types [69]. CIViC currently provides 1678 interpretations of clinical relevance for 713 variants affecting 283 genes associated with 209 cancer subtypes and 291 drugs. The variants in CIViC are annotated by provenance of supporting evidence and allowed users to transparently generate current and accurate variant interpretations [69].
Altogether, these comprehensive resources of genomic variants with disease-related annotations are not only valuable for investigating the functions and mechanisms of coding genes and ncRNAs in human diseases, but also helpful for developing computational tools to functionally predict and interpret clinical significance of genomic variants in exome and genome sequencing data. According to the maturity and the annotation quality, HGMD, ClinVar, CIViC and COSMIC are highly recommended in this category.

Population genomic data

Population genomics examines genomic variations within and among various populations. NCBI’s dbSNP is the first published population genomic database [20], which deposits SNPs and other classes of minor genetic variation including indels, copy number variations (CNVs) and structure variations from multiple resources [77]. With the NGS technology being widely adopted, several international projects have been launched to construct and integrate large number of genomic databases associated with populational phenotypes and features. These projects include National Heart, Lung and Blood Institute Exome Sequencing Project (NHLSBI ESP), Exome Aggregation Consortium (ExAC), 1000 Genome and Kaviar (Table 2). NHLBI ESP [79] has offered an unprecedented depth to identify rare variants located in protein coding regions from about 6500 individuals who have been clinically diagnosed with heart, lung and blood disorders. Similarly, ExAC [118] has discovered rare variants from over 130 000 subjects whose exomes have been sequenced as part of various disease-specific and population genetic studies. Compared to NHLBI ESP and ExAC, the 1000 Genomes project provides a comprehensive resource for over 88 million human genomic variants in 2504 individuals from 26 populations [80–82]. 1000 Genomes also offers freely available RNA expression data from RNA sequencing and expression arrays, which can be explored to determine whether the genomic variants are associated with the changes of gene expression in RNA level [119]. Another consolidated database for allele frequencies is Kaviar [83] that contains genotype information of over 162 million variants from 35 projects, encompassing 13 200 genomes and 64 600 exomes. dbSNP is recommended for its quality annotation and maturity, Kaviar is recommended for its large scale of data in both genomes and exomes and 1000 Genomes is preferable for studying diseases associated with different populations.

Genetical organism models

Despite the recent success in identifying causative associations between genetic alterations and disorders, GPAs remain uncovered for many diseases. For example, almost half of the known genetic disorders recorded in the OMIM knowledgebase are still unclear for causative genes [120]. With the advanced technology of gene modifying and gene editing such as RNAi, Zinc-Finger Nuclease, TALENs and CRISPR/Cas system, a number of genetic modified organism models have been constructed to investigate genetic mechanisms in human diseases and to identify GPAs. The disease-associated information of genetically modified organism models is annotated and available from different databases, such as MGD [84], MouseNet [85], Mouse Tumor Biology (MTB) [86], RGD [87] and ZFIN [88, 121] (Table 2).

MGD is a highly integrated and curated database, housing comprehensive knowledge about mouse genes, genetic markers and genomic features as well as associations to various human diseases [84]. MGD also provides a portal of the Human-Mouse Disease Connection to facilitate the investigation of phenotypic similarity between mouse models and human patients. Similarly, RGD is a comprehensive data repository for laboratory rat, involving genomic and genetic variants as well as disease data [87]. The various disease portals at RGD are entry points of data and tools related to 12 classes of diseases, including cancer, diabetes, aging and cardiovascular disease. Compared to MGD, MTB is a database for mining data on tumor development and patterns of metastases [86]. It can facilitate the selection of strains in cancer research. In addition, Zebrafish (Danio rerio) is another useful model organism to investigate human disease, especially in developmental disorders. ZFIN is a central resource for zebrafish genomic, genetic, phenotypic and developmental data [88]. MGD, MTB, TGD and ZFIN house thousands of disease associations between the model species and human beings, involving cancer, mutation, congenic and transgenic constructions, etc. Other special organism model resources for rhesus monkey [122], dog [123], chicken [124], Drosophila [125] and Caenorhabditis elegans [126, 127] have also integrated confirmed association information between genetic makers and disorders. Thus, genetical organism models associated with diseases are useful resources for demonstrating and identifying the relationships between genetic alterations and phenotypes of human diseases.

Environmental exposures

Except for genetic factors, accumulative evidence has suggested that EFs have a great contribution to the development of many diseases, especially in complex disorders such as cancer and cardiovascular diseases [128–131]. Moreover, complex interaction between genetic factors and environmental exposures plays critical roles in developing the phenotypes of diseases. Several databases have been established to associate environmental factors with protein coding genes and phenotypes of diseases [44, 90, 132–134] (Table 2). For example, the CTD [89] is a comprehensive repository of interactions between chemicals and gene products, as well as their relationships to diseases. The latest CTD contains over 30.5 million toxicogenomic relationships for the interactions of chemical-gene, chemical-disease and gene-disease [89]. Different from CTD, the Exposome Explorer database focuses on annotating biomarkers of exposure to environmental risk factors and dietary [44].

Recently, like other genetic factors, it has been suggested that miRNAs, lncRNAs and other type of ncRNAs also have complex interactions with a wide spectrum of exposure factors such as drugs [135], stress [136], alcohol [137], cigarette [138], virus [139], radiation [140], air pollution [141] and diet [142] in the development of diseases. With the rapid growth of interaction data between ncRNAs, environmental exposures and development of diseases, a number of databases have been generated to describe their relationships, such as SM2miR [91], miREnvironment [92], DLREFD [93] and LncEnvironmentDB [43] (Table 2). SM2miR is the first established database to provide experimentally validated effects of small molecules on miRNA expression and hosts manually curated association data between miRNAs and small molecules across 17 species [91]. Compared to SM2miR, miREnvironment not only provides manually curated information on environmental exposures and miRNA expression, but also offers phenotypes associated with miRNAs and EFs [92]. Different from SM2miR and miREnvironment for miRNAs, DLREFD [93] and LncEnvironmentDB [43] focus on the lncRNAs that are exper-
mentally or computationally associated with environmental exposures and disease-related phenotypes.

These environment-related databases (Table 2) are valuable data resources for investigating the impacts of EFs on the development of human diseases at the molecular level as well as at the network level. Due to the large numbers of associations, CTD is highly recommended for coding genes associated with environmental and chemical exposures in this category.

Drugs and their targets

To facilitate successful medicine research with comprehensive information across drug discovery and development process, several public repositories have been established to dedications across phenotypes, drugs, chemicals and their targets (Table 2). Therapeutic Target Database (TTD) is the earliest repository [143] to provide information about drugs, targets and their associations with specific pathways. DrugBank [95] and DrugCentral [96] are the other two main databases, hosting comprehensive drug-target interactions and drug action information captured and integrated from online non-commercial resources, e.g. US Food and Drug Administration (FDA), European Medicines Agency and Japan Pharmaceutical and Medical Devices Agency, as well as curated data from published research articles and drug labels. DrugBank and DrugCentral have become the referential drug source for a number of well-known public databases such as PubChem [144], ChEMBL [94], PharmGKB [98], UniProt [145] and SuperTarget [146]. Moreover, TTD, DrugBank and DrugCentral link to targets and pathways to in silico drug discovery efforts. Other notable databases include PharmGKB [98] for impact of human genetic variations on drug responses, and the Drug-Gene Interaction Database (DGIdb) [99] for drug–gene interactions and gene druggability. Moreover, several databases have integrated drug-target information with special medical indications, such as cancer [100, 147, 148], side effects [149], pharmacophores [150] and special metabolic pathways [151]. The data resources of drugs with diseases enable the investigations of drug effects in specific genetic contexts and provide new insights in drug action at the molecular level. Due to the maturity and the data quality, ChEMBL and DrugBank are recommended for drug annotation in this category. On the other hand, PharmGKB is recommended for the interpretation of impact of human genetic variations on drug responses.

Software tools and web platforms

Software tools and web platforms are another type of computational resources, accelerating deeper understanding associations between multiple disease-related factors. Most of the available public software tools used to bridge the gaps between biology, medicine and clinic are driven by either genomic features and ontologies. These tools can be downloaded and used to analyze data in a standalone computer. To analyze online, several web platforms have been constructed to include interactive applications that comprehensively integrate a variety of disease-related data sources and software tools to prioritize disease-related associations spanning genotypes, phenotypes and treatments.

Genomic feature-driven tools

To facilitate clinical interpretation of genetic and genomic factors, many computational tools have been developed based on various features including evolutionary conservation, sequence homology and genomic and epigenetic annotations (Table 3). These computational tools have been widely used to annotate, predict and prioritize functional effects of varieties of genomic variants from high-throughput sequencing data, including KGGSeq [152, 153], ANNOVAR [12] and wANNOVAR [154] for functional annotation of genetic variants, VEST3 [155] and REVEL [156] for prioritization of rare missense variants, GWAVA [47] and Deepsea [14] for prioritization of noncoding variants, MutationTaster [157], VAAST [46], CADD [49], DANN [158], FATHMM-MKL [159] and Eigen [13] for prediction of the functional consequences of both coding and non-coding variants (Table 3). Some past research attempted to compare the usage and performance of these tools. It has been shown that Eigen has better discriminatory ability than CADD using disease-related variants and putatively benign variants in both noncoding and coding regions [13]. Moreover, M-CAP [160] and InterVar [161] were developed to eliminate the majority of variants of uncertain significance and facilitate interpretation of clinical significance of variants (Table 3). Furthermore, SIFT [45], LRT [162], PolyPhen2 [11], MutationAssessor [163], PROVEAN [164], FATHMM [165], MetaSVM [166] and IMHOTEP [167] have been developed to predict functional impacts of amino acid substitutions (Table 3). On predictions of polymorphisms and mutations with variants causing single amino acid substitutions, MutationTaster2 [168] had the highest accuracy compared to SIFT, PolyPhen-2 and PROVEAN. Different from all the above tools, ClinLabGeneticist [169] was established to manage clinical genetic variants from whole exome sequencing based on extensive variants annotation data (Table 3). ClinLabGeneticist contains information of data entry, distribution of work assignments and selection of variants for validation, report generation and communications between various personnel, and the entire workflow of ClinLabGeneticist has been integrated into a single data management platform.

Ontology-driven tools

The ontology databases in life science, such as Human Phenotype Ontology (HPO) [170–174], Mammalian Phenotype Ontology [175], Disease Ontology [176], Gene Ontology (GO) [177] and Experimental Factor Ontology (EFO) [178], provide standard terminologies and controlled vocabularies to describe and classify molecules, diseases, genotypic and phenotypic features, etc. The ontologies can be utilized to support computational tools that allow sophisticated search and analysis routines. For example, HPO offers standard terminologies for phenotypic features and diseases, to bridge the gap between genome biology and clinical medicine [179]. Several tools use phenotypic ontologies to enable deep interpretation for the analysis results of NGS data, including eXtasy [180], PhenIX [15], Exomiser [181], PhenGen [182], Phexpandor [48] and PhenogramViz [183] (Table 4). eXtasy, the earliest tool of them, ranks the damaging impacts of nonsynonymous single-nucleotide variants (nSNVs) by genomic data fusion. PhenIX evaluates and prioritizes impacts of SNVs, splice sites and short indels in the exome sequencing data of Mendelian diseases based on pathogenicity of variants and semantic similarity of HPO-based phenotypes [15]. Compared to PhenIX, PhenGen implements an exome-centric approach to rank the impacts of coding mutations, and a genome-wide approach to prioritize pathogenicity of non-coding variants (Table 4). Similar to PhenGen, the recently developed tool Exomiser [184] integrates a number of algorithms, including HiPHIVE [185], PHIVE [186], ExomeWalker [187] and OWLSim [188], to enable the clinical interpretation of variants in exome
Table 3. Genomic feature-driven tools for annotation and evaluation of clinical significance of variants

| Application                                      | Year of first deployment | Regular update          | Based on                                                                 |
|--------------------------------------------------|--------------------------|-------------------------|--------------------------------------------------------------------------|
| Functional annotation of genomic variants        | 2010: ANNOVAR [12]       | Yes, annually since 2015| Functional annotation of genetic variants from high-throughput sequencing data |
|                                                  |                          |                         |                                                                         |
|                                                  | 2012: wANNOVAR [154]    | Yes                     | Functional annotation of genetic variants from high-throughput sequencing data |
|                                                  | 2012: KGGSeq [152, 153] | Yes, bugs fixed monthly | Three different levels: genetic level, variant-gene level and knowledge level |
| Prediction of functional impact of amino acid substitutions | 2003: SIFT [45]          | Last update in Aug 2011 | Sequence homology based on PSI-BLAST                                      |
|                                                  | 2009: LRT [162]          | Last update in Nov 2009 | Sequence homology                                                         |
|                                                  | 2010: PolyPhen2 [11]     | Last update in 2016     | Eight sequence-based and three structure-based predictive features       |
|                                                  | 2011: MutationAssessor [163]| Last update in Dec 2015| Sequence homology of protein families and subfamilies between species      |
|                                                  | 2012: PROVEAN [164]      | Last update in Jan 2015 | Sequence homology                                                         |
|                                                  | 2013: FATHMM [165]       | Last update in May 2015 | Sequence homology                                                         |
|                                                  | 2015: MetaSVM [166]      | Last update in 2016     | 9 prediction scores and allele frequencies in 1000Genomes                |
|                                                  | 2017: IMHOTEP [167]      | Unknown                 | 9 popular predicted tools                                                 |
| Prioritization of rare missense variants         | 2013: VEST3 [155]        | Yes, quarterly          | 86 sequence features                                                     |
|                                                  | 2016: REVEL [156]        | Last update in 2016     | 13 popular predicted tools                                                |
|                                                  | 2016: M-CAP [160]        | Last update in 2016     | Pathogenicity likelihood scores and direct measures of evolutionary, conservation, the cross-species analog to frequency within the human population |
| Prioritization of noncoding variants             | 2014: GWAVA [47]         | Last update in 2014     | Various genomic and epigenomic annotations                               |
|                                                  | 2015: DeepSEA [14]       | Yes, annually           | Regulatory sequence code                                                 |
| Prediction of functional consequences for both coding and non-coding variants | 2010: MutationTaster [157] | Yes                     | Conservation, splice site, mRNA features, protein features and regulatory features |
|                                                  | 2011: VAAST [46]         | Last update in Sep 2016 | Variant frequency data with AAS effect information on a feature-by-feature basis |
|                                                  | 2014: CADD [49]          | Last update in Apr 2018 | 63 annotations including 949 sequence features                           |
|                                                  | 2015: DANN [158]         | Last update in 2015     | 63 annotations including 949 sequence features that is same to CADD       |
|                                                  | 2015: FATHMM-MKL [159]   | Last update in 2015     | 1281 sequence features                                                   |
|                                                  | 2016: Eigen [13]         | Last update in 2016     | Functional, evolutionary conservation and regulatory annotations          |
| Interpretation of clinical significance of variants | 2017: InterVar [161]     | Yes, last update in Jan. 2018 | The-2015-ACMG-AMP-Guidelines                                             |
|                                                  | 2015: ClinLabGeneticist [169]| Last update in 2014    | Extensive variant annotation data source and prioritization of variants   |

The tools are classified into different categories according to their uses.

and genome sequencing data. Instead of postulating a set of fixed associations between genes, diseases and phenotypes, Phevor dynamically integrates various knowledge of multiple biomedical ontologies into the variant-ranking process [48]. This enables Phevor to improve its accuracy not only of established gene-disease-phenotype associations but also of previously atypical and undescribed disease statements. PhenogramViz focuses on the interpretation of candidate CNVs and their pathogenicity prioritization from the data analyses of array comparative genome hybridization (aCGH) and NGS [183].

In the performance aspect of causal gene identification, previous researches indicate that Phen-Gen gains 13–58% improvement in sensitivity over eXtasy, Phevor, PHIVE and the earlier version of Exomiser [182]. Bone et al. [181] suggest that Exomiser is slightly favorable compared to Phen-Gen in the causal gene identification for autosomal dominant disorders and autosomal recessive disorders as well as the detection of novel variant-disease associations [181]. Moreover, Exomiser can analyse multiple samples or families per run for both Mendelian and multifactorial disorders, while Phen-Gen can only handle single sample or family per run for Mendelian disorders (Table 4).

eXtasy and Phen-Gen have both online and standalone versions of programs. The standalone eXtasy has many library dependencies of bioinformatics, statistics and machine learning algorithms (Table 4). Exomiser has the standalone version only, while PhenIX and Phevor have online versions instead. PhenogramViz can be downloaded, installed as an application in Cytoscape [189], and used through the Cytoscape interface. The standalone tools can be installed locally and run within hospital firewalls, thereby relieving the concerns of privacy and security for the information of patients. On the other hand, the online version tools are more acceptable and usable for many biologic researchers and clinicians, who lack bioinformatic and computing skills. In the timing aspect, the online eXtasy
Table 4. Comparison of phenotype-driven tools for interpretation of clinical significance of variants

| Year  | tool          | Availability          | Operation System | Requirements                                                                 | Algorithms implemented                   | Input data and parameter                                                                 | Application scopes                                      |
|-------|---------------|-----------------------|------------------|-----------------------------------------------------------------------------|------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------|
| 2013  | eXtasy [185]  | Online & Standalone   | Linux            | Ruby; Tabix; Bedtools; R Statistical Framework with randomForest; RobustRankAggreg libraries | Random Forests; Phenomizer               | VCF file; TSV for HPO term(s)                                                            | Mendelian and oligogenic disorders; nSNVs; Exome analysis; (Only 1 sample per run) |
| 2014  | Phen-Gen [187]| Online & Standalone   | Linux (Ubuntu, CentOS, & RHEL) |                                                            | Bayesian framework; Random walk–with-restart; Variant-predicted pathogenicity score; Phenomizer | VCF file; text file for HPO term(s); Pedigree(PED) file; Inheritance models; Type of prediction-genomic or coding; Discard de novo and Stringency | Mendelian and oligogenic disorders; nSNVs, splice-sites and short indels and non-coding variants; Genome and Exome analysis; (Only 1 family or 1 sample per run) |
| 2014  | PhenIX [15]   | Online                | -                |                                                            | Semantic similarity score; Variant-frequency score; Variant-predicted pathogenicity score | VCF file; HPO term(s); Inheritance modes; Frequency sources; Number of candidates to show | Rare disorders; SNVs, splice-sites and short indels; Exome analysis; (Only 1 sample per run) |
| 2014  | Phevor [54]   | Online                | -                |                                                            | Disease-gene association score; Variant-prioritization score | VAAST simple or Table for variants; Ontology Term(s); Ontologies to link to HPO | Rare disorders; SNVs; Exome analysis; (Only 1 sample per run) |
| 2016  | Exomiser [186]| Standalone            | Linux; Mac OS X; Windows | ~4GB RAM for an exome analysis and ~12GB RAM for a genome analysis; >3 GB free RAM (8 GB preferred); Java 8 or above | HPHIVE; PHIVE; PhenIX; Exome Walker; OWLSim; Logistic regression | YML file that include VCF file name; HPO term(s); PED file name; inheritance modes, Probands; Frequency sources; Pathogenicity scores and other alternative parameters | Mendelian, oligogenic and multigenic disorders; SNVs, splice-sites, short indels and non-coding variants; Genome and Exome analysis; (Multiple samples or families per run) |
| 2014  | Phenogram Viz [188]| Cytoscape app         | Windows          | Cytoscape Version 3.1.0. and above | Phenogram-score (PHS), NAG, OBE, OPA, HI score | Enter symptom(s) directly for symptoms or create file with HPO term(s); Lists of CNVs (include types, Chromosome, Start, End); Lists of genes | Mendelian disorders; CNVs; aCGH and exome analysis; (Only 1 sample per run) |

The availabilities, the requirements and the use of these tools are detailed in the table.

It takes about 15 min to analyze a whole exome data sample with ~82 000 variants, while the online PhenIX takes about 100 s to complete the same analysis, much faster than eXtasy. Exomiser consumes about 10~15 min to analyze an exome and genome sample or family, approximately 5~15 min faster than the online Pen-Gen (http://54.173.20.191). Moreover, Exomiser produces HTML, tab-delimited and VCF format files that can be incorporated into many bioinformatic workflows. Taken together, the standalone versions of Phen-Gen and Exomiser are recommended to skilled bioinformaticians for the interpretation of SNVs, splice-sites, short indels and non-coding variants from data of exomes and genomes. Exomiser is also suggested for the analysis of multiple samples or families. Phevor is recommended for the prioritization of variants pathogenicity related to previously atypical and undescribed disease statements, and PhenogramViz for the interpretation of CNVs pathogenicity.

Interactive platforms

To tackle the hurdles in utilizing disease-related data resources, several web platforms have implemented a number of analysis software tools to allow users to search, analyze and visualize the resources through web interface and APIs (Table 5). Most of these platforms, such as DisGeNET [190], Open Targets [16], Monarch Initiative [52] and MalaCards [51], target on human Mendelian and complex diseases, involving data of genotypes,
phenotypes, genetically organism models, drugs targets and chemical molecules.

The distinctions between different platforms are reflected in their different focuses and different applications. DisGeNET [190] is designed to collate GPAs and to offer tool applications for medical and biological research. It can be plugged into Cytoscape for visualisation and explore gene-disease associations in bipartite networks [17]. Open Targets and MalaCards have been considered as effective platforms for gene-disease associations in human; 14973 variant-phenotype associations in human; 19783 disease models.

The focus of software and database development is being shifted from the connection between genotypes and phenotypes to the identification of target-diseases related to approved drugs, clinical therapies as well as to evaluate prognosis. However, challenges remain in many aspects, such as building complex networks of associations, database design for bigger data, data analysis with more effective tools and platforms, data interpretation in consistent and standard manners, result representation with user friendly interfaces and so on.

Phenotype plays a central role in connection with other disease-related factors in the current network (Figure 2). The focus of software and database development is being shifted from the connection between genotypes and phenotypes to the association among multiple factors. As wider collaborations have been made to establish interoperable systems across international projects, much bigger data are being generated by many complete genomes of whole populations. Difficulties exist in connecting much more complex and multi-dimensional data.
Figure 2. Framework of a comprehensive web platform. A comprehensive web platform should integrate various disease-related information including genotypes, phenotypes, environmental factors, life styles and so on. The available information in the platform should be homogenously annotated by controlled vocabularies and community-driven ontologies, such as GenBank, dbSNP and miRBase for genotypes, HPO and DO for phenotypes, EFO and ChEBI for environmental factors and life styles, DrugBank and PubChem for drugs. Moreover, the platform should have solid scoring models to prioritize associations between different factors, such as genotype-phenotype associations (GPAs), environmental factor-phenotype associations (EFPAs), genotype-environmental factor-phenotype associations (GEFPAs), phenotype-treatment associations (PTAs), genotype-treatment associations (GTAs) and genotype-phenotype-treatment associations (GPTAs).

Moreover, additional data types including multi-omics results, extensive environmental contexts and life styles of patients are necessary to integrate and associated in the current network. Obviously, more effective algorithms and software tools are greatly needed to take more related factors, additional data types and bigger size of data into account.

Although the approaches of deep phenotyping are helpful for clinical diagnosis in Mendelian disorders and rare diseases, patients with similar features or at the same stage of illness often have various clinical outcomes in cancer and many complex diseases [2]. Existing spectrum of phenotype states is not optimally captured by current phenotypic ontology systems. Therefore, substantial efforts are required to better integrate the ontologies and enable the full interpretation of clinical outcomes of genetic mutations that may lead to the precision management of diseases.

Currently, there are abundant biomedical resources that cover disease information involving in genotypes, phenotypes, environmental exposures and their associations. However, most of the popular resources only represent a fraction of available information. Therefore, more comprehensive platforms are needed to integrate other ever-growing biomedical information, such as noncoding genetic factors, multi-omics and extensive environmental contexts and life styles (Figure 2). In addition, these platforms should integrate clinical, environmental contexts and life styles of patients to enable reliable and useful diagnoses and discoveries, and also make data fully accessible and easily interpreted through with highly graphical representation. Moreover, the available information in majority of databases is represented and annotated by heterogenous vocabularies (Supplementary S-Table 2). Thus, better platforms are needed to comprehensively integrate the available information with controlled vocabularies and community-driven ontologies and present analysis results in a consistent and standard manner (Figure 2). Recently, MNDR has been updated to offer confidence score of each ncRNA-disease association based on a simple classification of supporting evidences [62].

However, to better support translational research and precision medicine, there is a great need to develop solid scoring models or to refine current models based on experimental evidences to assist the prioritization of associations, such as GPAs, EF-phenotype associations, genotype-EF-phenotype associations, phenotype-treatment associations, genotype-treatment associations and genotype-phenotype-treatment associations (Figure 2).

In this review, we detail the human disease-related computational resources, including databases, software tools and online platforms. These resources are classified by disparate data types with focuses on association among genotypes, phenotype, EFs, organism models, drugs and chemical molecules. We also provide some of the resulting needs and requirements that should be regarded as imperative for the development of databases, tools and platforms (Figure 2).

From the view of precision medicine, better services of computation resources and more training on these services will accelerate better medical research and clinical diagnoses as well as treatments. Life scientists, bioinformaticians and clinicians are suggested to cooperate to develop more comprehensive databases, more accurate software tools and more practical platform systems to facilitate the goals of precision medicine, enabling reliable and useful diagnoses and discoveries.

Key Points

- The present study is a comprehensive review of available computational resources of human diseases, including databases, software tools and interactive platforms to assist in the appropriate selection and use of relevant resources.
- Bioinformaticians have developed more than 100 computational resources to integrate omics data and discover associations among genotypes, phenotypes,
environmental exposures, drugs and chemical molecules.

- According to scopes and data associations, the databases can be categorized into seven groups, including coding genes, noncoding RNAs, genomic variations, population genomic data, genetical organism models, environment exposures and treatments.
- Most of the available public software tools used to bridge the gaps between biology, medicine and clinic are driven by either genomic features or ontologies.

Supplementary data

Supplementary data are available online at https://academic.oup.com/bib.

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