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Genetic basis of type 2 diabetes – recommendations based on meta-analysis

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Abstract. – OBJECTIVE: Despite intensive effort to understand the genetic basis of type 2 diabetes, only a few genes responsible for relatively rare monogenic and syndromic subsets of diabetes are known; however, gene(s) responsible for genetic predispositions to common type 2 diabetes are unknown. The current study was obtained a better understanding of the genetic architecture of type 2 diabetes.

MATERIALS AND METHODS: Comprehensive literature search was performed and the extracted data was analyzed. The proportion of variance explained by validated genetic factors for a range of metabolic quantitative traits was analyzed.

RESULTS: A fully elucidated landscape of type 2 diabetes genetics may well depict perhaps a hundred or more common variants individually with low impact on disease.

CONCLUSIONS: Every individual harbors a combination of different risk alleles and only special compilations of these variants in combination with other genetic and non-genetic components will likely lead to disease.

Key Words:

Type 2 diabetes, Risk factors, Genetic variants, Meta-analysis.

Introduction

Type 2 diabetes mellitus, obesity and the inflicted complications are major global health problems due to markedly increasing prevalence in both the western world and in the developing countries[1]. The total number of people worldwide with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 corresponding to a predicted increase in prevalence from 6.0% in 2000 to 7.3% in 2030[2]. Type 2 diabetes is primarily caused by obesity, insulin resistance in liver, skeletal muscle and adipose tissue and a relative deficient insulin secretion by the pancreatic b-cell[3,4]. Moreover, type 2 diabetes clusters with dyslipidemia and hypertension; which together with insulin resistance, glucose intolerance and visceral obesity are hallmarks of the metabolic syndrome[5]. Type 2 diabetes is often accompanied by severe complications of the cardiovascular system, eyes and kidneys leading to increased morbidity and mortality from cardiovascular disease (CVD) and end-stage renal failure.

The large increase in incidence and prevalence of type 2 diabetes and obesity seems to be largely due to lifestyle changes such as high-fat diet and physical inactivity, yet, several genetic epidemiological studies demonstrate that both obesity and type 2 diabetes are highly inherited traits[6-9]. However, despite much research, the dissection of the specific causes of these common disorders at the molecular level is still in its infancy. More detailed insights into the molecular mechanisms of the metabolic diseases are thought to improve the chances for a more targeted treatment and in some cases also for prevention of disease development.

For years it has been well-known that genetic factors are crucially important for the development of type 2 diabetes[10]. Despite a great effort in seeking to understand the molecular genetic basis, until a few years ago, only a handful of genes responsible for relatively rare monogenic and syndromic subsets of diabetes were detected and progress in finding genetic predispositions to common type 2 diabetes was lacking. However, the last couple of years have brought by a revolution in genetics of common, complex traits leading to renewed optimism for the validity of this research. Despite this great success major tasks are still undone to fully understand the genetic architecture of type 2 diabetes and related phenotypes.

Materials and Methods

Data Sources and Searches

Clinical literatures were identified via Ovid MEDLINE, Ovid EMBASE, SCOPUS, and

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Cochrane Database (source, 1975 to 2012). Both database-specific controlled vocabulary and general free text terms were used to maximize retrieval. MeSH terms used were “type 2 diabetes”, “genetic susceptibility”, “obesity”, “lipidemia”, and “cardiovascular disease”. Searches were limited to literatures available in full text and humans within a valid limit within the database. Hand searching of key article reference lists was used to locate additional relevant articles. Eligibility assessment and data abstraction were both performed independently in an unblended standardized manned by 2 independent reviewers.

Data Extraction and Analysis

Results from all searches were combined and duplicates were removed. Inclusive criteria were studies describing general data (study design), patients (number of included patients, mean age, gender), type of diagnostic criteria and/or intervention strategy used, timing of determination. The outcomes of the collected manuscripts were synthesized and formed the basis for further analysis and description, which was done following recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines[11]. Exclusion criteria were (1) initial diagnosis in reported patients was more than 12 months from entry date into the study, and (2) history of tumorigenesis in included patients that can severely confound conclusions. A meta-analysis of the present and published studies was performed using RGui version 2.2.1 (available at http://www.r-project.org). The quality of the evidence for a specific outcome was based on the study design, risk of bias, consistency of results, directness (generalizability), precision (sufficient data) and potential bias for the reporting of results across all studies that measured that particular outcome.

Results

For several years progress in finding the molecular genetic predisposition to type 2 diabetes and other complex traits was sparse but the last couple of years this has changed dramatically. Yet despite the fact that at present 19 validated risk-loci for type 2 diabetes, 36 loci for fasting lipid levels and 18 loci influencing risk of obesity have been found (Table I and data not shown) the genetic background of these diseases and phenotypes remain mostly obscure.

First this is due to the lack of biological and functional knowledge of mechanisms behind these new loci and genes. Massive efforts are needed to find causal variants and elucidate biological pathways and pathogenic impact for this growing list of associated variants. Second, for all these metabolic traits the explained proportion of the variance of the trait or of the genetic contribution is rather low indicating the existence of a number of other genetic risk elements.

In Figure 1 is shown the proportion of variance explained by validated genetic factors for a range of metabolic quantitative traits in the population-based Inter99 cohort. Analyses of insulinogenic index and HOMA-IR included validated type 2 diabetes variants and for fasting plasma glucose, in addition, variants in GCK[39], G6PC2[40,41] and GCKR[42]. Analyses of BMI and lipids included a range of validated variants for the specific traits, however not all validated variants were included. We saw that no single variant for any trait explained more than 1% of variance. Estimates of total variance explained by all variants for each trait ranged from ~1% for HOMA-IR to ~3.5% for serum total cholesterol (Figure 1). These rather low estimates of variation in quantitative metabolic traits explained by identified genetic variants are in agreement with findings in the literature.

The two most recent GWA studies found explained proportion of the variance of triglyceride, LDL- and HDL-cholesterol levels of 3-5%[43] or somewhat higher estimates of 7-9%[44] when combining nearly all risk loci. A combination of all BMI associated loci may explain as little as 1% of the variation in BMI[45].

Estimating the explained proportion of type 2 diabetes by 19 validated variants is somewhat different given the categorical outcome data. From family data it has been estimated that the sibling relative risk, l_S, attributable, to the initial nine gene variants was merely ~1.07[15] compared to an estimated l_S of 2-3 of type 2 diabetes[46]. Generally, it has been stated that current genetics explain 5-10% of the genetic component in type 2 diabetes[47]. This aspect is also reflected in the rather poor prediction potential of the common validated type 2 diabetes variants estimated by receiver-operating characteristics (ROC) curves. This procedure, when done in a longitudinal setting, evaluates the potential to predict incident type 2 diabetes cases from a glucose tolerant background population and the area under the curve (AUC) can range from 0.5 (as by random) to 1

Table I. Validated type 2 diabetes susceptibility loci.

Chr.	Regional gene(s)	SNP ID	RAF	Discovery method	Cellular function	Putative intermediary mechanism	OR	Ref.
1p13	NOTCH2	rs10923931	0.11	GWA	Regulator of cell differentiation	Unknown	1.13	(12)
2p21	THADA	rs7578597	0.90	GWA	Apoptosis	Unknown	1.15	(12)
3p14	ADAMTS9	rs4607103	0.76	GWA	Proteolytic enzyme	Unknown	1.09	(12)
3p25	PPARG	Rs1801282	0.85	Candidate	Adipocyte function and differentiation	Insulin resistance	1.14	(13-15)
3q27	IGF2BP2	rs4402960	0.35	GWA	Developmental growth and stimulation of insulin action	Insulin response	1.14	(15-18)
4p16	WFS1	rs10010131	0.60	Candidate	Endoplasmic reticulum stress and β-cell apoptosis	Insulin response	1.11	(19-21)
6p22	CDKAL1	rs10946398	0.36	GWA	Cell cycle regulation in the β-cell	Insulin response	1.14	(15-17, 22, 23)
7p15	JAZF1	rs864745	0.50	GWA	Zinc-finger protein with unknown function	Insulin response	1.10	12, 24
8q24	SLC30A8	rs13266634	0.72	GWA	Zinc transporter in β-cell insulin granules	Insulin response	1.15	(25, 26)
9p21	CDKN2A,	rs10811661 CDKN2B	0.86	GWA	Cell cycle regulators	Insulin response	1.20	(15-17)
10p13	CDC123,	rs12779790 CAMK1D	0.18	GWA	CDC123: cell cycle regulation CAMK1D: Regulator of granulocyte function	Insulin response	1.09	12, 24
10q23	HHEX, IDE	rs5015480 rs1111875	0.63	GWA	HHEX: pancreatic development; IDE: cellular processing of insulin	Insulin response	1.15	(15-17), (23-26)
11p15	KCNQ1	rs2237895	0.41	GWA	Electrical depolarization of the cell membrane	Insulin response	1.25	27, 28
11p15	KCNJ11	rs5215	0.40	Candidate	Subunit of the β-cell K+ channel, involved in insulin secretion	Insulin response	1.14	(15-17), 29, 30
11q21	MTNR1B	rs10830963	0.27	GWA (QT)	Receptor for melatonin	Insulin response	1.15	(31-33)
12q14	TSPAN8,	rs7961581 LGR5	0.27	GWA	TSPAN8: Cell surface glycoprotein LGR5: G protein-coupled receptor	Insulin response	1.09	12, 24
16q12	FTO	rs9939609	0.40	GWA	Possible hypothalamic effect	Obesity	1.17	(15-17, 34-36)
17q21	HNF1B	rs4430796 (TCF2)	0.47	Candidate	Transcription factor influencing pancreatic development	Unknown	1.10	37, 38

All loci have shown genome-wide statistical significance. Effect sizes are presented as odds ratio per allele and are based on the currently available data. OR, odds ratio; RAF, risk allele frequency.

(perfect discrimination). In such a study, Van Hoek et al[48] showed that 18 of the type 2 diabetes susceptibility variants generated an area under the ROC curve of 0.60. In a cohort study of ~19,000 subjects followed for ~23 years, Lyssenko et al[49] similarly showed an increase in AUC from 0.74 to 0.75 to predict incident type 2 diabetes when adding 16 genetic variants to conventional clinical risk factors. In 2,377 participants of the Framingham Offspring study 18 genetic variants, likewise, slightly improved the discriminative ability of basal phenotype characteristics[50]. Corresponding findings have been found in a cross sectional study[51]. Together these findings indicate that the risk variants known at present have a weak potential for prediction with no clinical relevance at this time. This lack of predictive ability may be due both to incomplete understanding of genetic risk factors as well as environmental factors not accounted for in the analyses.

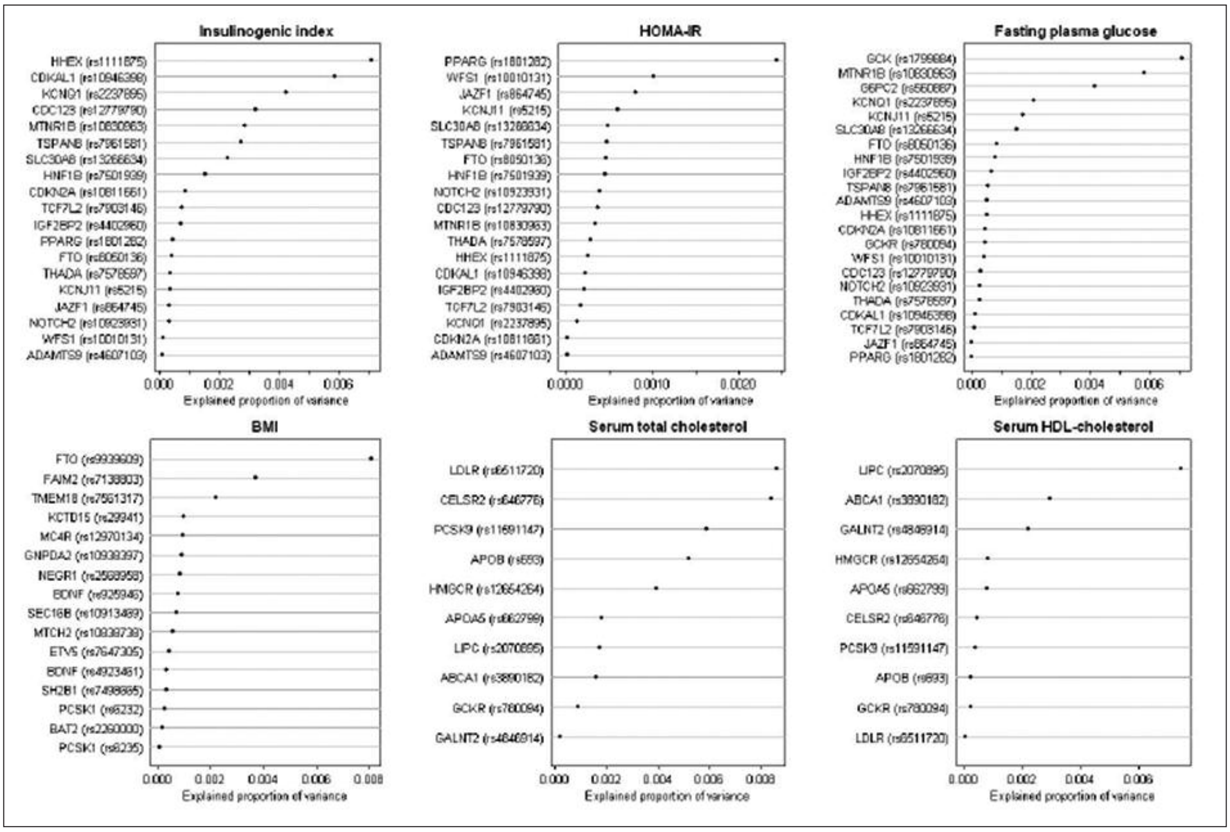

Figure 1. Explained proportion of variance for a range of diabetes-related quantitative phenotypes in the population-based Inter99 cohort including participants with normal glucose tolerance, IFG, IGT or screen-detected treatment-naive type 2 diabetes. For all traits a range of validated genome-wide significant variants is included. Analyses of insulinogenic index and HOMA-IR include validated type 2 diabetes variants and fasting plasma glucose in addition variants in GCK, G6PC2 and GCKR. Analyses of BMI and lipids included a range of validated variants for the specific trait, however not all validated variants were included (data not shown). Estimates of total variance explained by all included variants were: Insulinogenic index: 3%, HOMA-IR: 1%, fasting plasma glucose: 2.5%, BMI: 2%, serum total cholesterol: 3.5%, serum HDL-cholesterol: 1.5%. Analyses were performed using RGui.

All these data imply that even by the most optimistic estimation only a fraction of the genetic contribution to type 2 diabetes and related traits has been explained by the current validated genetic associations. This leaves a question as to why this is the case. Hence, our subsequent aim was to consider the different possibilities and identify which factor or a combination of factors can serve as explanation.

Discussion

More Low-Impact, High-Frequency Variants

As a clearer picture of the association of common nucleotide variants with common complex traits emerges it is evident that with very few exceptions all loci infer only a modest increase in risk of disease. A consequence of this is the notion that all individual GWA studies for type 2 diabetes performed; thus, far have been statistically underpowered to detect the modest effect of an individual locus[52,53]. Despite this fact, these studies have been very successful in finding new risk variants. This probably reflects the underlying genetic background in the sense that what has been identified is, besides maybe the three strongest risk-alleles, a somewhat random subset of a much larger panel of common susceptibility variants with modest impact (OR below ~1.15) on disease risk. This is underlined by the fact that merging data from three samples of the initial wave of GWA studies in the DIAGRAM consortium disclosed six new genuine low-impact variants simply by increasing statistical power and genomic coverage[12].

Despite the possibility that many more frequent, low impact variants exist, they are not likely to neither greatly increase the explained proportion of the genetic contribution neither to type 2 diabetes nor to significantly improve the area under the ROC curve for discrimination between type 2 diabetes cases and glucose-tolerant individuals. In Figure 2A, ROC curves and corresponding AUCs for three different scenarios of common variants based on simulated data are shown. These scenarios include common variants (MAF 25%) with relative risk (RR) of 1.15 combined with variants with a RR of 1.10. A RR of 1.15 and MAF of 25% is equivalent to the average type 2 diabetes variant identified thus far. Simulations were done assuming an additive genetic model since none of the validated variants identified so far seem to substantially deviate from this model[54]. Furthermore, these simulations did not incorporate possible gene-gene interaction. From the simulations it is evident that increasing the number of common type 2 diabetes variants will also improve the discriminatory ability; however, adding further variants with a very modest effect size of ~10% risk-increase per allele per SNP will not improve the AUC of the ROC curve greatly (Figure 2A). Of course, the predictive value of genetic testing, i.e. the AUC of the ROC curve consisting of solely genetic data is limited by the heritability of the trait[55].

These analyses indicated that a vast number of genuine common risk alleles are needed in order to explain type 2 diabetes and to achieve clinical value in predictive testing. This point is also illustrated using real data. In the Danish cross-sectional case-control material, increasing the genetic information from the three initially found genes (PPARG, KCNJ11 and TCF7L2) to all cur-

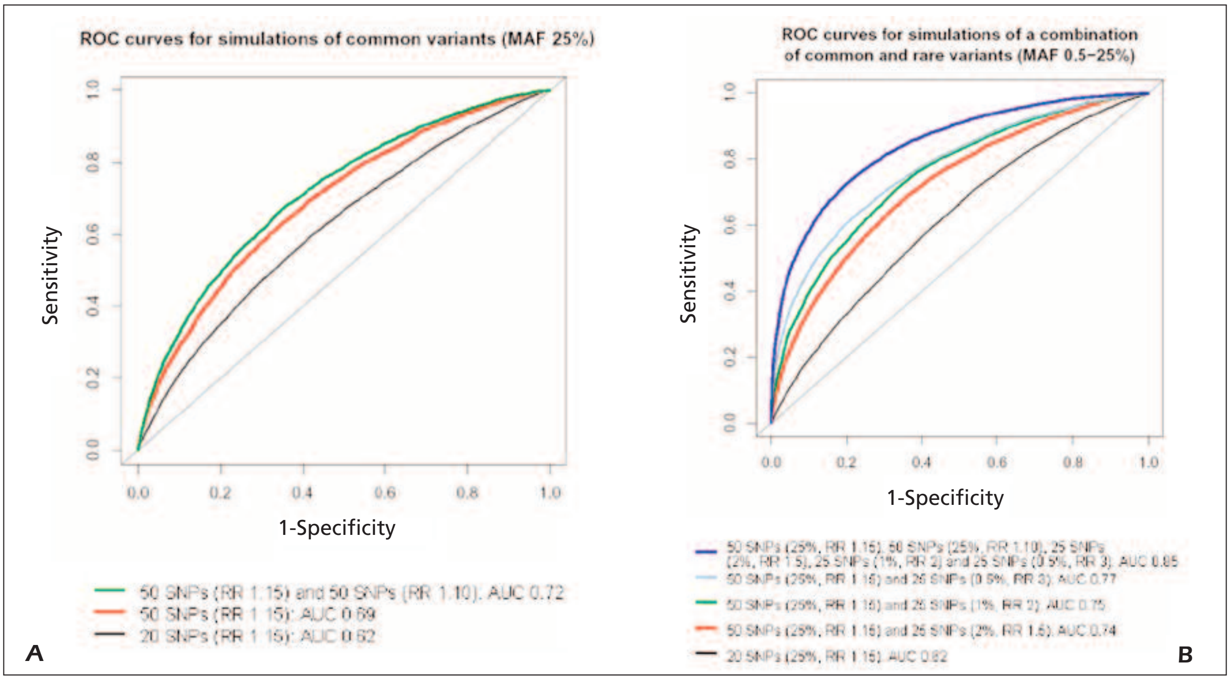

Figure 1. ***A,*** Receiver-operating characteristics (ROC) curves for simulated case-control data of common variants for three different scenarios. Black line: 20 SNPs with a minor allele frequency (MAF) of 25% and relative risk (RR) of 1.15; AUC: 0.62. Red line: 50 SNPs with MAF 25% and RR 1.15; AUC: 0.69. Green line: 50 SNPs with MAF 25%, RR 1.15 and 50 SNPs with MAF 25%, RR 1.10; AUC 0.72. Simulation of genotype data for 10,000 cases and 10,000 controls were done under the assumption of a MAF of 25% in the population, an additive genetic model and a disease prevalence of 8%. ROC was performed by logistic regression. Simulations and ROC were performed by RGui. ***B,*** Receiver-operating characteristics (ROC) curves for simulated case-control data of a combination of common and rare variants for five different scenarios. Black line: 20 SNPs with a minor allele frequency (MAF) of 25% and relative risk (RR) of 1.15; AUC: 0.62. Red line: 50 SNPs with MAF 25%, RR 1.15 and 25 SNPs with MAF 2%, RR 1.5; AUC: 0.74. Green line: 50 SNPs with MAF 25%, RR 1.15 and 25 SNPs with MAF 1%, RR 2; AUC: 0.75. Light blue line: 50 SNPs with MAF 25%, RR 1.15 and 25 SNPs with MAF 0.5%, RR 3; AUC: 0.77. Blue line: 50 SNPs with MAF 25% RR 1.15, 50 SNPs with MAF 25%, RR 1.10, 25 SNPs with MAF 2%, RR 1.5, 25 SNPs with MAF 1%, RR 2 and 25 SNPs with MAF 0.5%, RR 3; AUC: 0.85. Simulations of genotype data for 10,000 cases and 10,000 controls were done under the assumption of an additive genetic model and a disease prevalence of 8%. ROC was performed by logistic regression. Simulations and ROC were performed by R Gui.

rently validated 19 genes (Table I) only increased the area under the ROC curve from 0.57 to 0.61 (data not shown). Similar observations are found in British reports[51]. Although the main limit for future progress in finding susceptibility variants with low effect is sample size, it may prove impractical to gather sufficiently large sample sets to give a complete accounting.

Low-frequency and Structural Variants in Common Disease

Most of the studies of genetics of type 2 diabetes and related traits for the past several years have been based on the HapMap resource of sequence variation[56] forming the basis for selection of tag SNPs for candidate gene studies and for genome-wide array platforms. While HapMap offers good proxies for most common SNPs with a frequency above 5%, the coverage rapidly declines for alleles with lower frequency[57]. Such low-frequency variants may be particularly important as deleterious variants are maintained at low frequency in the population by natural selection. Also analysis of HapMap data has illustrated that rare variants are more likely to be disease predisposing than are common variants[58].

Variation below 5% in frequency can be intermediate frequent with allele frequencies above ~0.5-1%. The panel of SNPs with such a frequency can probably be characterized in the population and studied in regular association studies with due respect to considerations of statistical power. However, because of the high number of intermediate frequent variants in the population, constructing such a catalogue is a major task and the abundance of SNPs poses further statistical challenges for GWA studies[58]. Yet the relative risk of disease may be substantially larger than for common variants. It has been estimated that 30 variants with a frequency of 1% and an allelic OR of 3 could explain all the residual inherited risk of type 2 diabetes (314). In Figure 2B, are illustrations of ROC curves for a combination of common and low-frequency variations based on simulated case-control data. It is evident that the existence and identification of variants with MAF of 0.5-2% but higher allelic effect sizes (RR 1.5-3) will add significantly to enable genetic variants to predict type 2 diabetes and to explain residual risk. The simulations indicate that when combining 175 SNPs with RR between 1.10 and 3 and frequencies of 0.5-25% the AUC will increase to 0.85 making it potentially clinically useful. This ROC AUC is based solely on genetic variants and it will increase further when adding conventional clinical risk factors (e.g. BMI, fasting plasma glucose and insulin, age and family history of type 2 diabetes) to the prediction model. Also, it is possible that discoveries of specific genetic risk variants may pinpoint novel intermediate biomarkers which are stronger predictors of disease than the original genetic risk component itself[59].

All things considered, the frequency-spectrum of functional susceptibility variants in complex traits is probably wide, with ranges from rare to common even within the same susceptibility gene. Also, other types of genetic variation may contribute to common disease at the population level. Structural variants, as for instance copy-number variation (CNV), may contribute to the genetic component of type 2 diabetes. The discovery and validation of CNVs is proceeding rapidly[60,61] and a study published in 2008 showed proof-of-concept by associating a 593 kb micro deletion and micro duplication with risk of autism[62]. Yet, the importance in inheritance of common metabolic diseases remains to be determined. A fully elucidated landscape of type 2 diabetes genetics may well depict perhaps a hundred or more common variants individually with low impact on disease. Every individual harbors a combination of different risk alleles and only special compilations of these variants in combination with other genetic and non-genetic components will likely lead to disease.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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