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Genetic prediction of common diseases. Still no help for the clinical diabetologist!

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Abstract

Genome-wide association studies (GWAS) have identified several loci associated with many common, multifactorial diseases which have been recently used to market genetic testing directly to the consumers. We here addressed the clinical utility of such GWAS-derived genetic information in predicting type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) in

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Additional Information:

- The National Human Genome Research Institute (NHGRI) catalog of published genome-wide association studies <http://www.genome.gov/gwastudies>
- United States Government Accountability office. “Direct to consumer genetic test. Misleading test results are further complicated by deceptive marketing and other questionable practices”, GAO-10-847T, July 22, 2010 www.gao.gov/new.items/d10847t.pdf
- Network Italiano di Genomica in Sanità Pubblica: “La genomica in sanità pubblica” http://istituti.unicatt.it/igiene_1830.html
- Comitato Nazionale per la Bioetica, Comitato Nazionale per la Biosicurezza, le Biotecnologie e le Scienze della Vita: “Test genetici di suscettibilità e medicina personalizzata”, Presidenza del Consiglio dei Ministri, July 15 2010 http://www.governo.it/biotecnologie/documenti/Test_genetici2.pdf.
- 1000 Genomes: <http://www.1000genomes.org>

Conflict of interest

The authors declare no conflict of interest.

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diabetic patients. In addition, the development of new statistical approaches, novel technologies of genome sequencing and ethical, legal and social aspects related to genetic testing have been also addressed. Available data clearly show that, similarly to what reported for most common diseases, genetic testing offered today by commercial companies cannot be used as predicting tools for T2DM and CAD, both in the general and in the diabetic population. Further studies taking into account the complex interaction between genes as well as between genetic and non genetic factors, including age, obesity and glycemic control which seem to modify genetic effects on the risk of T2DM and CAD, might mitigate such negative conclusions. Also, addressing the role of relatively rare variants by next-generation sequencing may help identify novel and strong genetic markers with an important role in genetic prediction. Finally, statistical tools concentrated on reclassifying patients might be a useful application of genetic information for predicting many common diseases. By now, prediction of such diseases, including those of interest for the clinical diabetologist, have to be pursued by using traditional clinical markers which perform well and are not costly.

Keywords

Common; multifactorial disease; Genome-wide association studies; Genetic counseling; Direct-to-consumer testing; Ethical; legal; social issues; Diseases prediction models; Next generation sequencing

Introduction

Multifactorial, common, diseases are caused by the combination of many environmental and genetic and factors with the latter being mostly unknown. Since 2006, more than 950 genome-wide association studies (GWAS) have been carried out by analyzing hundreds of thousands of single-nucleotide polymorphisms (SNPs) in very large samples [1; 2] which have identified several loci associated with many common diseases [<http://www.genome.gov/gwastudies>].

GWAS have addressed only common variants (i.e. minor allele frequency, MAF, > 5%) and have shown they have moderate effect with each allele increasing disease risk only by 10–50% (odds ratios, ORs, ranging 1.10–1.50)[2] ; thus, a large number of loci are needed to significantly influence any single disease.

Based on these results, in the last 2–3 years we have faced the explosion of commercial ventures which are marketing GWAS-based genetic testing directly to the consumers (DTC) for medical purposes.

The possibility of using these data for predicting the development of common diseases is intriguing; in fact, in contrast to clinical markers, genetic markers do not change with time and might help identify high risk subjects several decades before disease onset so that early preventive programs can be implemented.

The aim of the present article is to address the issue of clinical utility of genetic information in predicting T2DM and coronary artery disease (CAD) in diabetic patients. Several collateral, but extremely important, issues including the development of new statistical approaches and novel technologies of genome sequencing which will be largely available in the close future and ethical, legal and social aspects generated by such testing will be also addressed.

Prediction of T2DM

T2DM is a classical example of a common disease in which both genetic and non genetic factors play a pathogenic role [3–5].

In the last 5 years several GWAS have identified more than 40 loci with modest effects (i.e. ORs, ranging 1.10–1.40) which are strongly associated with T2DM. Most of these are likely to modulate insulin secretion while a few are related to obesity and/or insulin resistance [3]. Unfortunately, as for many other common diseases, data from GWAS explain only a small proportion of T2DM genetic background, thus leaving a high proportion of missing heritability yet to be unraveled [3]. This may well be due to some intrinsic characteristics of the genetic background of T2DM which have not been addressed by study designs so far utilized. Firstly, it has been recently reported that heritability for T2DM is higher in patients with disease onset in the range of 35–65 yrs than in those diagnosed at older age [6]. Secondly, both gene-gene [7] and gene-environment (i.e. diet) [8; 9] interaction has been reported to modulate the risk of T2DM. Thus, concentrating our future efforts on specific subset of patients according to their clinical features including age at diabetes onset [6, 10–12] as well as taking into account the role of gene effect “modifiers” (including the protective effect on body weight of whole grain intake [13] is likely to help unravel, at least partly, the yet unknown genetic background of T2DM. Given the yet preliminary status of our understanding of the genetics of T2DM, it is not surprising that using GWAS data for predicting T2DM in the clinical set has been frustrating [12, 14–18] (Table 1). While most of these studies [12, 14–17] described a strongly significant association between a GWAS data-derived genetic risk score and the development of future T2DM (with an increased allelic risk ranging 4–12%), none of them turned out to be of clinical utility in predicting incident events when genetic information was added to models based on classical, non genetic factors.

Prediction of CAD in patients with T2DM

Atherosclerosis too is heavily influenced by genes, with 30 to 50% of its variance being accounted for by heritable factors [19–21]. Thus, genetic markers could also be used to predict the risk of vascular complications in the general population as well as among diabetic subjects. In this latter subgroup, great effort has been dedicated to coronary artery disease (i.e. CAD), a principal cause of increased morbidity and mortality in T2DM [22].

One strategy has been to search for such genetic markers among GWAS-derived loci associated with CAD in the general population [23–28].

In a joint analysis of the Joslin Heart Study (JHS), the Nurses Health Study (NHS), and the Health Professional Follow-up Study (HPFS), five of these loci were found to be associated with CAD also among individuals with T2DM (Table 2) [29].

While the effect of each genetic variant was as modest as in the general population, considered jointly these five loci had an influence on CAD risk among diabetic subjects similar in size to that of major cardiovascular risk factors. Carriers of more than eight risk alleles at any of these five loci (about 20% of the diabetic population) had a two-fold increase in CAD risk as compared to carriers of less than five risk alleles (about 30% of the diabetic population). This effect, however, did not translate into a large improvement in risk discrimination over that provided by clinical predictors of CAD. The area under the ROC curve (AUC-ROC; see below for methodological details) was 0.59 for the five loci considered together as compared to 0.70 for the clinical model. Addition of the five loci to the clinical predictors produced only a small, though statistical significant, increase in AUC-ROC (from 0.70 to 0.715; $p=0.001$). The improvement in risk prediction seemed somewhat

more substantial when expressed as Net Reclassification Improvement (NRI; see below), with about 15% of diabetic individuals being correctly reclassified into the correct risk group by the addition of genetic information in the predictive model.

Another approach to identify genetic predictors of CAD in diabetes has been based on the “common soil hypothesis”, which postulates that insulin resistance and T2DM share some of their genetic background with coronary artery disease [30]. On this basis, one recent study has evaluated whether loci that have been found to date to be associated with T2DM may also predict CAD events [31]. A genetic risk score based on the 38 T2DM loci was associated with a modest increase in the risk of incident CAD (OR per score tertile=1.08, $p=0.02$). However, this effect lost its significance after adjustment for diabetes status (OR per score tertile=1.05, $p=0.09$), indicating that most of the predisposing effect on CAD was mediated by the increased risk of T2DM. The AUC-ROC was unaffected by the addition of this genetic score to a clinical model. These negative results may have been due to the fact that the T2DM genes identified to date are mostly involved in insulin secretion rather than insulin action. In this regard, genes involved in insulin signaling, such as *ENPP1*, *IRS1*, and *TRIB3* have yielded better results. In three cohorts of subjects at high cardiovascular risk, about half of whom with diabetes, a risk score based on three non-synonymous variants placed in these genes and previously reported to be associated with insulin-resistance [32–34] predicted cardiovascular events with an hazard ratio per risk allele equal to 1.18 ($p=0.0009$). The risk score improved the survival AUC-ROC from 0.678 to 0.688 in the overall population and from 0.759 to 0.789 among obese subjects, and determined the reclassification in the correct risk group of 18% of study subjects, which went up to 59% in the obese subgroup (V. Trischitta, personal communication). Along the same line a recent study reported that variability at the *FTO* obesity locus is associated with cardiovascular events in people with abnormal glucose homeostasis [35]. These studies, though preliminary, stresses how important may be to look at the effect of genetic variability occurring in specific pathways known to modulate disease risk.

Despite these somewhat encouraging results, the efforts to improve the prediction of cardiovascular disease in diabetic patients by means of genetic markers have not met the expectations. Very similar negative results have been obtained also in the general population [36]. At least among diabetic patients such negative conclusions should be mitigated by the possibility that as yet unidentified genetic factors that predispose to CAD specifically in the presence of T2DM do exist. Identification of these genes through GWAS specifically targeted to the diabetic population may provide more powerful tools to predict CAD risk in these subjects.

New statistical tools for predicting complex diseases

Because of the specific scope of this review article, the present section is mainly focused on the novel measures of classification/prediction ability which allows taking into account the interplay between genetic and clinical risk factors. In contrast, because of space constrain, important aspects related to how to address gene-environment interactions [37–41] are not discussed here.

A clinical model performs well when subjects who will experience say a cardiovascular event receive a higher probability of such event than subjects who will not. To this purpose, the simple statistical significance (i.e. based on p-values) which may be obtained in presence of large sample studies regardless of clinical relevance, is not appropriate [42].

Alternative established approaches such as the geometrical area under a receiver-operating-characteristic curve (AUC-ROC) which contrasts the false positive and true positive rates by the different cut-points for predictive probability of the event) The perfect classification,

therefore, corresponds to a AUC-ROC equal to one, while the minimum value they can assume is 0.50 (corresponding to classification by chance, say, as if determined by the toss of a coin). Unfortunately, AUC-ROC are scarcely sensitive to the inclusion of new risk predictors (i.e. genetic information) within a well-established clinical model [42].

Another common criterion to define an accurate predictive tool is the ability of measuring the agreement between observed and predicted proportion of events in the whole sample, known as calibration [42]. Indeed, high discriminatory capacity of individuals at high or low risk (i.e. an AUC-ROC close to 1) does not necessarily correspond to high ability to estimate disease probability in the whole sample (i.e. good calibration).

Greater attention has been recently given to novel indices which are focused on what a new marker can actually add to clinically-established prediction models (i.e. the ability in reclassifying what had been incorrectly classified before) [42, 43] namely Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI). IDI is defined as a difference in the means of the model-based event probabilities, that is a subtraction of the nonevents from the events. IDI has been proved to be closely related to the R-square.

Suppose we have mean predictive values p for the old model (i.e., the clinically established model; Old) and the new model (i.e. the model which includes, say, the genetic factor whose added value we want to assess; New) separately for subject with (D) and without (ND) disease, that is respectively: $p_{Old,D}$, $p_{New,D}$, $p_{Old,ND}$, $p_{New,ND}$, absolute IDI corresponds to $(p_{New,D} - p_{Old,D}) - (p_{New,ND} - p_{Old,ND})$, while relative IDI is $(p_{New,D} - p_{Old,D}) / (p_{New,ND} - p_{Old,ND}) - 1$.

NRI assesses the correct movement (upward for diseased and downward for non-diseased) in pre-defined categories of the predicted values based on reclassification tables built separately for subjects with and without disease. A worked example is as follows. In a sample of 177 obese patients with T2DM (extracted from the Gargano Heart Study, prospective design [44]) a clinical model, including baseline patients' age, gender, smoking status, BMI and presence of hypertension, was used to predict incident major cardiovascular events. As a didactic example of NRI as compared to ROC curves, we here assess the improvement in model performance introduced by the inclusion of *ENPP1* K121Q genotype, a functional aminoacid change which is associated with insulin resistance [32]. For simplicity of presentation, all performance measures are assessed for a binary outcome, ignoring follow-up time. The ROC curves for the model without and with K121Q genotype are presented in Figure 1. The corresponding AUROC-OCs were 0.82 and 0.86, with the difference being not statistically significant (p-value=0.228). For NRI, three risk categories of potential clinical utility (i.e. low, medium, high risk) were created and used for both the old model and the new model. Table 3 cross-classifies subjects who experienced (i.e. patients, upper panel) or not (lower panel) cardiovascular events. For patients, the upper off-diagonal elements (light grey background) represent those who were reclassified correctly (i.e. into a higher category of risk by the new model); in contrast, the lower off-diagonal elements (dark grey background) are patients who were reclassified incorrectly. A symmetrical approach is used for the non-diseased subjects with the new model performing better if it reclassifies non-diseased subjects into lower category of risk. NRI is obtained by the sum of these differences between correct and incorrect reclassification. In the upper panel, classification on the new model improved for 4 and became worse for 1 patient, with the net gain in reclassification proportion of 13% (3/23). In the lower panel (i.e. non-diseased individuals), 50 individuals were reclassified correctly down and 23 were reclassified incorrectly up with the net gain in reclassification proportion of 17.5% (27/154). Overall, the NRI was estimated as 30.5% (i.e. 13+17.5) and was highly significant (p-

value=0.006), that is the new model including *ENPP1* K121Q genotype correctly reclassifies in the correct risk group 30.5% individuals of the whole sample. This didactic example serves the important function to show how new statistical tools, focused on what a new marker can add to clinically-established models, may provide novel and possibly alternative information as compared to classical tools. In conclusion, although strengths and weaknesses of their application are still matter of ongoing research [45, 46], IDI and NRI now do belong to the standards for transparent reporting of genetic risk prediction studies [47].

New technologies of genome sequencing

Beside the “common disease-common variants hypothesis”[48], the “common disease-multiple rare variants hypothesis”, in which few rare alleles are determining a large effect [2, 49], is also believed to underlie the genetic background of common diseases.

To capture such rare variants, it will be necessary to sequence entire genomes, instead of genotyping a catalogue of variants. Until recently, this was a daunting task.

The automated sequencing (also known as “automated Sanger sequencing”) had dominated the research in the genetic field for almost two decades, leading to a number of monumental accomplishments, including the completion of the only “finished-grade” human genome sequence [50]. However, the limitations of Sanger sequencing, due to the small size of fragments to be run beyond the specific sequencing primer and to the long time required to sequence discrete chromosomal regions, have called for new technologies able to massively sequence large numbers of human genomes in a reasonable time, referred to as Next-Generation Sequencing (NGS).

NGS technologies, which include a number of methods that are grouped broadly as template preparation, sequencing, imaging and, finally, data analysis, have the potential to discover the entire spectrum of sequence variations. The unique combination of specific protocols distinguishes one technology from another and determines the type of data produced from each platform [51].

Today’s commercially available platforms are typically able to generate tens or hundreds of Giga bases (i.e 1Gb=10⁹ bases) of short reads sequence. As a result, the average NGS experiment generates terabytes (i.e 1Tbyte=10¹² bytes) of raw data, making data analysis and management particularly laborious. Given the vast amount of data produced by NGS, developing a massive data storage and management solution and creating informatics tools to effectively analyze data is essential to the successful application of this technology [51].

The ability to sequence the whole genome of several individuals, as for the “1000 Genomes Project” [52], in which whole genomes from 1,000 individuals of several ethnicities have been entirely sequenced have already revolutionized our knowledge in terms of numbers of genes or genomic regions actually known involved in the pathogenesis of several human diseases including both Mendelian and complex disease [53,54]. A major advance offered by NGS is the ability to produce an enormous volume of data at reasonable cost (~7,500 US \$ for a whole genome; ~ 2,500 US\$ for an exome).

NGS technologies are not restricted to the only DNA sequencing. A variety of additional application are actually available for the analysis of chromatin immunoprecipitation coupled to DNA microarray (ChIPchip) or sequencing (ChIP-seq), for RNA sequencing and quantification (RNAseq), for profiling of epigenetic marks, including analysis of methylation (methyl-seq and DNase-seq) [51].

Overall, there is no doubts that, thanks to NGS, the rapidly evolving field of genomics is dramatically changing our understanding of many diseases, by documenting the large pathogenic contribution of human genomic variations.

Ethical, legal and social issues

So far, we have provided clear evidences that genetic testing is not clinically useful for predicting T2DM and CAD in diabetic patients. Very similar conclusions can be drawn for most common diseases [55].

Nonetheless, as a likely consequence of the several Web-mediated commercial ventures, DTC genetic testing is becoming more and more familiar to patients and clinicians.

A critical appraisal of such commercial tests, based on predictive genomic profiling offered by seven companies, pointed out that there was “insufficient scientific evidence to conclude that genomic profiles are useful in measuring genetic risks for common diseases or in developing personalized diet and lifestyle recommendations for disease prevention” [55].

More recently, the United States Government Accountability Office (GAO) has evaluated the results of DTC genetic testing on five donors, including 10 tests, purchased from four companies. Fifteen common diseases that were tested, including CAD and T2DM. Two DNAs samples from each of five donors were sent to the four companies, one using factual information about the donor, and one using fictitious information, such as incorrect age and race or ethnicity. The GAO’s fictitious consumers received test results that were misleading and contradictory across the four companies and of little or no practical use. For example, one donor was told that he was below-average, average, and above average risk for prostate cancer and hypertension. In addition, DNA-based disease predictions conflicted with the actual medical conditions. For example, a patient who had a peacemaker implanted 13 years before to treat an irregular heartbeat, was defined at low risk for developing this condition. Finally, three companies failed to provide an expert advice. These observations suggested that although these tests show promise for the future, the consumers should not rely on any of these results at the present time [www.gao.gov/new.items/d10847t.pdf]. The Italian Network of Public Health Genomics has collected available knowledge on the potential use of genomics for preventing complex diseases and highlighted a number of principles that should direct the access to genomic information and services [http://istituti.unicatt.it/igiene_1830.html]. This document concluded that the predictive value of most markers identified so far is insufficient to meet the standards for clinical use.

Specific concerns on DTC genetic testing have been raised also by the European Society of Human Genetics [56] and by the Italian Committee for Bioethics and the National Committee for Bio-security, Biotechnology and Life Sciences (http://www.governo.it/biotecnologie/documenti/Test_genetici2.pdf) has reached similar conclusion on DTC. It is also of note that awareness of genetic risks may have negative social consequences, in terms of stigma, employment, insurance or other. Also personal consequences have to be taken into proper account. While it has been reported that genetic testing for common diseases would make patients much more motivated to adhere to medications [57], there are no data about the psychological harm that such tests may cause in both users and their relatives with increased asking for costly medical advices and laboratory testing. So, appropriate studies are definitively needed to assess both benefits and harms of such type of information [58].

Finally, is the general practitioner (GP) or the specialist who should help the direct consumer to manage such genetic information? Should the specialist be a non-genetic clinicians (i.e. diabetologist and/or cardiologist in our case) or a clinical geneticist? Are these clinicians trained to independently do their job or do they need to collaborate? In this

respect, it is likely that genomic knowledge needs to be increased for all health professionals [59] with core competences being different for primary (GP), secondary (non genetic specialist) and tertiary (genetic specialist) care [60].

In conclusion, advances in the comprehension of the genetic background of common diseases have generated a number of ethical, legal and social implications which tend to be overlooked in the rush to have these genetic tests spread in the market.

Improved public and professional knowledge about genetics of common diseases definitively needs to be paralleled by adequate assessments of such implications if translation of genetic testing into clinical care with a most favorable benefits-to-harms ratio is our ultimate goal for the near future.

Perspective and conclusion

Available data clearly indicate that genetic testing offered by commercial companies cannot be used for predicting most common, multifactorial diseases, including T2DM and cardiovascular disease [55, 61]. This is mainly due to the fact that genetic data thus far obtained refer mostly to common variants with modest effect size in a scenario where a large proportion of disease risk is under the control of environmental factors. Further discovery of yet unidentified predisposing genetic factors might importantly change the present scenario. These new discoveries are likely to take place by the use of novel study designs and tools which are here briefly listed.

Firstly, when creating prediction models in which genetic factors are considered, it should be taken into account the complex gene-gene interaction that might occur in modulating common diseases and which has been, in fact, suggested for T2DM [7].

Secondly, the interaction between genetic and non genetic factors should be also taken into account. In fact, preliminary evidences point to age [10, 12], body mass index [7, 11, 44, 62, 63] and glycemic control [64] as potential modifiers of genetic effect on the risk of T2DM [7, 10–12, 62] and cardiovascular disease [44, 64].

Third, new statistical tools concentrated in reclassifying patients subgroup of patients might also play a role in rendering GWAS-derived genetic testing clinically useful for predicting many common, multifactorial diseases.

Finally, all the GWAS conducted to date have been focused on relatively common variants with minor allele frequency generally greater than 5%. The study of less frequent variants, such as those included in the recently released ExomeChip or identified by ad hoc re-sequencing efforts using NGS (see above), may lead to the identification of stronger genetic effects, which may have a larger aggregate impact on risk discrimination of both T2DM and cardiovascular disease than that offered by common variants.

By now, prediction of such diseases, including those of interest for the clinical diabetologist, have to be pursued by using traditional clinical markers which perform well and are not costly.

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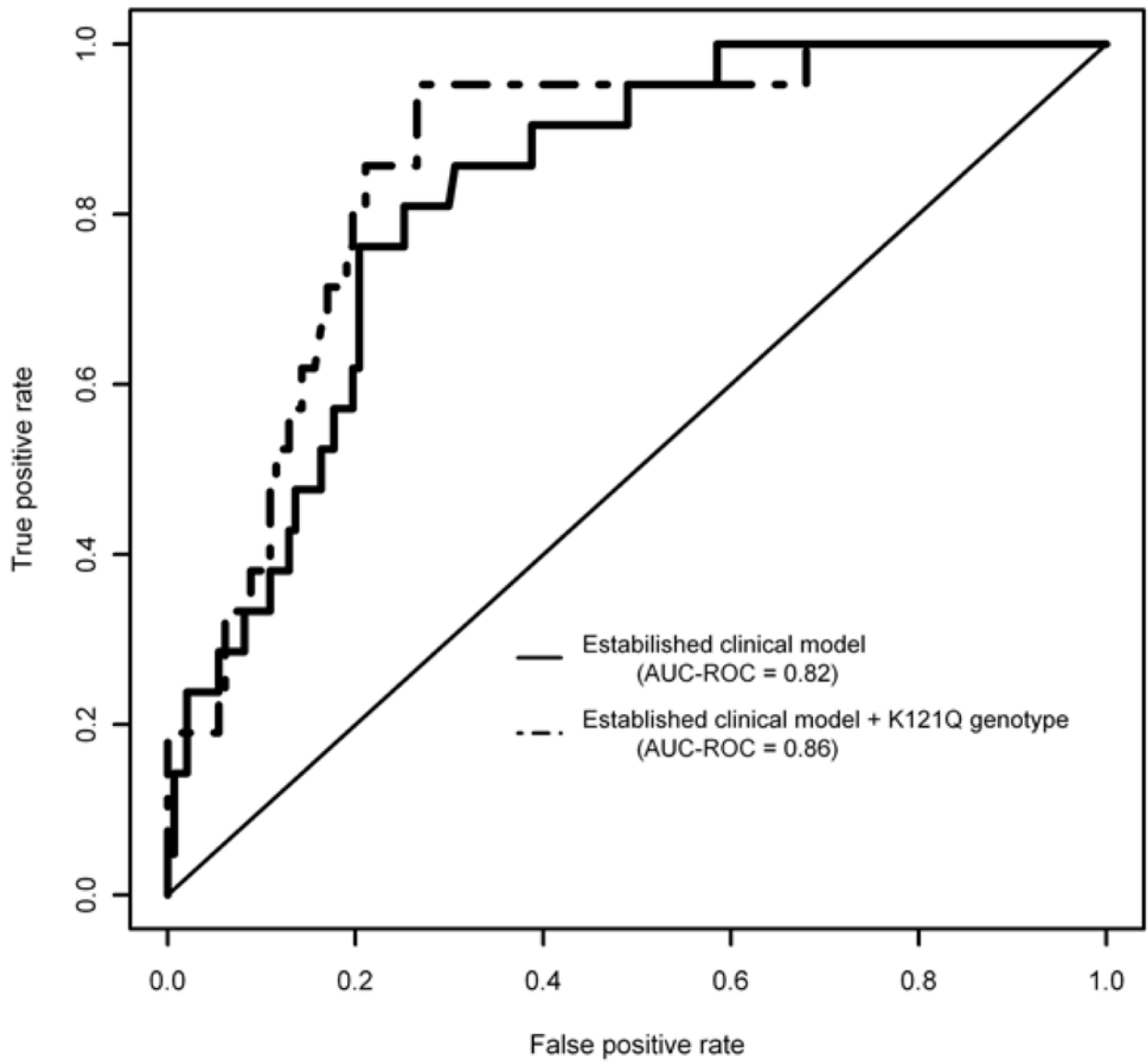


Figure 1. AUC-ROC curves for cardiovascular events probabilities estimated by a clinical model, including baseline patient's age, gender, smoking status, BMI and hypertension and by the same model plus ENPP1 genotype.

Table 1

Genetic prediction of incident T2DM in prospective studies

Study	Subjects (n)	SNPs (n)	AUC-ROC		
			Genetic model	Clinical model	Both models
MPP+Botnia Study (14)	18,831	11	0.62	0.74	0.75*
FOS (15)	2,377	18	0.58	0.9	0.901*
DESIR (16)	3,877	3	0.56	nr	nr
Rotterdam Study (17)	6,544	18	0.6	0.66	0.68*
Whitehall II Study (18)	5,535	20	0.55	0.78	0.78
FOS (12)	3,471	40	0.6	0.903	0.906*

MPP: Malmoe Preventive Program

FOS: Framingham Offspring Study

DESIR: Data from the Epidemiological Study on the Insulin Resistance Syndrome

AUC-ROC: area under the receiver-operating-characteristic curve

nr: not reported, though assessed

* = significantly different as compared to clinical model

Table 2

Associations with CAD of previously reported SNPs in the general population and in T2DM.

Locus	Closest Gene(s)	Risk allele	General Population		T2DM [†]	
			OR (95%CI)	Ref. (n)	OR (95%CI)	P value
9p21	CDKN2A/CDKN2B	G	1.29 (1.25–1.34)	(23; 24; 65; 66)	1.21 (1.08–1.35)	0.0007
6p24	PHACTR1	C	1.12 (1.08–1.17)	(65)	1.25 (1.10–1.41)	0.0002
1p21	CELSR2-PSRC1-SORT1	T	1.19 (1.13–1.26)	(23; 65)	1.17 (1.02–1.34)	0.03
12q24	HNFI A	T	1.08 (1.05–1.11)	(25)	1.17 (1.04–1.32)	0.0048
1p32	PCSK9	T	1.15 (1.10–1.21)	(65)	1.26 (1.09–1.47)	0.0013

[†]Data are from the study by Qi et al. (29)

Table 3

Reclassification among people who experienced or not incident cardiovascular event during follow-up.

Old model (without genetic information)	New model (with genetic information)			Total
	Low risk	Medium risk	High risk	
Frequency				
<i>Participants with event</i>				
Low risk	2	0	0	2
Medium risk	1	0	4	5
High risk	0	0	16	16
Total	3	0	20	23
<i>Participants without event</i>				
Low risk	55	8	0	63
Medium risk	38	2	15	55
High risk	3	9	24	36
Total	96	19	39	154

Light grey background cells represent patients who were reclassified correctly, while dark grey background cells represent patients who were reclassified incorrectly (see also the text for further details).