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Understanding human diseases with high-throughput quantitative measurement and analysis of molecular signatures

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Microarray and deep sequencing technologies have provided unprecedented opportunities for mapping genome mutations, RNA transcripts, transcription factor binding, and histone modifications at high resolution at the genome-wide level. This has revolutionized the way in which transcriptomes, regulatory networks and epigenetic regulations have been studied and large amounts of heterogeneous data have been generated. Although efforts are being made to integrate these datasets unbiasedly and efficiently, how best to do this still remains a challenge. Here we review major impacts of high-throughput genome-wide data generation, their relevance to human diseases, and various bioinformatics approaches for data integration. Finally, we provide a case study on inflammatory diseases.

genomics, epigenomics, phenomics, integration, data analysis

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Twelve years ago, the unveiling of the first human reference genome sequence [1,2] inspired researchers to believe that genome-based discoveries would revolutionize the study and clinical treatment of human diseases. As genome sequences from different individuals became available, comparative genomics using computational approaches emerged as a powerful method for understanding gene functions at the genome-wide level. These approaches unveiled more variations between individuals than were initially expected [3]. Genomic variations (including single nucleotide polymorphism (SNPs) and insertions and deletions (indels)) responsible for some of hereditary diseases have been identified and applied to examine genomes of thousands of individuals for correlations between the presence of variants and traits of interests [4]. First microarrays were used, then exon sequencing, and now whole genome sequencing has become a popular tool [5,6]. Currently, many variations from numerous sites in the genome have been successfully connected with different human diseases including various types of cancers [6] using DNA sequencing technology which underwent a 14000-fold drop in cost between 1999 and 2009 [7], and computational imputation methods [8].

Though most studies have focused on the connection between genomic variations (both common and rare) and human diseases, mechanisms underlying many of the DNA variations have not been clearly addressed. Genome information alone is not sufficient to interpret complex diseases [9]. Evidence at epigenome, post-transcriptome, and even the human microbiome levels is beginning to shed new light on human disease-related studies beyond the genome level.

1 Epigenome and human diseases

Epigenetics is commonly defined as the study of heritable changes in gene activity and expression without changes in

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the genomic sequence. Epigenetic mechanisms, which mainly consist of states and changes in DNA methylation, histone modification, non-coding RNAs (ncRNAs), and higher-order chromatin structure, are believed to play important roles in regulating genome functions such as gene transcription and genomic DNA replication [10]. Emerging lines of evidence indicate that epigenetic modifications significantly contribute to normal cellular developmental processes and aberrant epigenetic controls are linked to many types of diseases [11]. For example, epigenetic mechanisms have a profound role in cancer development. On the one hand, numerous changes in DNA methylation and histone modification accompanied by genomic mutations in many loci of the epigenetic regulator genes have been found in multiple types of cancers, indicating that epigenetic alterations contribute to cancer development [12]. On the other hand, epigenetic mechanisms provide novel targets for therapeutic intervention, exemplified by the use of histone deacetylase inhibitors (HDACi) to treat several types of cancers such as T-cell lymphoma [13]. In addition to its role in cancers, epigenetic dysregulation can lead to many immune and neuron disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis, type 1 diabetes, Rett syndrome and Alzheimer's disease [14–18]. Although knowledge of epigenetic mechanisms in these diseases is growing fast, a more comprehensive understanding of epigenetic processes is still required for safe and efficient diagnosis and treatment of these diseases.

The first step to understand epigenetic mechanisms is to identify the epigenetic changes that contribute to cellular phenotypes in normal development and in diseases. Thanks to recent advances in next-generation sequencing (NGS) technologies, genome-wide maps of the epigenome can be generated at a much lower cost, thus providing landscapes of DNA methylation, histone modification and other chromatin features. In 2007, the first comprehensive epigenome map of human CD4 cells was drawn using a pioneering combination of chromatin immunoprecipitation followed by high throughput sequencing (ChIP-seq); this map includes 20 histone modifications as well as histone variant H2A.Z, RNA polymerase II, and insulator binding protein CTCF [19]. In 2008, the NIH Roadmap Epigenomics Mapping Consortium was launched with the aim of generating a public epigenomic data resource for biomedical research. In this project, multiple levels of epigenetic features in different cell types are to be mapped; for example, DNA methylation is assayed by bisulfite sequencing (BS-seq) which treats genomic DNA with sodium bisulfite before sequencing [20], histone modifications are mapped by ChIP-seq as mentioned above, and chromatin accessibility is evaluated by sequencing DNase I hypersensitive sites [21].

Although these novel genome-wide approaches can generate epigenome data sets at different levels, challenges are still to integrate them with the transcriptome (all RNA transcripts), to discover epigenomic signatures in a specific cell type or disease, and to identify important epigenetic regulators that contribute to normal and disease developmental processes. In addition, huge amounts of epigenome data are generated by high-throughput sequencing, which requires the development of novel computational tools to analyze it. For example, Yu et al. [22] have developed a Bayesian network model to infer combinational interactions of various histone modifications and their effect on transcriptional regulation. In addition, using comparative epigenomics from both DNA and histone modifications can further reveal regulatory features of the genome [23].

Epigenomes and combined integrative computational analyses have also revealed some of the crucial regulatory roles that epigenetic modifications play in many human disease-related processes such as aging [24–26] and T-cell maturation [27,28].

2 Transcriptome and human diseases

The transcriptome in a given organism/cell can be very different between individuals, tissues, cell-types, and developmental stages. The recent advent of high-resolution tiling arrays and next-generation deep sequencing technologies have changed the way in which transcriptomes are studied, and also made it possible to link transcriptome changes with human diseases at the single nucleotide resolution level. For example, whole transcriptome analyses have demonstrated consistent differences between the normal and autistic human brain, and provided further evidence of transcriptional and splicing dysregulation as underlying mechanisms of neuronal dysfunction in autism [29]. Another large-scale spatio-temporal transcriptome analysis of human brains provided a comprehensive data set of the human brain transcriptome as well as insights into the transcriptional foundations of human neurodevelopment and neurobiological diseases [30]. In addition, using a different enrichment method, Chen and colleagues uncovered a number of long noncoding RNAs (lncRNA) from introns [31]. Interestingly, further analyses showed that some of these lncRNA were capped with small nucleolar RNAs (snoRNAs) at both ends and were abundantly expressed from the imprinted region on chromosome 15 that has been implicated in human Prader-Willi syndrome [32]. Some preliminary evidence in both human and mouse has indicated the possible role of the microbiome in diabetes, obesity, and liver function, though in-depth clinical studies are still being carried out [33]. When "omic" datasets are combined, a much broader view of the mechanism underlying diseases is expected as a result [34]. Chen and colleagues showcased an integrative personal omics profile consisting of genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual over a 14-month period, which revealed extensive and dynamic changes across healthy and diseased conditions, and uncovered both DNA variation and an un-

expected post-transcriptional mechanism during healthy and diseased states [35].

3 Digital and quantitative phenome and human diseases

While novel sequencing technologies are rapidly expanding the borders of genomics, methodologies for collecting phenotype data are also facing major transitions. Large-scale high-throughput phenotyping is becoming increasingly important in the post-genomics era. A comprehensive set of phenotypic traits collected at cell, tissue, organ or organism level is defined as a phenome [36]. Thus, phenomics can be defined as the study of the phenome as well as how it is determined or affected by, aside from the environment, the other omics data including but not limited to the genome, transcriptome, and proteome.

A central interest of phenomic research is the study of morphology and appearance traits. The overall morphology and appearance of an organism results from coordinated biological actions at all levels. Phenotypes provide rich information for many research areas such as evolution, development and human disease studies. In large-scale genetic modification studies in model organisms, morphological changes are main pathological evidences of targeted mutations [37–39]. The soft tissue of the human face is a complex geometric surface composed of many important organs, including eyes, nose, ears, and mouth. Morphogenesis of the craniofacial structure is a sophisticated development process that involves, to name a few, neural tube closure, midline patterning, neural crest generation and migration, outgrowth, patterning, and differentiation of the facial primordia and the branchial arches [40]. All of these processes are under the elaborate control of many signaling pathways such as SHH, FGF and BMP pathways [41]. Given its essential biological functions and structural complexity, the human face can tell a great deal about an individual's health conditions, from genetic defects to common diseases, and from aging to mental health. Rare genetic disorders in many syndromes cause characteristic abnormal facial features; for example, Down syndrome [42], Rubinstein-Taybi syndrome [43], Sotos syndrome [44] and Noonan syndrome [45]. More generally, common genetic variants were found associated with higher risks of facial dysmorphisms such as cleft palate and cleft lip [46–49]. Interestingly, some cleft lip risk alleles were found associated with facial morphological deviations in parents of patients as well as in normal individuals [50], suggesting the potential use of face examination in disease risk evaluation. In fact, traditional Chinese medicine has long used face examination for general disease diagnosis. Apart from disease research, the human face has been intensively studied in a wide range of medical fields such as forensics [51], psychology [52,53] and aging [54, 55].

Novel technologies and algorithms are being developed to either capture comprehensive phenome data or to extract specific physiological information from the human face. Quick face recognition algorithms have for a long time been deployed mainly in security surveillance [56,57]. Recently, weak signals extracted from video data were used to measure cardiac pulse from human face [58]. The introduction of high resolution three-dimensional (3D) image acquiring technologies such as the 3dMDface® system (www.3dmd.com), enabled the collection of complete facial shape and texture data at the phenome level. Nonetheless, most current studies use only a small fraction of such data, usually a set of landmarks and/or their mutual distances and angles [59–61]. This has largely constrained the power of technologies to associate facial patterns with specific diseases, because the pathological phenotype is usually the sum of subtle curvature and pigmentation changes over the entire facial surface. Nonetheless, methods have been developed to register the 3D facial images by their dense surface meshes (3D dense surface registration, 3D-DSR), which allow the thousands of 3D pixel points for each of sample faces to be anatomically aligned across genders, age groups, ethnicities as well as disease/control groups [62–64]. Inferences and analyses can therefore be carried out on the face phenome data in a fully quantitative way that is analogous to how the genome data is used. Recently, Guo et al. [65] incorporated a novel algorithm of accurate 3D face landmarking into the registration method, which achieved complete automation of 3D-DSR at high throughput and robustness. 3D-DSR methods have been used to calculate average faces for different ethnicities, genders and various syndromes [66–68], and to fit trajectories of face growth over age [69]. More importantly, facial signatures of many genetic disorders were extracted using 3D-DSR, rendering unprecedented power and efficiency to automatic disease discrimination [70]. Similar methods have also been tested for complex diseases such as autisms and epilepsy [71,72]. Unfortunately, as most of these disease studies were carried out in European populations, results cannot be directly applied to other ethnic groups because of the obvious divergence of basal facial shapes and genomic backgrounds. Peng et al. first revealed that, in a Han Chinese population, a locus that was associated with non-syndromic cleft lip was also associated with common facial morphological variations in healthy individuals (unpublished data). In the long run, subtle characteristic features may be extracted not only to diagnose rare genetic disorders but also to manage general health conditions, such as common disorders like skin aging and stress. Given the non-invasive nature of face imaging technologies, advances in this field may strongly promote applications of personalized medicine.

4 Integrative analyses of heterogeneous high-throughput data

High-throughput data is increasing rapidly at the molecular level by microarrays and deep sequencing and at the phenotypic level by digitized and quantitative imaging. There is an urgent need to develop approaches that can efficiently integrate different data sets in an unbiased manner. Methods ranging from simple correlation based network analysis to more sophisticated Bayesian network analysis have all been elicited to address this need [73]. New algorithms have also been developed to specifically address the problem of integrating different layers of data. For example, flow optimization algorithms were used to identify main pathways from protein-protein interaction networks that link genetic screen hits to gene expression changes involved in neurodegeneration [74], microRNA (miRNA) expression changes and mRNA expression changes in response to extremely high altitudes [75], or Genome-Wide Association Study (GWAS) hits to differentially expressed genes between control and disease cohorts [76]. These innovative integration approaches for different types of data from different layers have the potential to identify global regulation patterns, and also to provide detailed biological insights regarding complex biological processes, such as the development of complex phenotypes and diseases (Figure 1).

5 A case study: application to immune diseases

As discussed above, unprecedented insights that have been revealed using sequencing technologies are almost countless. One of high impact areas for translational medicine is related to the study of autoimmune diseases, which affect populations in unexpected proportions (2.5 times more than cancer and slightly more than heart diseases; American Au

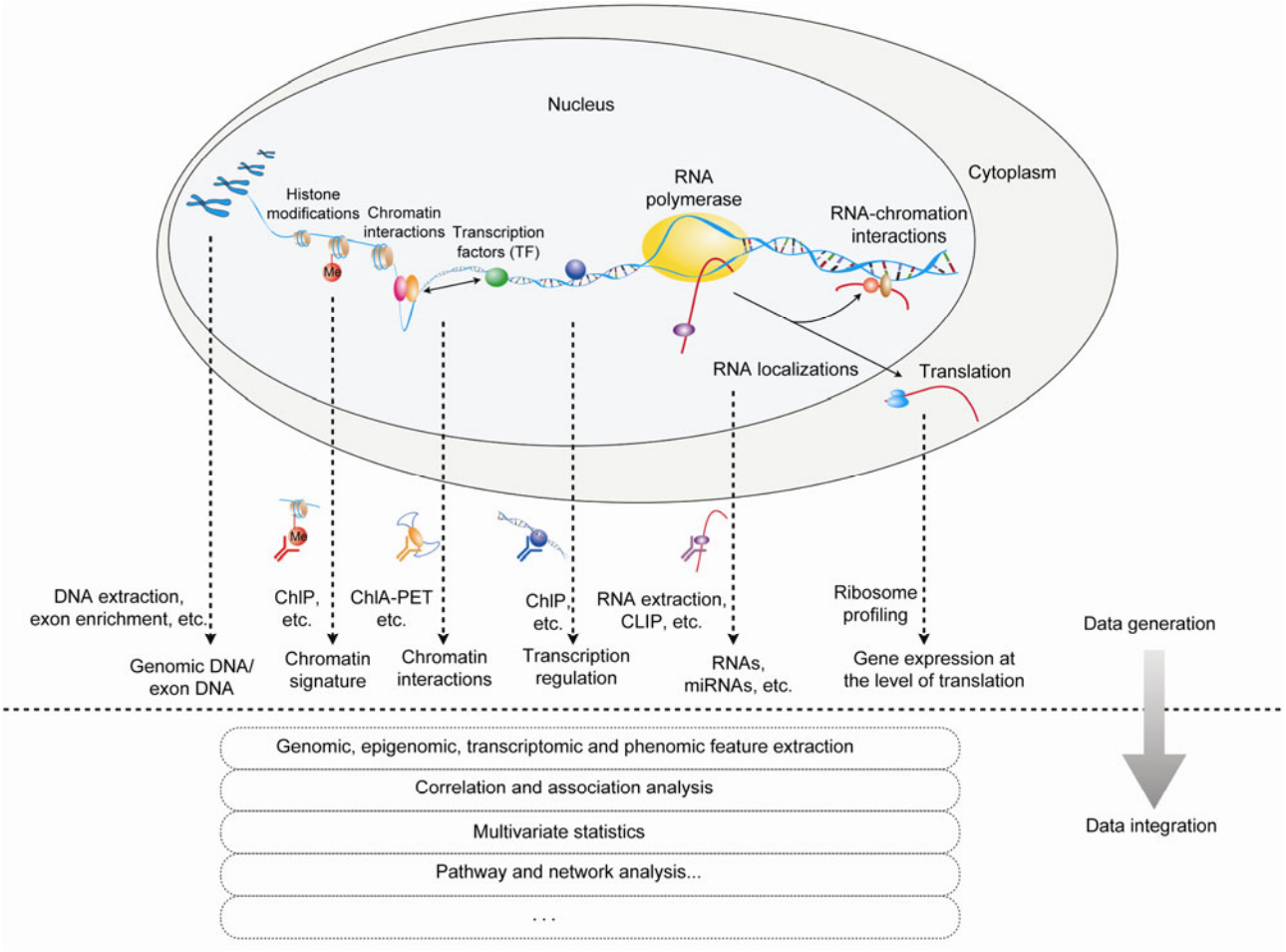

Figure 1 Strategy for data generation and integration of multi-layer high-throughput data sets. By generating and computationally integrating high-throughput data at various systems levels, a comprehensive atlas of detailed molecular signatures for complex human diseases can be depicted. The atlas can then be used to develop systematic explanations of clinical practices and diagnosis for complex diseases, thus laying foundations for the development of personalized medicine in the future. Relevant experimental methods for interrogating functional genomic elements and other biomolecules and the major downstream analysis approaches are listed (see text for details). ChIP, chromatin immuno-precipitation; ChIA-PET, chromatin interaction analysis with paired-end tag sequencing.

toimmune Related Diseases Association, Inc. (AARDA) statistics (http://www.aarda.org/autoimmune_statistics.php)). These maladies often affect patients during their productive age.

Rheumatoid arthritis (RA) is often used as a model disease for autoimmune diseases. RA is a disabling disease with a still unknown etiology that attacks the synovial tissue of the joints, leading to loss of function and mobility. It affects 1% of the population worldwide and about 4 million in China. RA is strongly prevalent in women (about 70% of sufferers are women) [77]. RA, in fact, responds to the definition of 'complex genetic disease'. A recent meta-analysis [78] conducted on Europeans has shown how complex the disease is by adding to the known susceptibility genes, 7 more, one of which is also shared by the Asian population [79]. These results have helped better characterize RA in the European and Asian population.

Challenges that lie ahead include the development of appropriate algorithms and statistics to handle all available omics data sets and integrate them into a systems perspective. Data integration will also help to clarify how existing therapies can be used in novel ways and dosages to counterbalance the side effects of conventional therapies.

Liu et al. have shown that to achieve this kind of integration, the translation of existing algorithms can be successful, for example, on metagenomic data [80], and that the integration of multi-omics data sets warrants a larger information base than the analysis of single layers. The use of multivariate statistics (such as factor analysis) to analyze jointly different types of omics data, for example mRNA and miRNA, was shown to successfully identify features that could not be found by the differential analysis of the mRNA and miRNA data sets separately [81,82].

Other approaches rely on the flexibility of network representations, which allows more information than a list of molecules can provide, to be embedded in the algorithms. Wu et al. [83] have recently constructed a comprehensive RA map of all available transcriptional and post transcriptional information from omic screens (at the time mostly microarrays for gene expression). The map was integrated with information from known pathways to achieve a well interconnected map which could assist topological analysis. Interestingly, using this approach we were able to suggest a convincing explanation of the systemic effect of R406 inhibitor in the treatment of RA and to recommend novel contraindications, in particular, for the translation of diabetes therapies to RA patients (Nardini et al., in preparation).

6 Conclusion

Different layers of omics data suggest that distinct molecular and regulatory signatures are involved in disease processes. By combining high-throughput sequencing methods with computational approaches, researchers can now develop comprehensive atlases of sequence-based mechanisms together with detailed molecular signatures for further understanding human diseases in a systematic way. In clinical terms, findings can be applied to personal diagnosis and then personalized medicine.

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