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Advances in Diabetes

Novel Insights

GR Sridhar

Foreword
PV Rao

2nd Edition

JAYPEE

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CHAPTER 4

Genomics and Diabetes: 20 Years after the Human Genome Project

Ganesh Chauhan, Dwaipayan Bharadwaj

ABSTRACT

One of the greatest achievements in medicine has been unraveling the blueprint of life that is the sequence of the human genome. This has opened doors to multiple research fronts, technologies, and far deeper insight into diseases unparalleled by any other effort by mankind. Here, we visit the advancements in our understanding of the pathophysiology of diabetes that has been possible because of understanding the genetic basis of the disease. We take you through the exciting journey of the first gene discovered for diabetes in 2005 through candidate gene-based studies to hundreds of loci identified using genome-wide association studies and whole-genome sequencing approaches. We visit the international efforts modeled on the basis of the Human Genome Project such as the HapMap and 1,000 Genomes projects and how these have made a difference to the advancement in the field of diabetes genetics. Here, we also highlight the efforts that have gone from simple gene discovery to the functional disease model for diabetes, the population risk based on genetic discoveries, and stepping into the era of precision medicine. A big realization in recent times has been to increase the diversity of the ethnic groups being studied in order to take these advancements to the entire human population. Once genetic discoveries begin to saturate, as we are only able to discover new loci with small effect sizes, the focus has now to change on harvesting the benefits of these discoveries for translational research and simultaneously keep on discovering new genes. We have taken a giant leap into the genetic discoveries for diabetes in the last two decades since the unraveling of the first draft of the human genome and we now need to capitalize on these findings if we have to achieve the goal for precision medicine and find a suitable cure or preventive measures for diabetes.

Keywords: *Human genome project, Genome-wide association studies (GWAS), Whole-genome sequencing, Next generation sequencing (NGS), Precision medicine.*

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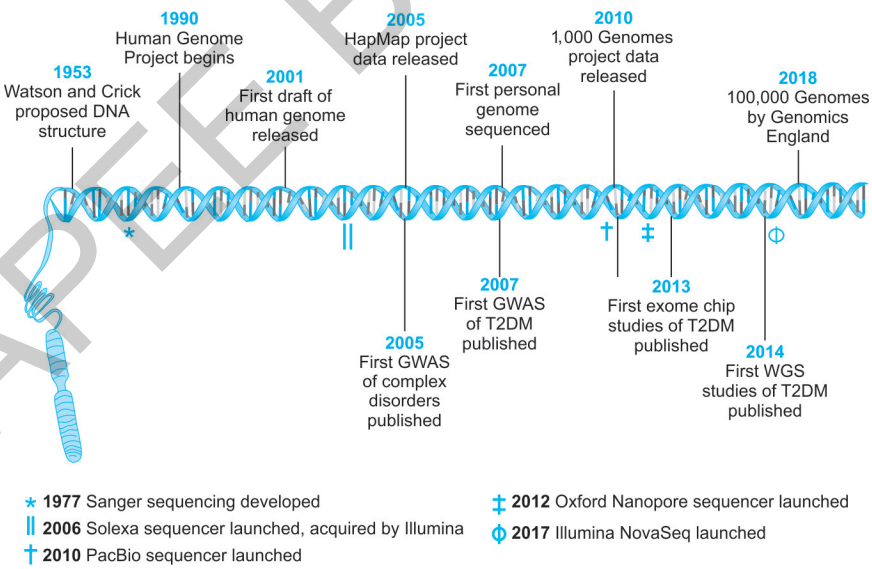
INTRODUCTION

"Nature" (genes) and "nurture" (environment) together interact to bring about a phenotype. Once deoxyribonucleic acid (DNA) had been identified as the genetic material and the structure was proposed, the interest in the sequence of nucleotide bases that make a gene and code for proteins became an important goal for medicine to tease out the components of "nature" that affected diseases. This led to one of the most ambitious international projects, the "Human Genome Project", that took close to a decade and huge economic and manpower resources across the world to get the first draft of the 3.2 billion base pairs that make us who are as a species (**Fig. 1**).[1,2] Like many other diseases, the field of diabetes has also been reaping the benefits of this huge effort that stands out as one of the brilliant examples of global scientific collaboration. Within 5 years of the release of the human genome sequence, we had our first few genes for diabetes. Once we had access to the human genome, our next challenge was to identify the genetic variations that make each one of us different in physical appearance and physiological response and might predispose us to diseases. On the same lines of the Human Genome Project, another international effort, the "HapMap project", was initiated to identify the haplotype structure of the human genome based on the genetic variations across multiple major ethnic groups of the world.[3] This led to the creation



(DNA: deoxyribonucleic acid; GWAS: genome-wide association studies; T2DM: type 2 diabetes mellitus; WGS: whole-genome sequencing)

FIG. 1: Milestones in the era of genomics and diabetes genomics.

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of technological platforms where we could interrogate thousands of genetic variations covering the entire genome in one go and this approach today known as genome-wide association study (GWAS) is still the main drivers of gene discovery for complex disorders like diabetes. About 5 years down the lane, further refinement to the HapMap project (genotyping approach) led to the "1,000 Genomes project" (sequencing approach) that led to better coverage and interrogation of genetic variants with lesser frequencies and also included structural variants.[4] More importantly, the 1,000 Genomes project led to the development of tools and techniques that made it possible to sequence large number of genomes. Today with the substantial drop in sequencing cost, the world has seen announcement of national projects where 100,000 to 1 million people are being sequenced (https://www.genengnews.com/insights/the-100000-genomes-club/) and completion of sequencing of 100,000 people by the Genomics England has already been announced in 2018 (https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/).

From getting the first draft of the human genome that took 10 years and millions of dollars and international effort to sequencing the human genome in a couple of days by spending <$1,000, we have come a long way in fulfilling the aspirations of the Human Genome Project. The field of diabetes has been one of the direct beneficiaries of these efforts leading to discovery of hundreds of loci for diabetes and its related conditions bringing us closer to the dream of precision medicine. In this review, we will focus on the genes discovered in this span of 20 years since the release of the first draft of the human genome but more importantly, we will also discuss the other outcomes of these gene discoveries and the use of this to further increase our knowledge of the mechanisms leading to the disease and possible treatment options.

CANDIDATE GENES AND LINKAGE STUDIES

Linkage analysis was one of the primary drivers for gene identification. In the initial phases, it had aided in discovery of many monogenic disease-associated genes. The same tool was also applied to complex disorders that yielded multiple candidate genes under the linkage peak with limited success. Follow-up studies of these candidate genes led to the identification of three genes: (1) *KCNJ11*; (2) *PPARG*; and (3) *TCF7L2*.[5-7] Importantly, these three genes have been replicated since then in most of the genetic studies that followed their discovery including GWAS. These loci had high effect sizes and were strong candidates that were involved in monogenic forms of diabetes (*PPARG*) or were targets of drugs (*KCNJ11*) being used to treat diabetes. Although the exception was *TCF7L2* where it opened the doors for the involvement of Wnt signaling pathway that was never a strong candidate prior to the discovery of this gene for type 2 diabetes mellitus (T2DM). *PPARG* and *TCF7L2* have been implicated in many other metabolic conditions with

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TCF7L2 often being the lead signal in many diabetes studies conducted across populations.

GENOME-WIDE ASSOCIATION STUDIES ERA

Genome-wide association studies have been the main pivots for gene discovery in complex disorders till date including for diabetes. Finer understanding of the haplotype structure and tagging single nucleotide polymorphisms (SNPs) led to the advent of genome-wide chips where common genetic polymorphisms tagging multiple common variations across the genome were genotyped in one attempt in one individual. The genome-wide approach without bias to focus on a favorite candidate gene or pathway is what popularized this method and earned it the name of an "agnostic approach" or a "hypothesis-free approach". An important outcome of having genome-wide data was the ability to do better quality checks including correction for population stratification that are notorious in giving false positives in association studies. However, we must still keep in mind that the GWAS approach is not an absolute hypothesis-free approach as it was based on the "common disease-common variation" model and in the initial phase the list of genetic variations were biased toward the population groups in the HapMap project and many ethnic groups have only a minor representation including South Asians.

The first GWAS study that identified genes for age-related macular degeneration was published in 2005. About 2 years later, a series of studies on complex metabolic disorders were published including the three studies on T2DM. These studies in total identified close to 10 loci and that was a remarkable achievements considering the fact that prior to this only three genes for T2DM had been identified. However, little did we realize that these would open the flood gates for identifying genetic loci and probably in those times we had never dreamt that there would be hundreds of loci with small effect sizes.

Prior to the GWAS era, genetic studies were notorious for nonreplication of findings in independent studies that were often due to the limited knowledge of disease biology, bias in studying of favorite genes by different groups, smaller sample sizes, and most likely lack of correction for population stratification in the absence of genome-wide data. Another important aspect that led to nonreproducibility of results was the choice of *p*-values of nominal significance ($p < 0.05$ or similar range) for declaring association. The GWAS era changed all of this as it was invariably associated with large sample sizes in order to find anything significant at the genome-wide threshold *p*-value $<5 \times 10^{-8}$. Such a stringent *p*-value is necessary in GWAS to account for correction for multiple testing of approximately 1 million haplotype blocks. The use of standard quality check across studies using genome-wide data was a game changer for GWAS as till date most of the loci identified have been replicated in the next study with a larger sample size.

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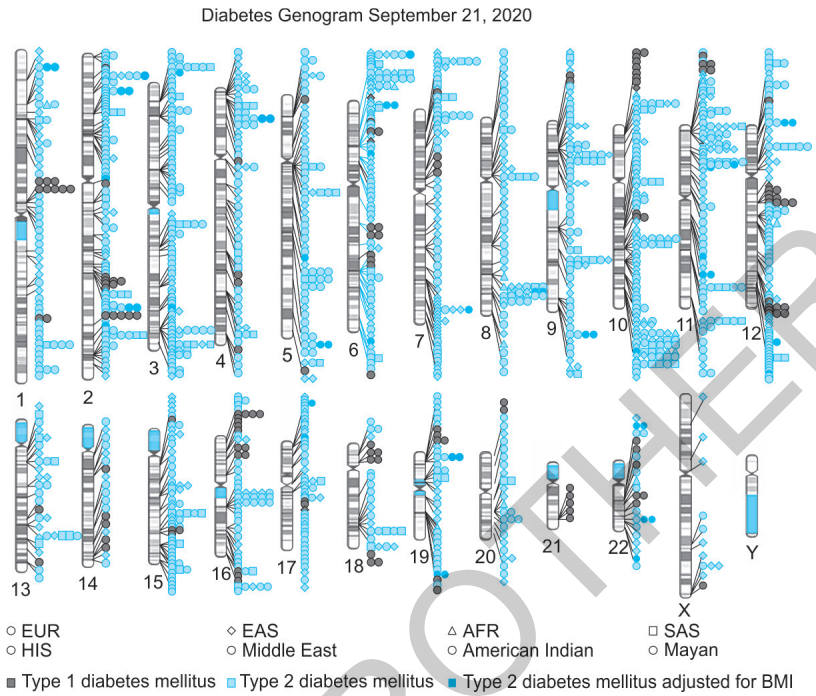

(BMI: body mass index; GWAS: genome-wide association studies)

FIG. 2: Genes identified for diabetes using genome-wide approaches. This figure was generated using the "phenograms" application from Ritchie laboratory (http://visualization.ritchielab.org/home/index). All genetic variations shown to be associated with type 2 diabetes mellitus and type 1 diabetes mellitus were downloaded from the GWAS catalogue (https://www.ebi.ac.uk/gwas/) as on 21st September, 2020. The variations are plotted to show the location of these variations across the autosomes and sex chromosomes. The signals originating from different ethnicities are coded using different shapes and the color denotes the phenotype of interest.

Importantly, all the loci identified by GWAS were replicated in many studies of diverse ancestry.[8-12] This was what built trust in association studies in the post-GWAS era and led to the opening of floodgates for larger GWAS studies including those in non-Europeans. Due to drop in cost in GWAS genotyping chips that can be close to US$ 30, many cohort-based studies have employed genome-wide genotyping on their samples as it is in the similar range to having a detailed blood biochemistry of the samples.

Presently, >400 loci have been identified and majority have very small effect sizes (**Fig. 2**). These loci in-total explain about 20% of the genetic variation for diabetes that is close to half of the genetic variation that has been predicted to be explained by genetic variation on the GWAS chip. This is quite a remarkable achievement considering the fact that many complex disorders are still in the range <5% of the genetic variations explained.

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GENOME-WIDE ASSOCIATION STUDIES OF DIABETES IN NON-EUROPEANS

The success of the first series of GWAS for diabetes in the European population encouraged GWAS studies in non-Europeans. The first major non-European study was on Japanese population that led to the identification of *KCNQ1*.[13,14] The discovery of *KCNQ1* was a good example to suggest that difference in allele frequency and linkage disequilibrium pattern between ethnicities would lead to identification of new genes, if we studied multiple ethnicities. Prior to the Japanese study, even larger studies in Europeans could not identify *KCNQ1* due to low allele frequency in their study population.

The other intuitive reason for identifying these novel variants in different populations could also be due to gene-environment interactions like the effect of such variants in carbohydrate metabolism or central obesity that could have a higher impact on Asians rather than Europeans. South Asia including India where there is a high prevalence of diabetes and an earlier year of onset apart from having a higher prevalence of vascular risk factors like central obesity had not been studied for genetics of diabetes. The first GWAS for diabetes from India was published in 2012 that identified a novel locus on 2q21 for T2DM in addition to replicating many loci identified in European.[15] Interestingly, these GWAS findings have now also been validated by functional studies.[16] Similarly, there have been multiple studies on other ethnicities of the world (**Fig. 2**) including the one in the most ancestral populations like the Africans.[17,18] The importance of studying such ancestral populations has been of interest as the size of the linkage disequilibrium block is small in such populations and chances of locating the causal variant are higher on a smaller block.

Another important aspect of studying the same disease in different ethnicities is to use this approach for fine mapping. The linkage disequilibrium block will have varying sizes in different ethnicities, but the causal variant remains the same. By filtering out variants that do not support association in multiple ethnicities, we can reduce the set of variations to a much smaller number that will include the causal variant. This strategy has been effectively used to fine map loci for diabetes.[19] Despite these efforts, the contribution of non-European population to disease genetics has been very low.[20] Taking an example of South Asia that accounts for approximately one-fourth of the human populations but the contribution of samples from South Asia for disease identification is only approximately 2%.[20] Similarly, despite realization of the importance of ancestral population in disease genomics, the contribution of African population is again on the same scale as that of South Asians. This has led to increased inclusion of non-Europeans in large national efforts like the National Heart, Lung, and Blood Institute (NHLBI) Trans-Omics for Precision Medicine (TOPMed) program of the United States, where the proportion of non-Europeans subjects is close to 60%

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(https://www.nhlbiwgs.org/). The recent use of just the sequencing data from 100,000 participants of this program (https://bravo.sph.umich.edu/freeze8/hg38/) for genotype imputation has given a major boost not only to the number of genetic variations in terms of imputation but a huge jump in the confidence of the imputed variants (https://imputation.biodatacatalyst.nhlbi.nih.gov/#!). This was applicable to all ethnic groups including Europeans.

EXOME AND WHOLE-GENOME SEQUENCING STUDIES

Technological advancements and drop in cost for sequencing led to upliftment of association studies from GWAS to whole exome and genome sequencing. The first large scale whole-genome study did not have much success in identifying new genetic variations as most of the identified loci clustered around known loci.[21] The idea of reaping a large number of rare variants with big effect sizes was also not met. However, this was mainly because of the smaller sample sizes to begin with and not realizing that rare variants would mostly have modest effect sizes. Studies with larger sample sizes are in the pipeline and will definitely lead to novel findings. The largest exome sequencing project for diabetes was successful in identifying new loci including rare variants.[22] This included 12 gene sets that were drug targets of diabetes and candidate genes based on knockout mice studies. The sample sizes for exome and whole-genome sequencing studies for diabetes are yet to catch up with those for GWAS studies but they have clearly implicated new insights both in terms of allelic architecture and actionable genes.

ALLELIC MODEL OF DIABETES

Multiple hypotheses regarding the spectrum of allele frequency of genetic variants implicated in diabetes have been proposed. The most popular hypothesis at the beginning years of diabetes genetics was the "common disease-common variation" hypothesis. This was mainly popular as in the beginning it was believed that rare variants had very high effect size and were more involved in monogenic conditions rather than complex disorders. The natural selection process often excluded these variations due to their high penetrance and they did not find their way into common disorders that affect a large number of people. For the first time, "the mosaic model" was proposed that modified this hypothesis to state that in addition to common variations, rare variations also had a role in complex disorders and till date this is the most accepted model and has been proven by studies on exome chip, exome sequencing, and whole-genome sequencing studies.[23] Interestingly, this hypothesis was proposed even before findings from GWAS studies were known.

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Though exome chip, exome sequencing, and whole-genome sequencing-based studies have identified genetic variants in diabetes, the hope for identifying a large number of rare variants with large effect sizes was not met. However, these results have to be interpreted keeping in mind that rare variants may not have large effect sizes as anticipated previously and statistical methods like burden test often used for testing association of rare variants by combining them in groups have limitations. Thus, larger studies and newer statistical approaches are required to better resolve this problem. Thus, the "mosaic model" still prevails albeit with fewer rare variants without large effects and a long chain of common variants with very small effects.

FUNCTIONAL STUDIES OF GENES IDENTIFIED THROUGH GENOME-WIDE ASSOCIATION STUDIES

At the end of the day, GWAS and sequencing approaches only tell us if a genomic region is associated with diabetes or not, they are not designed to infer causality. The outcome of these methods is a region of interest, which often has a large number of genetic variations and we are not sure that one of them is the causal variation. Interestingly, we are also not aware of the functional element this casual variation might affect, i.e., that protein coding gene or regulatory element. Thus, these genetic methods of statistical associations at best give us a "lamp post" to hover around and many times these may be located in "no man's land", i.e., intergenic regions. One of the biggest criticisms of association studies has, thus, been inability to pinpoint causal genes and due to the low effect sizes of the identified variants, straightforward functional studies like those for Mendelian disorders have not been possible.

Again international efforts such as the Encyclopedia of DNA Elements (ENCODE) project[24] and the Genotype-Tissue Expression (GTEx)[25] project have come to the rescue of association studies by giving some guidance by indicating the regulatory nature of the variations present under the "lamp post" and suggesting the genes whose expression might get affected due to the genetic variations under consideration.

Despite the difficulties associated with designing functional studies for signals indicated by association studies, there are multiple success stories. The 2q21 locus that was identified to be associated with diabetes in a study from North India has been successfully resolved to indicate the mechanisms of the causal gene *TMEM163* in pathophysiology of diabetes. Fine mapping of this locus indicated a nonsynonymous variation in *TMEM163* that increased glycemic index. Knocking down of this *TMEM163* in MIN6 cell lines increased the concentration of zinc in the intracellular space and amount of insulin. This silencing of *TMEM163* led to increased glucose uptake by the cells. This is an excellent example from locus identification to fine mapping to understanding mechanisms through which the gene causes the disease.

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SLC30A8 is another solute carrier that codes for the islet zinc transporter 8 (ZnT8) and was identified in the first series of GWAS studies to harbor common variants associated with diabetes.[26-28] Studies on diabetes patients and their relatives in Finnish populations followed by functional studies on human-induced pluripotent stem cell (iPSC)-derived β-like cells have suggested rare loss-of-function allele p.Arg138* that results in reduced *SLC30A8* expression.[29] Further, fine mapping of this gene has led to identification of at least 12 protein truncating variants that collectively reduced the risk of diabetes. Studies in animal models have also proved that common variants in this protein destabilize the zinc transport function. Thus, genetic studies in this gene have now suggested that ZnT8 inhibition as a new strategy for diabetes prevention.[29,30]

GENETICS OF DIABETES INFORMING MECHANISMS AND TREATMENT OPTION FOR OTHER DISEASES

Diabetes may be classified as a metabolic disorder, but it has far-reaching consequences on the health of an aging individual. Effects of diabetes on other conditions such as retinopathy, neuropathy, nephropathy, obesity, and cardiac condition are well-known complications that affect the micro- and macrovasculature. There have also been numerous clinical and epidemiological reports that suggest causal relationship between diabetes and mental health like association with psychiatric disease like schizophrenia[31] and neurological diseases like Alzheimer's disease.[31-33] Due to development of new statistical approaches that can interrogate genetic correlation based on summary statistics and many consortia making these statistics freely available, it is now possible to correlate a large number of diseases for genetic basis.[34,35] The linkage disequilibrium score regression (LDSC) tool employed on LD Hub (http://ldsc.broadinstitute.org/) can rapidly do such analysis on hundreds of phenotypes. Such genetic correlation analyses have suggested genetic correlation of diabetes with many of the diseases and especially related risk factors such as intracranial volume, educational attainment, etc. (**Fig. 3**). This knowledge corroborates previous epidemiological and clinical observations, but also pinpoints loci, genes, and pathways that are common to these diseases. There are no medications for treating Alzheimer's diseases, but these types of strong indicators have led to opening of doors for drugs being used for treating diabetes for treating Alzheimer's diseases.[35,36]

GENETIC RISK SCORES

The concept of genetic risk score comes from the idea of predicting a disease based on the genetic variants known for a disease. In Mendelian disorders, it is very simplistic, i.e., if an individual carries the disease-causing allele of

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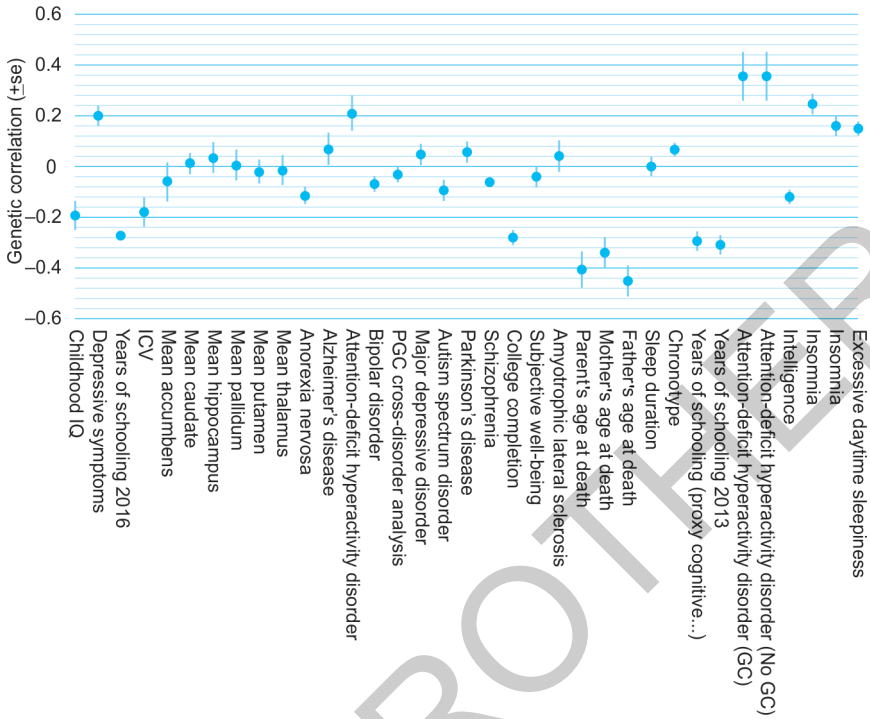

(GWAS: genome-wide association studies; PGC: Psychiatric Genomics Consortium; LDSC: linkage disequilibrium score regression)

FIG. 3: Genetic correlation of diabetes with other disorders. The genetic correlations were calculated using the method implemented in LDSC using the resources on LD Hub (http://ldsc.broadinstitute.org/). Genome-wide association summary statistics for type 2 diabetes mellitus (T2DM) were included from one of the largest GWAS on European ancestry (Mahajan et al. 2018, PMID: 30297969).[41] Genetic correlation was performed on LD Hub for traits grouped as "neurological diseases, sleeping, cognitive, education, brain volume (ENIGMA), psychiatric diseases, and aging" on LD Hub server (Date: 21st September, 2020). These phenotypes were specifically targeted to check association of T2DM genetics on mental health.

the mutation, then the individual will have the disease. However, in complex polygenic disorders like diabetes, there are a large number of polymorphisms involved instead of one mutation. Thus, the probability of an individual to get the disease increases depending upon the number of risk alleles present in the set of polymorphisms being considered for the analysis. Hence, the count of number of risk alleles is used as the exposure variable in the regression analysis to estimate the chance of the individual to get the disease. It is to be noted that the count of the alleles are weighted for the effect size of the polymorphism such that polymorphisms with higher effects get more weightage. The regression coefficient, beta, is used as the weight for effect size and not the popular measure of effect size for case–control studies, i.e.,

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odds ratio. Genetic risk score analyses are also sometimes referred to as polygenic risk scores and these can include a selective set of polymorphisms, all genome-wide polymorphisms, or all polymorphisms with genotypes after filtering based on *p*-value, allele frequency, and degree of linkage disequilibrium. This weighted count of the risk alleles is used as the exposure variable in the regression analysis.

A recent analysis using genome-wide genetic risk score for diabetes has found that it could predict >3-fold increased risk for 3.5% subjects in UK Biobank subjects.[37] The authors suggested that this is more than the number of people being diagnosed for monogenic conditions of diabetes.[38] Providing preventive care for these subjects at increased risk can considerably delay the onset if not prevent diabetes and definitely lowers the public burden of the disease. These genetic risk scores can also be used to perform receiver operating characteristic (ROC) curve analysis for disease predictions and include other covariates such as age, gender, and body mass index (BMI). The area under the curve of ROC (AUROC) is indicative of the chance that such a curve will correctly predict a diabetic subject. Based on results from multiple studies, it seems the predictive power of known diabetes genes (AUROC ~0.7) is still low and definitely not at par with clinical factors (AUROC ~0.9). Improvement has been observed if age, gender, and BMI have been included in the analysis (AUC ~0.8). However, these analyses are more relevant to individuals of European ancestry and power of ROC analysis drops badly for African and other populations, i.e., a clear indicator that these loci identified mainly through genetic studies in Europeans do not predict diabetes in non-European populations. This has led to the speculation that the clinical utility of current genetic findings will have large disparities as it is mainly derived from studying individuals of European ancestry.[20]

PRECISION MEDICINE

The use of multidimensional data to gain precision in prediction, treatment, and diagnosis is often referred to as precision medicine. Though genomics data has mainly been highlighted to play an important role in precision medicine, other sources of omics data and data from wearable devices and medical data from large records have also played an important role in designing strategies for precision medicine. A relatively new entry to this multiomics data is genetic variants affecting protein expression data or protein quantitative trait loci (pQTL) and has been recently used to better inform the disease biology of diabetes.[39] Precision medicine is already a reality in the field of diabetes as genomics data is being used for precise diagnosis and treatment of many monogenic forms of diabetes.[40] Classification of monogenic forms of neonatal diabetes based on genetics can identify sets of individuals who will respond to oral sulfonylureas that often leads to good glucose management. While there are some forms of neonatal diabetes

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[maturity-onset diabetes of the young type 2 (MODY2)] that will not respond to this therapy and focus should shift other forms of glucose management. However, the same has not been possible for T1DM and T2DM and needs further discoveries in the field of diabetes and related conditions.

ROAD AHEAD

We have had tremendous success in the discovery of loci associated with diabetes and currently this has become a function of number, ethnicity, and genotyping technologies. Saturation has reached in terms of identifying genetic loci with high effect sizes. We still are not sure about the genes through which these genetic variants act and much further from identifying how the identified gene causes or protects us from diabetes. This is a big opportunity for functional studies in various model systems both in vitro and in vivo. Transferability of this genetic knowledge to different ethnicities of the world should be one of the major goals as it has been in other fields of medicine. So far, approximately 2% of the subjects studied are non-European and this must shift somewhere near to the middle line to prevent disparity. The use of these large genetic discoveries will remain limited if more ways to use this in informing the drug discovery process and design of intervention strategies is not found.

CONCLUSION

Twenty years may appear a long time, but it is a much shorter period in the history of disease treatments, and we have seen a tremendous leap in our understanding of the genetic basis of diabetes, thanks to the Human Genome Project. Within this time period we have witnessed the discovery of the first gene for common form of diabetes to large-scale multi-nation studies that have identified hundreds of genetic loci including both common and rare variants. We have witnessed studies involving single gene to whole genomes of thousands of individuals. Today we are convinced that diabetes is a multifactorial disease not just based on environmental exposure but also based on genetic basis as genetic determinants of diabetes are shared across many other metabolic conditions and neurological conditions. This has re-emphasized our previous believes that treating root cause of diabetes could prevent many other diseases. This change in scenario for diabetes; "no gene to hundreds of genes", "common to common and rare", "single gene to whole genome studies", "hundreds of individuals to hundred thousands of individuals" has been made possible in these twenty years greatly due to the Human Genome Project. As we enter the era of precision medicine if we can fill the gap of ethnic inclusion and genetic discovery to functional studies, we will move much closer towards treatment of diabetes and realizing the ultimate goal set by the Human Genome Project.

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Advances in Diabetes

Novel Insights

Second Edition

The new volume of Advances in Diabetes Novel Insights comes at an unusual time: diabetes has reached a point where "established" concepts need a relook, changes occurred in the management of known complications; in addition, exciting avenues opened up in our understanding of diabetes, its predisposing conditions and comorbidities. Besides, artificial intelligence has made inroads into mainstream management of diabetes. COVID-19 epidemic shot both teleconsultation and corticosteroid use into the limelight.

- Redefining diabetes classification
- Adipomyokines in diabetes
- Air pollution and metabolic syndrome
- Genomics in diabetes: 20 years on
- Diabetes, cerebrovascular disease, peripheral artery disease, and nephropathy
- Skin vasculature in diabetes
- Late metabolic effects of hypertension in pregnancy
- Male sexual dysfunction
- Artificial intelligence in retinopathy, hypoglycemia
- Teleconsultation in diabetes
- Mindful meditation and geletology as adjuvant therapy
- Targeting nerves to adipocytes in metabolic syndrome
- Time-related eating
- Recent indications for SGLT2is
- Corticosteroids in COVID-19
- Exercise mimetic agents

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