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MINI REVIEW

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Network medicine and type 2 diabetes mellitus: insights into disease mechanism and guide to precision medicine

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Abstract

Understanding the genomic basis of type 2 diabetes mellitus is a major challenge. Simple genome-wide association studies (GWAS) have identified ~250 loci that link to the phenotype; however, the great majority have tiny effect size of uncertain mechanistic significance. Polygenic risk score strategies do nothing more than integrate these statistical association into a single scalar parameter, again offering limited mechanistic insight. The new discipline of network medicine offers an approach by which to provide useful mechanistic information from GWAS and other omic data sets. To understand disease in the network context requires using a predefined comprehensive network—in our case the protein–protein interaction network, or interactome—as a template upon which to map loci from GWAS or other data sources. These loci have been shown to cluster in a subnetwork in the interactome (as is the case for most diseases), exploration of which identifies novel pathways that regulate disease pathogenesis and uncovers novel targets for therapeutic intervention. Such an approach is essential for utilizing the growing pool of omic data in a mechanistically rational way as we move increasingly towards precision medicine for this highly prevalent disorder.

Keywords Systems biology · Network medicine · Complex systems · Genomics · Interactome · Metabolism

Diabetes mellitus is a highly heterogeneous group of metabolic disease phenotypes that contribute enormously to global health burden. Recent estimates indicate that in 2017, there were 450 million adults with diabetes worldwide, an estimate that is expected to increase to nearly 700 million by 2045 [1]. Both genetic and environmental factors conspire to promote the development of diabetes, and the contribution of these two sets of determinants varies greatly by diabetic pathophenotype. Ranging from the relatively rare monogenic forms, including maturity onset diabetes of the young and neonatal diabetes (~3.6%), to the much more prevalent polygenic forms of type 1 and type 2 diabetes, the diverse genomic etiologies make the hope for a truly precision-based approach to the treatment of the disease(s) [2] quite challenging. The rather straightforward, convergent biochemical phenotype of hyperglycemia or glucose intolerance reflects an overarching consequence of multiple causative (interacting) molecular pathways. No longer can we consider the comparatively simple view that type 1 diabetes results exclusively from immune-mediated destruction of pancreatic beta-cells, and type 2 diabetes from insulin resistance and beta-cell failure; rather, within each broad class there are multiple endophenotypes, each with unique time trajectories and each with differing implications for prevention and therapy.

Further complicating the problem of understanding the genomic basis for these disorders is the diversity of clinical pathophenotypes to which the genotypes need be matched, including gestational, mitochondrial, and syndromic forms [3]. Each of these pathophenotypes is further subdivided based on the relative prevalence of the panoply of clinical and biochemical features that define the most inclusive of them. As one example, consider diabetes associated with lipodystrophy and its range of characteristics: insulin resistance, loss of adipose tissue, hypertriglyceridemia, and muscular mass. This level of complexity of genotype and phenotype, and their environmental influences (epigenetic and clinical consequences of dietary or infective agent exposures) render the possibility of true precision medicine approaches to diabetes a major challenge.

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Having outlined briefly the scope of the problem of a precision medicine approach to diabetes in general, let me now turn specifically to type 2 diabetes to explore the problem in greater detail. Over the past decade, the strategy for understanding the genetic basis of type 2 diabetes has focused largely on genome-wide association studies. The result of these efforts has been to accumulate as many as ~250 loci of genome-wide significance, some of which have given (modest) insight into potential causative mechanisms for the development of the disease(s) [4]. In addition, the identification of these loci has led to a growing integrative multiomic enterprise that includes functional studies that have explored key mechanistic pathways relevant to the phenotype, such as beta-cell failure, insulin resistance, appetite regulation, and obesity and adipocyte storage.

Notwithstanding this extraordinarily expansive collection of rich data sets from a wide range of populations predisposed to type 2 diabetes and the mechanistic information they have revealed, these insights have been of rather limited use in prediction or pre-emptive precision therapeutics [5]. In part, this shortcoming is a consequence of: (1) the small effect sizes for the great majority of loci and the lack of clear mechanistic implications; (2) sample size limitations (even with these very large population data sets) for exploring in a statistically rigorous way epistatic interactions, and their potential contribution to disease pathogenesis; and (3) the fact that the mechanisms that have been identified rely on prior knowledge of pathways (Kyoto Encyclopedia of Genes and Genomes, and Gene Ontology databases), yielding affirmation of what is known with modest modification, among others. These serious limitations in defining truly novel mechanisms of disease pathogenesis and in refining subtypes of disease have been met by the genomics community with suggestions for more of the same: larger-scale sequencing and massive scale biobanks [5], neither of which can possibly provide the necessary sample sizes to explore gene-gene interactions in a meaningful way given the heterogeneity of the pathogenotypes.

Genome-wide polygenic risk scores have recently been touted as an alternate strategy for identifying individuals at significant risk [6]. In this approach, a cumulative score is created from the linear weighted associations of multiple loci with a particular trait. Used in plant and animal breeding for some time [7], its true utility in human disease (where inbreeding is limited and the population genomes highly heterogeneous) has been of uncertain value, including in type 2 diabetes [8]. Warren, in a recent editorial [9], explored the limitations of this approach, which include the lack of true effect of the great majority of associated loci in view of their very modest effect sizes. Designing a score that provides a single parameter may be helpful from a simple analytical or epidemiological perspective, but, once again, gives no or marginal insight into disease determinants.

The major limitations of genetic association studies are that they are limited by the inclusiveness of the typical disease phenotype ('type 2 diabetes'), and they fail to account mechanistically meaningfully for interactions among multiple loci that contribute to the phenotype. These complex traits are governed by an equally complex set of (variant) gene product interactions that must be explored to appreciate the distinctions among disease pathophenotypes. Our group's efforts in applying molecular interaction networks and network medicine analytical approaches to complex pathophenotype have been used successfully to gain insights into disease causation and potential therapeutic interventions. We have focused on the comprehensive physical interactome of all ascertainable protein-protein interactions as a template through which potential disease-causing genes (proteins) can be identified and functionally studied. When we mapped the known disease-associated gene products for 299 diseases to this unbiased interactome, we were able to demonstrate that the great majority of these disease gene product collections cluster in unique and discrete modules or subnetworks within the interactome [10]. These disease modules can be explored with respect to their relationship (module overlap) to other diseases, and pathways that govern phenotype. Because the comprehensive interactome provides the 'missing links' that associate known disease-associated gene products, study of the disease module provides insights into pathways and mechanisms that would otherwise not be ascertainable.

We applied these principles to type 2 diabetes in earlier work [10]. At the time of the analysis, there were ~200 genetic loci linked to the pathophenotype, with the great majority (>90%) of these loci having very small effect sizes. We mapped these loci to the type 2 diabetes disease module *ad seriatim* as a function of decreasing effect size and followed the z-score for clustering. We observed abrupt increases in *z*-score after the addition of 3 discrete proteins previously unappreciated as important determinants of the disease (growth factor receptor-bound protein 14, GRB14; calmodulin 2, CALM2; and protein kinase C-alpha, PRKCA), illustrating that these proteins serve as physical and (presumably) functional hubs through direct physical interaction with several other gene products and, as a result, pathways within which each operates [10].

In addition to these benefits of network analyses of molecular interactions, one can apply network principles to address precision medicine diagnostics and therapeutics. Specifically, one can map gene/protein variants and differentially expressed proteins to the disease module of interest for an individual, and, thereby, create an individual

'reticulotype' (after the Latin for network) [11]. This reticulotyped module—which links the individual's genotype to (patho)phenotype—can then be studied to determine the functional consequences of each variant and their interactions, and optimal drug targets or rational combinations of targets [12] that can be used to restore the normal phenotype. Equally important, one can use network medicine approaches for the identification and mechanistically rational repurposing of approved drugs whose (known) targets (for other diseases) are closely linked to pathways within the disease module of interest [13].

Returning to the importance of phenotyping, it is critical to emphasize that the success of any of these genomic network strategies hinges on the precision of distinguishing among even subtly different pathophenotypes. Biochemical endophenotypes abound in diabetes, which, as continuous variables, can be helpful in establishing predictive algorithms for relevant outcomes [14]. In addition, a variety of machine learning [15] and big data [16] strategies have begun to be employed with varying success for predicting disease expression and pathophenotype features. Achieving the best outcome for preventing the development of diabetes in susceptible patients and in effectively treating those with the disease(s) world-wide [17] will require continued improvement in these network medicine strategies for defining precision medicine approaches to determining molecular mechanism, molecular biomarkers, disease targets, and disease phenotypes [18].

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Compliance with ethical standards

Conflict of interest The author is a scientific cofounder of Scipher Medicine, Inc., which uses molecular network approaches for precision diagnostics and therapeutics.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

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