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Environmental and genetic contributions to diabetes

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ABSTRACT

Diabetes mellitus (DM) is a heterogeneous group of disorders characterized by persistent hyperglycemia. Its two most common forms are type 1 diabetes (T1D) and type 2 diabetes (T2D), for which genetic and environmental risk factors act in synergy. Because it occurs in children and involves infectious, autoimmune or toxic destruction of the insulin-secreting pancreatic beta-cells, type 1 diabetes has been called *juvenile* or insulin-deficient diabetes. In type 2, patients can still secrete some insulin but its effectiveness may be attenuated by 'insulin resistance.' There is also a group of rare forms of diabetes in the young which are inherited as monogenetic diseases. Whether one calls the underlying process 'genes vs. environment' or 'nature vs nurture', diabetes occurs at the interface of the two domains. Together with our genetic background we are born *tabula rasa*—a blank slate upon which the story of life, with all its environmental inputs will be written. There is one proviso: the influence of epigenetic inheritance must also be considered. Thus, in the creation of databases that include "big data" originating from genomic as well as exposome (defined as: the totality of environmental exposure from conception to death), a broad perspective is crucial as these factors act in concert in such chronic illnesses as diabetes that, for example, are likely to require adoption of an appropriate lifestyle change. Also, it is becoming increasingly evident that epigenetic factors can modulate the interplay between genes and environment. Consequently, throughout the life of an individual nature and nurture interact in a complex manner in the development of diabetes. This review addresses the question of the contribution of gene and environment and their interactions in the development of diabetes.

1. Introduction

1.1. History of diabetes mellitus

Diabetes finds its place in antiquity as being one of the first-described diseases. From the discovery of diabetes mellitus (DM) as an illness until the much more recent breakthroughs in its treatment, many brilliant scientists have been involved in the enthralling history of DM [1]. One of the earliest descriptions of diabetes can be found in certain Egyptian manuscripts. The Ebers Papyrus—one of the most ancient medical treatises, dating back to approximately 1500 BCE—describes an ailment as "too great emptying of the urine" [2]—probably referring to T1D. Around 230 BCE the term "diabetes" (Greek "to pass through") was coined by a disciple of Hippocrates named Appolonius of Memphis. The first clinical description of diabetes was made by Aulus Cornelius Celsus in first century CE. In the 2nd century CE, the Greek physician Aretaeus of Cappadocia distinguished the two main forms of diabetes we now call diabetes mellitus and diabetes insipidus. In India, ancient physicians used the term *madhumeha* ('honey urine') because it attracted ants and this effect on ants provided the first clinical test for diabetes. The two major forms of diabetes mellitus were defined by the Indian physicians Suhruta and Charaka in the 5th Century CE (type I and type II). Type 1 diabetes was associated with youth and type 2 with obesity, thereby implicating genes and environment. The terms *juvenile diabetes* and *diabetes of obesity* were actually used until recently [2]. The Persian seer, Avicenna, in his 'Canon of Medicine', completed in 1025 CE, described the sweet taste of urine, abnormal appetite and collapse of sexual function, in addition to the cardiovascular complications of diabetes. In 1798 the British Surgeon-General, John Rollo coined the term mellitus (Latin, 'sweet like honey') in order to distinguish this diabetes from the other type, "insipidus" where kidneys are unable to conserve water and the urine is tasteless [2]. The role of the pancreas in pathogenesis of diabetes was discovered by Mering and Minkowski (Austria) in 1889. This discovery provided a foundation for the achievement of insulin isolation and its clinical use by Banting and Best (Canada) in 1921.

1.2. Diabetes: one of the most challenging health problems of the 21st Century

Based on surveys by the International Diabetes Federation, diabetes is one of the most challenging health problems of the 21st Century: There were 425 million adults with diabetes in 2017 worldwide and

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this number is expected to increase to 630 by 2045. Moreover, there were 4 million deaths from diabetes worldwide in 2017, making it among the 10 most common causes of death [3]. DM with its increasing risk of related morbidity, including macrovascular (coronary artery disease (CAD), stroke)/ microvascular (diabetic nephropathy, diabetic retinopathy, peripheral neuropathy) complications, end-stage renal disease (ESRD) [4], leads to a substantial economic burden on health care systems [3]. DM is a significant risk factor for the development of Alzheimer's disease and other disorders of cognition [5].

In Canada, where New Brunswick is one of the provinces with the highest incidence of diabetes, diabetes prevalence increased approximately 70% in the past decade making it the leading health challenge of the country [6]. According to Canadian Diabetes Association roughly 80% of Canadians suffering from diabetes die from a heart attack or stroke and close to 25% experience depression [7]. In the US, a recent study based on National Health Interview Survey (NHIS) between 1997 and 2009 reported that approximately 12% of deaths are due to diabetes, making it the third leading cause of death in the US in 2010 [8]. The situation in Europe is similar [9]. The most prevalent form of diabetes mellitus (T2D) accounts for >80% of cases diagnosed as DM, greatly exceeding the prevalence of type 1 diabetes (T1D), which constitutes approximately 5%−10% of DM patients [10].

Both T1D and T2D are multifactorial, complex diseases resulting from the interplay of genetic, environmental and epigenetic factors. Accordingly, the impact of TD1 and T2D differs by population, depending on such variables as age, race, ethnicity, geography, and socioeconomic status [11].

T1D (juvenile/insulin-dependent diabetes) is largely owing to T cell-mediated destruction of pancreatic β cells in genetically susceptible individuals. T1D's lack of insulin is different it from T2D where the hyperglycemia is due to insulin resistance combined with some deficiency of insulin [12]. The other forms of diabetes, that will not be reviewed here, are monogenic forms of diabetes MODY (maturity-onset diabetes of the young) with autosomal dominant inheritance with the most prevalent type MODY 3 (~61%) accounts for only 1 to 2% of DM cases [13], GDM (Gestational DM) affecting 3%−10% of pregnancies in different populations [14], type 1b or idiopathic diabetes: an unusual form of phenotypic type1 diabetes with almost complete insulin deficiency, a strong hereditary component, and no evidence of autoimmunity, reported mainly in Africa and Asia, and LADA (latent autoimmune diabetes of adults) which occurs in adulthood with slower progression to insulin dependence [15].

Troubling information comes from epidemiological studies demonstrating that the incidence of both T1D and T2D independently and without relationships between the two, is increasing among young individuals [11,12]. Moreover, the distinction between type 1 and type 2 diabetes becomes blurred in later life. The increase in prevalence of diabetes in the general population can be explained in part because of increased longevity of both T1D and T2D subjects [11,12]. This situation has given rise to a change in the profile of complications and burdens to health systems, with fewer amputations and blindness but more heart disease and renal failures—the costliest chronic complications [4]. Moreover, as we will discuss further, in addition to genetics component, environmental factors are important players. As epidemiological and clinical data have indicated, a wide range of candidate environmental factors has evolved; namely, an obesogenic environment, sedentary lifestyle (i.e., physical inactivity and energy dense diet) [16], microbiota [17], medications, age, sex, and socioeconomic status [11]. A limited education is associated with an increase in the prevalence rate of DM [18].

Risk of diabetes does not appear to be evenly distributed across ethnic groups. Apart from evidence that prevalence of diabetes is higher among persons of non-European ethnicity, studies examining the prevalence of diabetes among migrants in provinces of Ontario, British Columbia and Quebec in Canada demonstrated a higher diabetes prevalence among immigrants suggesting that, along with genetic predisposition, environmental factors and health behavior changes after immigration could contribute to higher rate of diabetes among migrants [18].

Overall, even if our genome is the “Achilles heel” in subjects affected with the disease, it is only one piece of the puzzle. Thereby, also as discussed during 2nd International Congress on Personalized Health Care 2018 in Montreal [19], the creation of robust databases gathering genomic as well as “exposome” data, together with medical histories, social factors, and lifestyle factors is pivotal as these factors do not act in isolation, but in concert. These databases are essential tools for the establishment of personalized healthcare of such common multifactorial complex diseases as diabetes [20].

1.3. Gene-environment interplay in complex diseases

After passing through the phase of classical genetics devoted to monogenetic diseases, we entered the era of modern genetics (genomics), which is focused on the interaction between the environment and the genetic inheritance [20,21]. According to Prigogine's argument (Nobel laureate for physics in 1977), we are all, “an open system” that results from of constant communication between our genes and our environment—biological and psychological. The impact of each factor (genetic and environmental) in disease development is crucial. Moreover, biostatistical and informatics approaches play a pivotal role in determining risk of diseases [22,23]. We cannot change the structure of our genes, but we can influence the results of their expression; for instance, via epigenetic modulation of transcription (disease development/protection, drug metabolism and action) and via our lifestyle, so as to prevent or delay the onset of disorders [23]. Also, understanding the gene-environment (G × E and G + E) paradigm as relevant to complex diseases is one of the most important challenges of personalized healthcare. [20]. The concept of G × E interactions is not new; it was introduced by Jacques Monod, Nobel laureate in Medicine and author of the famous “Chance and necessity” (*“Le Hasard et la nécessité”*) [24].

According to R. Ottman [25], G × E interactions could be defined as “a different effect of an environmental exposure on disease risk in persons with different genotypes or, alternatively, a different effect of a genotype on disease risk in persons with different environmental exposures.” Understanding G × E interactions is essential to the elucidation of basic biological mechanisms. Through risk prediction, such an understanding also permits scientists to evaluate the advantage of changes in modifiable environmental exposures [26,27]. The success of G × E interaction studies depends upon the availability of high-quality epidemiologic investigations with exposure assessment conducted over a sufficient period of time [28] as well as using ethnically and geographically appropriate study populations with a broad range of exposure levels [26,27].

The *Environmental Genome Project (EGP)* was initiated in 1998 by the NIH's National Institute of Environmental Health Sciences (NIEHS) as a continuation of the Human Genome Project (HGP). The EGP is a multidisciplinary, collaborative effort focused on examining the relationships between environmental exposures, interindividual sequence variation in human genes, and disease risk in the U.S. populations. It is focused on multifactorial pathologies such as diabetes, cardio-vascular diseases, and cancer. The main goal of this project is to study interindividual variability in susceptibility to disease, related to the polymorphic effects of G × E interactions [29]. Following EGP initiative, the Genes, Environment and Health Initiative (GEI), that began with a genome-wide association study (GWAS) component was launched by the Department of Health and Human Services (HHS) and the NIH to lay a foundation for investigating the G × E interactions that underpin human disease [30]. All these initiatives underline the importance of G × E interactions in the development of complex diseases. Because of their high public health impact, they will create an enlarged capacity and new strategies for further research, leading to better predictions of disease outcomes and

disease prevention, as well as more precise approaches to the treatment of many diseases.

As discussed by Khoury et al, [21], the importance of genomic research in public health related to chronic common complex diseases with strong environmental determinants is not only to discover new genetic 'causes' of the diseases but also to better identify interacting environmental risk factors. The authors emphasised that ignoring the crucial contribution of genomic research to prevention with established environmental risk factors could cause a false competition between nature and nurture. Understanding G × E interactions, will certainly improve our understanding of the environment (in relation to risk) and how we can and should understand, assess and manage these risk factors. [20,21].

Since many disease-related phenotypes are quantitative traits with many interacting genetic loci where the effects of alleles are highly sensitive to environmental exposure, the strength of interactions between gene and phenotype depend upon the presence and/or absence of quantitative differences among additional factors such as other genetic variants or an environmental exposure affecting health or disease. Accordingly, in order to be successful, genetic discovery needs to rely on statistical strategies that comprise not only G × E interactions, but additive models (G + E) and multiplicative models (G × E) related to the complexity of the genotype-phenotype relationship. This is because etiology of complex diseases arises from complex interactions with environment that are more important than the independent main effects of any susceptibility gene [27].

Thus, while a multiplicative model has been suggested to be more appropriate for disease etiology of complex diseases, the additive model which measures risk differences is used predominantly in predicting disease risk [25].

1.4. Defining the genetic-environment and sex contribution to diabetes

Genetic factors can play an important role in the pathophysiology of diabetes, with numerous pathways influencing its progression, particularly in genetically predisposed individuals. In addition, non-genetic environmental factors can trigger pre-existing susceptibility genes [31]. Exposure to various adverse life events could give rise to different types of diabetes depending on the nature of the G × E interactions. Although exposure to adverse events can increase the risk of developing DM, the degree of risk is far from uniform; indeed, many variables are involved including diverse genetic susceptibilities to environmental exposure within a G × E interaction paradigm. Furthermore, different kinds of G × E exposure may lead to different treatment responses or gene-treatment interactions in individuals with different types of diabetes [31]. The example of the RAB38 gene recently published by the CKD Gen consortium [32] is worthy of mention. This study demonstrated an association between *rab38* gene and the urinary-albumin creatinine ratio (UACR), a hallmark of diabetes kidney disease. This association occurs in individuals with DM, but not in nondiabetic individuals, indicating the context peculiarity of genotype-phenotype associations. These findings are further explained by evidence that the *Rab38* gene is protective against albuminuria. While there was no apparent phenotype in Rab38-KO rats; it is only when the rats were made diabetic by injection of streptozotocin that they exhibited massive albuminuria [32]. This sequence of events gives support to the crucial concept that the association of a genetic locus with a specific phenotypic trait (or pattern of traits) is dependent on the concurrent presence of a disease-gene-disease interaction [27,32].

The relationship between DM, and sex-related inconsistencies is intriguing. A few studies looking at sex differences in etiology, epidemiology, prevention, and prognosis of DM have reported clinically meaningful differences in diabetes complications and diabetes management among men and women [33]. For example, a recent meta-analysis demonstrated that women with DM have a 27% greater risk of stroke, with worse survival and functional outcome than men [34], and other meta-analyses reported that diabetes is associated with a 19% greater relative risk of vascular dementia among women than men with diabetes [35].

The MONICA Augsburg Cohort Study, which is one of the first prospective population-based studies to assess the sex-specific incidence of T2D in a central European population called attention to the importance of sex-related dissimilarities that seem to be involved in disease development [36]. It was affirmed that, although mature women were affected by most common autoimmune disorders, girls and boys with T1D were affected to the same degree [37].

These findings underline the importance of sex-related dissimilarities which inter alia may affect the quality of diabetes self-care. Since one's sex is a fundamental biological factor and may play a key role in the regulation of homeostasis in health, further investigation is needed to explore the sex-related behavioral traits that influence health outcomes. The information that is generated by such research may be useful in improving the quality of personalized healthcare in diabetes management.

It should not be forgotten that in utero developmental represents a critical period during which environmental factors can impact epigenetic regulation and alter the expression of phenotypes. During this process, the interplay of prenatal environment and epigenetics constitutes a sort of "environmental epigenomics" which includes both endogenous forces, such as hormone levels, and exogenous factors such as nutritional factors. These are thought to be the most fragile environmental factors during embryogenesis leading to epigenetic remodeling [38].

A study tested the predictive adaptive response (PAR) hypothesis of developmental plasticity, a situation where the same genotype produces different phenotypes depending on inputs during development, in the highly inbred polydactylous rat strain (PD/Cub). Consequently, in this study the assessment of the early-and long-term exposure (1 week before breeding and throughout gestation and lactation) to high-sucrose diet (HSD) (70% calories as sucrose) in PD/Cub rats demonstrated that male offspring of sucrose-fed dams displayed increased liver triglyceride content, higher adiposity and elevated low-density lipoprotein (LDL) cholesterol levels, when compared to standard-fed dams. However, the considerable increases in the insulin sensitivity of skeletal muscle along with higher concentrations of adiponectin in the male offspring of sucrose-fed dams compared with the offspring of standard diet-fed dams [39] was puzzling.

1.4.1. Lessons learned from T1D

Genetics explains about 80% of the heritability of T1D [40]. It is reported that the major histocompatibility complex (MHC) accounts for approximately 40% to 50% of the familial aggregation of T1D [40]. The human leukocyte antigen (HLA) alleles are essential to the development of T1D, for which polymorphisms of class II HLA genes encoding DQ, DR (primarily HLA-DRB1, HLA-DQA1, and HLA-DQB1 genes) and, to a lesser extent, DP are significant genetic T1D determinants. However, alleles of the class I HLA-B gene are also strongly associated with T1D [41]. These HLA-DR/DQ alleles could be either risk predisposing or protective. For example, the DRB1*1501−DQA1*0102−DQB1*0602 allele is strongly associated with T1D protection [40,41]. Extensive familial and population genetic studies have revealed the strong association between HLA and T1D. GWAS have identified >40 non-HLA-T1D risk loci, such as PTPN22, CTLA4, interleukin 2 receptor a (IL2RA) and uromodulin (UMOD); however, the clinical impact of these loci on β-cell function in disease progression is still unknown [40].

The incidence of T1D has significantly increased over the past 30 years, varying worldwide in all ethnic groups. The highest rates in northern Europe occur in Scandinavia and North-West Europe. Even though both sexes are equally vulnerable during childhood, men are apparently more commonly affected in early adult life. Since T1D de facto has an early life penetrance, as discussed below, the potential

environmental triggers should be sought early in life [42]. The increase in T1D prevalence in Central Europe has been explained by studies of incidence trends ("catch-up phenomena") [42]. The rapid change in incidence magnitude cannot be readily explained by increased transmission of susceptibility genes from one generation to the next. Some important environmental influence seems more likely [42].

Geographical factors play significant role in the incidence of childhood T1D. For instance, in China, the more the distance from the equator increases, the more the risk appears to emerge, suggesting that T1D incidence among children between aged 0−14 years, but not in the older population, was strongly correlated with latitude, with higher rates in the north and lower in the South. Same gradient has been observed from Africa to Scandinavia. However, this North-South geographical variation is not observable in North America, even after adjusting for racial and ethnic variation [43]. For example, in Canada it is reported that the gradient trends of hypertension and obesity is the lowest in the West, rising to the highest in the East, with notable exception in the province of Quebec, in contrast with the absence of an East-West gradient of cholesterol. This difference can be explained by a higher genetic determination for cholesterol than hypertension [44]. Such examples demonstrate that relocation of people from a region of low to high incidence could lead to an increased risk of T1D. Therefore, evaluation of the geographic pattern of disease as playing a causative environmental role may reveal important etiologic clues related to G × E interactions.

It also seems reasonable that, in a more stable and homogeneous environment, an increase in the incidence of T1D can be associated with alterations in autoantibody profiles and increased penetrance of susceptibility genes. This scenario is consistent with evidence for the effect of changes in the environment on the pathogenesis of the disease [45].

It is reported that T1D incidence attains a peak at pubescence which occurs earlier in female adolescents than in male adolescents. This sex difference during the puberty could be mediated partly through genes regulated by estrogen— particularly in female adolescents who are carriers of *IL6-174CC* genotype. Thus, pubertal changes may contribute to accelerated onset of T1D in genetically susceptible females [46].

Different aspects of infant nutrition are involved as risk factors of T1D. In addition, T1D prevalence augmentation is believed to be caused by replacement of maternal breast feeding with cow milk, early introduction of cereals, and a decreased intake of vitamin D. However, the situation may become more complex in relation to microbiota and medications [47]. Besides breastfeeding, vitamin D, zinc, nicotinamide, and vitamins C and E have been reported as possible protection factors against T1D [37].

Apart from the role of nutrition, several studies have demonstrated the association between T1D incidence and seasonal variation. The seasonality of the incidence of T1D in children under 15 years of age appears to be a genuine phenomenon that is an independent of geographical location [48], however, it appears to parallel the environmental exposure to seasonal respiratory infection.

The multifactorial nature of T1D shows it to be a complex disorder that arises from gene-environment interactions. Future research studies that focus on the, imprint of genetics, evaluation of lifestyle factors and geographic patterning may provide important etiologic clues that will contribute to more effective prevention and treatment of T1D.

1.4.2. Lessons learned from T2D

Type 2 DM (T2D) is a group of complex metabolic disorders associated with an increased morbidity and mortality. Like other multifactorial polygenic diseases T2D rarely affects each person in the same way. It is more frequently diagnosed in late adulthood and its worldwide prevalence is increased in children and young adults who are obese [3,6]. It is widely recognized that genetic factors are involved in T2D, as demonstrated by studies of families and monozygotic twins. A positive family history of diabetes has been associated with a significantly increased risk of T2D. However, the relative contribution of genetic versus shared environment remains unclear. The most convincing evidence of the genetic and environmental contributions to T2D has been obtained from studies performed in the large sets of subjects included in the Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFUS). The data from such surveys indicate that, in their environmental contribution to T2D, first degree relatives have a correlation of approximately 23%, and that shared environment is responsible for about 32% of the association between parental history and T2D. What remains of the correlation is attributable to shared genetics [49].

The strength of this evidence arises from the large size of the subject population, and from measurement of many putative contributing factors. Included in the list are data concerned with family DM history, known environmental influences, lifestyle, body mass index (BMI), and estimates of energy expenditure, measures of known genetic factors (including 143 genetic variants associated with T2D), plus the *FTO* (body fat mass in concert with the *obesity-associated* protein) gene [49,50].

T2D and its micro- and macrovascular complications are typical examples of multifactorial polygenic complex diseases that arise from the interplay of multiple genetic and behavioral/environmental factors [4].

Since publication of the first GWAS in 2007, use of this model has become an important tool in the identification of susceptibility loci and SNPs associated with T2D such as *KCNJ11* (potassium channel, inwardly rectifying subfamily J, member 11), *PPARG* (peroxisome proliferator-activated receptor gamma), *TCF7L2* (transcription factor 7-like 2) [50]. GWAS revealed that monogenic diabetes genes are associated with T2D, but not T1D [51]. For example, as of today, 35 genes are involved in monogenic diabetes and 21 of them, including *KCNJ11, PPARG, HNF1A (*hepatocyte nuclear factor 1 homeobox A1 gene) are shared with T2D and its complications in the ADVANCE cohort [52]. T2D is a classical example of a complex polygenic condition. It results from a multifactorial interaction of environmental/lifestyle factors, such as "obesogenic" environment and genetic variations at multiple chromosomal loci. These variables raise the risk in a synergistic manner [53]. In as much as patients diagnosed with T2D have a variety of symptoms and susceptibilities to diabetes-related complications it is essential to understand this complex gene-environment architecture to gain insight into disease progression and to translate its genomic information into clinically useful knowledge for prevention and targeted patient management. In the case of obesity, adverse metabolic effects caused by obesity are usually associated with several metabolic abnormalities, including T2D. Thrifty genes, such as *FTO* and *PPARG* are associated with obesity and T2D as well. Their impact is modified by the environment. For instance, *FTO* is particularly susceptible to environmental modulation. Physical exercise attenuates by 40% FTO's impact on obesity [53]. We have also shown that *FTO* gene is associated with blood pressure status and this association can be completely neutralized by antihypertensive medication. The association of the *FTO* gene with hypertension is only seen after several week's withdrawal of antihypertensive medication [54].

The prevalence, severity and complications of T2D are also correlated with ethnicity. Some ethnic groups tend to be more predisposed to development of the condition than others, even in the same environment [55]. By means of principal component analysis (PCA), we identified two main ethnic groups (Celtic and Slavic) among T2D subjects of European descent of the ADVANCE trial. The ability to make this distinction enabled us to assess the relative effects of genetic and environmental factors on T2D's onset of complications by comparing ADVANCE participants with a Slavic genetic

background living in countries, of predominantly Celtic populations, with individuals with a Slavic background living in Slavic countries of Europe. The study demonstrated that significant differences between Slavs living in Slavic and Celtic countries were present for certain complications (more rapid decline of eGFR and increase of blood pressure), suggesting a predominant environmental/lifestyle effect on these complications. In contrast, no differences were observed for certain traits related to T2D (age of onset of T2D and albuminuria) between Slavs living in Celtic versus those living in Slavic countries suggesting a more dominant genetic influence for these traits and PROX1 gene was identified as a possible gene of susceptibility to early onset of T2D [55].

1.5. Gene × environment interactions and ethnicity in the prediction of antidiabetics treatment response

In addition to clinical factors, environmental exposure within the context of G × E interactions could help predict treatment outcome. For example, a recent metanalysis demonstrated that treatment response to antidepressants was lower in individuals with childhood abuse as compared with individuals without such an experience [56]. As to DM, there is significant interpatient variability in drug disposition, tolerability, incidence of adverse events as well as glucose-lowering response to oral antidiabetic drugs [57].

Besides non-compliance with drug therapy, this interpatient variability could be attributed to such 'non-genetic' biological factors as age, sex, body weight, nutritional status and co-medication as well as to microbiota. Moreover, genetic variation, which is comprehensively studied through pharmacogenomics (PGx) affecting drug metabolizing enzymes/transporters (DMETs), and receptor responses are crucial factors influencing the effects of, and adverse events associated with, OADs [57]. Additionally, in the context of G × E interactions, inter-ethnic differences within different environmental conditions could influence the genomic diversity in drug disposition causing heterogeneity of drug responses among different ethnic populations [58].

For instance, cytochrome P450 isoenzyme 2C9 (CYP2C9) is a principal metabolic pathway for sulfonylureas (Sus). In homozygous carriers of the CYP2C9*2, CYP2C9*3 and CYP2C9*5 alleles with defective enzyme activity, clearance is decreased, whereas following oral administration of various Sus, plasma concentration is increased leading to significant reduction in glycated hemoglobin (HbA1c) levels compared with wild-type homozygotes (*1/*1) and HbA1c level <7%. [57]. In contrast to *5 allele which is restricted primarily to sub-Saharan Africans and their descendants, the variants *2 and *3 are rare and little known in different African populations [58], leading to health implications for sub-Saharan Africans who are treated with SUs. In addition, in order to capture more complete mechanistic understanding of the G × E interactions involved in the potential treatment options of diabetes, not only pharmacogenomics but also transcriptomics, proteomics, metabolomics, epigenetics and metagenomics may provide greater power to predict disease background, progression and the potential success of novel therapeutic approaches.

1.6. Conclusion and future challenges

In this 'postgenomic' era rapid development of "omics" concepts are ready to help transform personalized healthcare. New approaches like these should lead us to a better understanding of the molecular underpinnings of different polygenic multifactorial chronic complex diseases like DM, which exercises a major burden on our healthcare system [59]. Hence, together with environmental factors, the deployment of personalized healthcare relies on the ability to characterize precisely relevant patient subgroups from extensive clinical and genomic datasets, in order to create a "tailored" health care approach to the detection, prevention and treatment of diseases [23]. Modern medicine is moving towards identifying clinical and molecular signatures initiating an important paradigm shift that emphasizes the "prediction/prevention" of future health outcomes, enables us to better predict disease susceptibility, and reduces the degree of uncertainty in treatment decisions [21].

Along with our initial genetic capacity, a better understanding of G × E interactions should permit us to prevent the development of diseases induced by the environment. Taking into consideration genetic and environmental components of diseases will help answer some of the most pressing questions related to existence of disease, their prediction**,** and their choice of treatment through PGx [20].

Considering the worldwide pandemic nature of DM together with its seriously negative impact on healthcare systems, the need to advance and—particularly—deepen our understanding of the complex interplay between genomic, environmental and epigenetic contributions is increasingly urgent [60]. To this end, in the study of complex diseases such as the "Nature *vs* Nurture" concept, applied to T2D, should be replaced by "Nature *and* Nurture", to get more comprehensive inputs combining genetic and non-genetic factors.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare. Both are members of the scientific committee of the Collège International de Recherche Servier (CIRS).

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