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REVIEW

Genetics of Type 2 Diabetes: It Matters From Which Parent We Inherit the Risk

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■ Abstract

Type 2 diabetes (T2D) results from a co-occurrence of genes and environmental factors. There are more than 120 genetic loci suggested to be associated with T2D, or with glucose and insulin levels in European and multi-ethnic populations. Risk of T2D is higher in the offspring if the mother rather than the father has T2D. Genetically, this can be associated with a unique parent-of-origin (PoO) transmission of risk alleles, and it relates to genetic programming during the intrauterine period, resulting in the inability to increase insulin secretion in response to increased demands imposed by insulin resistance later in life. Such PoO transmission is seen for variants in the *KLF14*, *KCNQ1*, *GRB10*, *TCF7L2*, *THADA*, and *PEG3* genes. Here we describe T2D susceptibility genes associated with defects in insulin secretion, and thereby risk of overt T2D. This review emphasizes the need to consider distorted parental transmission of risk alleles by exploring the genetic risk of T2D.

Keywords: type 2 diabetes · risk allele · parent-of-origin · SNP · single nucleotide polymorphism · heritability

1. Introduction

Type 2 diabetes (T2D) is an emerging epidemic today, estimated to affect more than 517 million people worldwide in 2015. Projections show that there will be 592 million people with this lifelong chronic disease in 2035. It is also estimated that there are 3-4 times more people with undiagnosed diabetes (http://www.idf.org/diabetesatlas). The accelerating incidence and prevalence of diabetes is inevitably associated with an increasing number of patients who develop devastating diabetic complications. Today, T2D is diagnosed on the basis of elevated fasting and/or postprandial glucose levels above a diagnostic threshold. However, the majority of patients has elevated glucose levels for many years before diagnosis. We and others have previously reported that the strongest risk factors associated with diabetes development include obesity, elevated fasting and/or postprandial glucose levels, dyslipidemia, and blood pressure [1, 2].

Although insulin resistance has been postulated as the driving force in the pathogenesis of T2D, using data from the large, prospective BOTNIA Study with longitudinal measurements of insulin secretion, we demonstrated that a decline in insulin secretion adjusted for the degree of insulin sensitivity is the key factor contributing to overt diabetes [3]. We and others have also reported α-hydroxybutyrate, linoleoyl-glycerophosphocholine, and copeptin as novel biomarkers to be associated with increased risk of T2D [4, 5]. However, these new biomarkers require a systematic evaluation and validation across different studies and populations before their actual diagnostic and prognostic value is confirmed. Among all risk factors for T2D, family history of diabetes consistently confirms a 1.5-3.0 fold increased risk for T2D in both cross-sectional and longitudinal studies [1-3, 6]. It has

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also been demonstrated that the risk for T2D is twice as high if the mother had diabetes [6]. However, the underlying mechanism for this parental transmission is largely unknown.

Here we describe T2D susceptibility genes associated with defects in insulin secretion, and thereby risk of overt T2D. This review emphasizes the need to consider distorted parental transmission of risk alleles by exploring the genetic risk of T2D.

2. Heritability of T2D and related metabolic risk factors

Relative genetic risk described as lambda (λs) is the risk of a patient's sibling developing the disease compared to the background population. For T2D, it is estimated to be approximately 3-fold greater than the risk of the general population. However, this figure represents only an average estimate over families with a clustering of different etiologies and pathogeneses. Earlier linkage studies in BOTNIA families have reported a linkage peak on chromosome 12 which was not seen until families were stratified for insulin-deficient phenotypes [7]. Similarly, the most replicated linkage peak on chromosome 18 was observed only after the data were stratified by BMI [8]. This underlines that the contribution of different risk factors varies across families and, thus, heritability estimates may be even larger when the underlying pathophysiology of the disease is taken into account. Another factor decisive in the heritability of T2D is age. Heritability estimates for T2D are reported to be strongest for the age group between 35-60 years [9].

Narrow-sense heritability estimates (h^2) for insulin secretion range from 20% to 88% in the published reports. Recent studies also reported a high heritability component of incretin-potentiated insulin secretion [10, 11]. Among other metabolic risk factors, lipids, specifically the suppression of plasma non-esterified fatty acids during oral glucose tolerance test (OGTT), showed the highest heritability of 63% to 76% [9].

3. Genetic risk factors for type 2 diabetes

During the last decade, progress in dissecting the genetic architecture of type 2 diabetes has been mostly made by unbiased and simultaneous assessment of a large number of common and rare genetic variants across the genome, so-called genome-wide association studies (GWAS) [12]. Prior to the GWAS era, a few successful studies using case-control, family, and linkage approaches have been performed and identified variants in *PPARG*, *KCNJ11*, *TCF7L2*, and *WFS1* genes to be robustly associated with increased susceptibility for T2D [12]. Today, more than 120 genetic loci have been discovered to be associated with T2D or glucose and insulin concentrations in European and multiethnic populations [13].

However, our understanding of the precise mechanisms by which these genetic loci contribute to T2D susceptibility is incomplete. One obstacle relates to the difficulties in identifying a causal variant responsible for the observed effects. Functional consequences of non-coding variants have been challenging to investigate. A successful example, where molecular mechanisms have been addressed in detail, includes genetic variation in transcriptional factor 7 like 2 (*TCF7L2*) which has so far provided the strongest statistical association with T2D [12]. The mechanisms by which genetic variants in the *TCF7L2* gene increase the risk of T2D seem to involve a multiple-tissue model, predominantly exhibiting effects in the pancreatic islets [14, 15] and possibly liver [16]. Another example includes the gene associated with fat mass and obesity, *FTO*. Large epidemiological Mendelian

Abbreviations:
CDKN1C – cyclin-dependent kinase inhibitor 1C
GRB10 – growth factor receptor-bound protein 10
FTO – fat mass- and obesity-associated gene
IGF2 – insulin like growth factor 2
IRX3, *IRX5* – iroquois homeobox 3, iroquois homeobox 5
GWAS – genome-wide association studies
H19 – H19, imprinted maternally-expressed transcript
KCNJ11– potassium channel, inwardly recrifying subfamily J, member 11
KCNQ1 – potassium channel, voltage-gated, KQT-like subfamily, member 1
KLF14 – Krüppel-like factor 14
MAGIC – Meta-Analyses of Glucose and Insulin-Related Traits Consortium
MOB2 – MOB kinase activator 2
MTNR1B – melatonin receptor 1B
mTORC1 – mammalian target of rapamycin complex 1
OGTT – *oral glucose tolerance test*
PEG3 – paternally expressed 3
PoO – parent-of-origin
PPARG – peroxisome proliferator-activated receptor gamma
shRNA – small hairpin RNA
SNP – single nucleotide polymorphism
THADA – thyroid adenoma associated
TCF7L2 – transcriptional factor 7 like 2
T2D – type 2 diabetes
WFS1 – Wolfram syndrome 1

randomization studies demonstrated causal effects of an *FTO* variant on the risk of T2D, and showed that FTO-associated risk of metabolic diseases is mediated via body mass index (BMI) [17]. Later, cis-effects of *FTO* on transcriptional regulation were found to be operated via *IRX3* and *IRX5* genes located approximately 500 kb downstream of the *FTO* gene [18]. Very recently, a study unraveled the molecular mechanisms by which *FTO-IRX* genes act on the risk of obesity and T2D, involving effects on thermogenesis and browning of adipose tissue [19].

4. Genetic risk factors for insulin secretion

Defects in beta-cell function and the inability to increase insulin secretion in response to increased insulin resistance represent the pivotal mechanisms in the pathogenesis of T2D. We have demonstrated that carriers of the risk variants in T2D-susceptibility genes were not able to improve their insulin secretion in response to decreased insulin sensitivity [1]. In addition to the effects on beta-cell function, we have shown that many of these variants are associated with glucagon secretion and alterations in islet function, and thereby affect glucose concentrations [20].

In our first GWAS of T2D, performed by the Diabetes Genetic Initiative, we analyzed quantitative traits such as insulinogenic and disposition indices. We identified a common variant in the melatonin receptor 1B (*MTNR1B*) gene (rs10830963) that was associated with impaired early insulin response to glucose during OGTT and 1.11-fold increased risk of future T2D [21]. The risk allele in the *MTNR1B* gene had a profound effect on impaired early insulin release in response to both oral (insulinogenic and disposition index) (effect size, beta ± SEM: -0.170 ± 0.021, $p = 5\times10^{-6}$, and -0.241 ± 0.022, $p = 5\times10^{-26}$, respectively) and intravenous (first-phase insulin response) glucose challenge (-0.065 ± 0.023, p = 0.004). Also, risk allele carriers maintained reduced insulin secretion over a 7-year follow-up period (insulinogenic index at baseline: -0.160 ± 0.026, $p = 6\times10^{-10}$ and at follow-up: -0.188 ± 0.026, $p = 1\times10^{-12}$) compared with non-risk allele carriers [21].

Supportively, studies from the Diabetes Prevention Program demonstrated that carriers of the *MTNR1B* rs10830963 risk variant exhibited a sustained impairment in early insulin release over a one-year period despite adjustment for the baseline trait, suggesting a progressive deterioration of the effect at this locus [22]. In our recent GWAS meta-analysis, investigating dynamic measurements of insulin secretion during OGTT in more than 10,000 non-diabetic individuals of European descent, *MTNR1B* rs10830963 was confirmed as the strongest signal (insulinogenic index, beta ± SEM: -0.17 ± 0.16, $p = 7\times10^{-28}$) for first-phase insulin secretion [23]. We have also shown that *MTNR1B* mRNA was expressed in human pancreatic islets. More specifically, non-diabetic individuals carrying the risk allele (mean ± SEM, GG: 3.773 ± 1.593, CG: 1.399 ± 0.380, CC: 0.457 ± 0.089, p = 0.001) and patients with T2D (5.00 5 ±0.475 vs. 3.142 ± 0.980, p = 0.14) display increased expression of the receptor [21]. These findings were further confirmed by a large gene-expression analysis of human pancreatic islets [24].

In line with inhibitory effects of exogenously administered melatonin on insulin secretion in rodents [7], we have shown that melatonin inhibits insulin release in response to glucose in INS-1 rat beta-cells. As expected from the pronounced effect of *MTNR1B* rs10830963 on fasting glucose levels (beta, 95% CI: 0.09 (0.07-1.1), $p = 1\times10^{-21}$) [25], the risk alleles significantly increased the risk of isolated impaired fasting glucose (OR, 95% CI, 1.64 (1.41-1.89), $p = 5.5\times10^{-11}$), but not the risk of isolated impaired glucose tolerance (95% CI 0.85 (0.72-1.00), p = 0.051) [26]. The same SNP was shown to impact the rate of progression from normal fasting glucose to impaired fasting glucose (95% CI 1.35 (1.281-1.42), $p = 5\times10^{-31}$), with an opposite effect on the rate of progression from impaired fasting glucose to T2D (95% CI 0.88 (0.81-0.95), p = 0.001) [27]. In addition to their effects on insulin secretion and isolated impaired fasting glucose, variants in the *MTNR1B* gene were also reported to be associated with hepatic glucose production (n = 77, beta, 95%CI: 0.4 (0.07-0.6), p = 0.017) [26, 28].

Notably, the risk carriers of *MTNR1B* were clear outliers when the known hyperbolic relationship between insulin secretion and the degree of insulin sensitivity was plotted [20]. This result suggests that the given impairment in insulin secretion is driven by a strong insulin-resistant phenotype. Furthermore, this scenario could also involve the islet-incretin axis as carriers of the *MTNR1B* variants were shown to be associated with increased incretin-stimulated insulin secretion [29]. Presently, studies are ongoing to evaluate whether administration of melatonin in carriers of the risk alleles in the *MTNR1B* gene is unwarranted, and may result in increased glucose levels.

5. Genes for type 2 diabetes and parent-of-origin effects

5.1 Growth factor receptor-bound protein 10 (GRB10)

Although impaired beta-cell function represents the key defect leading to overt type 2 diabetes, there are only a few large-scale studies that investigated genetic determinants of insulin secretion. To address this issue, the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) has performed GWAS meta-analyses for dynamic measurements of insulin secretion measured during OGTT in 10,831 individuals of European descent [23]. The analyses identified a variant in the imprinted growth factor-bound protein 10 (*GRB10*) gene to be associated with decreased early-phase insulin secretion. The association was stronger in females (insulinogenic index measured as corrected insulin response (CIR), beta ± SEM: -0.110 ± 0.019, $p = 1.52\times10^{-8}$) than in males (-0.038 ± 0.012, p = 0.0012, heterogeneity p = 0.0016) [23]. For the parental transmission of the risk alleles, we observed the following maternal parent-of-origin (PoO) effects of *GRB10*:

- Reduced insulin secretion (CIR, beta: -0.127, p = 0.014)
- Lower fasting plasma glucose (beta: -0.139, p = 0.0009)

There was a dual effect of risk alleles of *GRB10* on both decreased glucose-stimulated insulin secretion (beta: -0.051, $p = 3.14\times10^{-9}$) and reduced fasting plasma glucose (beta: -0.016, p = 0.007). We hypothesized that this could be due to the concomitant effects of *GRB10* on pancreatic glucagon-producing alpha-cells [30]. Indeed, we observed that disruption of *GRB10* by small hairpin RNA (shRNA) in human islets resulted in a reduction of both insulin and glucagon expression and secretion. It seems that the mechanisms by which alleles in the *GRB10* gene influence glucose homeostasis involve tissue-specific PoO effects on DNA methylation and imprinting of *GRB10* in human pancreatic islets. Hypomethylation of the *GRB10* gene has also been found in human skeletal muscle in subjects with positive family history of T2D [31], and in liver samples from obese T2D patients [32]. Recently, *GRB10* has been ascribed a key role in regulating mTORC1 signaling; it was thereby identified as a central regulator of adiposity, thermogenesis, and energy metabolism [33].

Imprinting is a genomic mechanism predominantly regulated by methylation to control differential gene expression alleles transmitted from the mother or father. It has been argued that imprinting is the reason why parthenogeny is impossible in mammals. DNA methylation, in concert with histone modifications, is a common mechanism of imprinting, and marks the imprinted genes differently in egg and sperm. Inheritance of these epigenetic marks leads to PoO-specific gene expression. The observed patterns of imprinting led to the formulation of a genetic conflict hypothesis because the allele derived paternally tends to be less related to the siblings of the same mother than the maternal allele. Hence, the paternal allele should evolve to be more aggressive in obtaining maternal resources, while the maternal imprinting attempts to conserve resources and to distribute them to all her offspring [34, 35]. In contrast, according to the co-adaptation theory maternal and paternal imprints co-evolve to become a function of compatibility and to maximize care of offspring [36-38]. While substantial evidence for either hypothesis is lacking, the significance of imprinting in embryonic development and growth cannot be overstated. While some of the inherited DNA methylation can be retained in all developmental stages and in all tissues, it has been observed and in many cases reported that these patterns can be tissue-specific and sometimes developmental stage-specific [39-41].

5.2 Potassium channel, voltage-gated, KQT-like subfamily, member 1 (KCNQ1)

KCNQ1 (11p15.5-p15.4) encodes a voltage-gated potassium channel required for the repolarization phase of the cardiac action potential. *KCNQ1* variants have been associated with the long QT syndrome, a disorder that affects heart electrical activity [42], Jervell and Lange-Nielsen syndrome [43], and familial atrial fibrillation [44]. Individuals with Beckwith-Wiedemann syndrome lose maternal-specific methylation at KvDMR1, a putative imprinting control region within intron 10 of the *KCNQ1* gene [45, 46]. This gene exhibits tissue-specific imprinting, with preferential expression from the maternal allele in some tissues at certain developmental stages, and biallelic expression in others [39, 40]. Variants of *KCNQ1* were associated with risk of T2D in Asian populations. These associations were consistently replicated in European populations, despite the higher frequency of the gene in the European (93%) than in

the Asian populations (61%) [47]. Further studies, combining long-range phasing of genotyping data and geneology information of 38,167 Icelanders, revealed a maternal allele-specific association of the risk variant with T2D [48]. Another study based on families of Pima Indian ancestry replicated these findings, and showed that the maternal C allele in SNP rs2299620 was associated with a 28% decrease in insulin secretion, and accounted for 4% of the variance in susceptibility to diabetes [49].

Hypermethylation of the maternal allele of *KCNQ1* was shown to result in monoallelic activity of the neighboring, maternally expressed protein-coding genes in fetal pancreas and biallelic activity in adult pancreatic islets, suggesting that the gene affects early pancreas development [40, 48]. It may thereby contribute to an increased risk of T2D later in life. Interestingly, recent observations in mice suggested an association of the paternal allele of the *KCNQ1* gene with reduced beta-cell mass, a phenomenon that seems to be mediated by epigenetic histone modification changes in the expression of another neighboring imprinted gene, *CDKN1C* [50].

Many imprinted genes in humans and mice regulate embryonic and placental growth and development. Furthermore, placenta-specific imprinting could provide evidence for inheritable epigenetic stages [51]. In mice, paternal repression along the KCNQ1 domain occurred through trimethylation at lys27 and dimethylation at lys9 of histone H3. Eed-Ezh2 polycomb complexes are recruited to the paternal chromosome, and potentially regulate its repressive histone methylation [52]. Studies on embryonic stem cells and early embryos supported the hypothesis that chromatin repression is established early in development, and is maintained in the placenta. In the embryo, on the other hand, imprinting is stably maintained only by genes that have promoter DNA methylation. These data underscore the importance of histone methylation in placental imprinting, and emphasize the role of the *KCNQ1* locus in embryonic and placental development.

5.3 Krüppel-like factor 14 (KLF14)

A variant upstream of the transcription factor *KLF14* at chromosome 7q32.3 was associated with T2D and HDL-cholesterol [53, 54]. It is assumed that *KLF14* is its ancient retro-copy due to its intronless nature and sequence homology to *KLF16*. Sequence variant analyses in various species revealed a greater variability in the human lineage, with a significantly increased number of non-synonymous changes, suggesting human-specific accelerated evolution. Therefore, it has been hypothesized that *KLF14* may be the first example of an imprinted transcript that has undergone accelerated evolution in the human lineage [55].

Maternally expressed *KLF14* was found to increase the risk of T2D when carried on the maternal chromosome [48]. It may act as a master trans-regulator of adipose tissue gene expression, influencing the expression of genes associated with BMI, HDL-cholesterol, triglycerides, fasting insulin levels, HOMA-IR (an index of insulin sensitivity), fasting glucose, and adiponectin [56]. The *KLF14* variant was also reported to have primary effects on insulin sensitivity [57]. In all embryonic and extra-embryonic tissue studied, *KLF14* was expressed monoallelically in both human and mouse. Epigenetic modifications in the *KLF14* CpG islands were hypomethylated, while the murine Klf14 lacked allele-specific histone modifications.

5.4 PEG3, H19, and IGf2

Imprinted genes showing PoO gene expression regulate the development of key metabolic organs, and work postnatally in the control of the metabolic axes. Since these genes rely on epigenetic mechanisms, they are especially vulnerable to environmental changes in the uterus. Germ-cell programming occurs, at least partially, *in utero*. It has been postulated that deregulation of this process may be involved in transgenerational developmental programming. Imprinted genes affect fetal nutrient supply through alterations in maternal environment and resource mobilization. Therefore, the significance of the intrauterine environment cannot be overstated. Several studies provided evidence for the presence of gene-related intrauterine effects, including:

- Gene and protein expression of glucose transporters *GLUT-1*, *GLUT-2*, and *GLUT-3* were decreased in embryos of hyperglycemic mice [58].
- Maternal diabetes mellitus perturbs *PEG3*, *H19*, and *Snrpn* gene expression in placenta, and impairs embryonic development [59].
- PEG3, a paternally expressed zinc finger protein, has been implicated in beta-catenin signaling and regulation of apoptosis through p53 and TNF pathways.
- $Peg3^{+/-}$ offspring had smaller placentas, and $PEG3^{+/-}$ mothers bearing wild-type pups failed

Table 1. Genetic variants showing parent-of-origin effects for the risk of type 2 diabetes

SNP	Gene	Population	R/O	RAF	OR paternal	OR maternal	Reference
rs2237892	*KCNQ1*	Icelandic	C/T	0.93	1.03	1.3	Kong *et al*. 2009 [48]
		Pima Indian	C/T	0.52	0.97	1.69	Hanson *et al*. 2013 [49]
rs231362	*KCNQ1*	Icelandic	C/T	0.55	0.98	1.23	[48]
		Pima Indian	C/T	0.9	0.69	1.42	[49]
rs4731702	*KLF14*	Icelandic	C/T	0.44	0.99	1.17	[48]
		Pima Indian	C/T	0.42	0.94	1.36	[49]
rs2334499	*MOB2*	Icelandic	T/C	0.41	1.35	0.86	[48]
		Pima Indian	T/C	0.58	1.16	0.76	[49]

Legend: R/O = risk allele / other allele. EAF = risk allele frequency. OR Paternal = odds ratio for paternal effect, OR Maternal = odds ratio for maternal effect.

to generate sufficient body reserves, resulting in growth restriction of wild-type offspring [36, 60]. These results indicate that maternal PEG3 is required to increase food intake appropriately in response to placental endocrine signals in wild-type offspring.

There is also evidence on how maternal obesity and diabetes may alter epigenetic patterns of the imprinted genes. This is demonstrated by the following set of findings:

- DNA methylation in a differentially methylated region of *PEG3* was altered in spermatozoa of offspring from obese mothers.
- DNA methylation of *PEG3* was not affected in spermatozoa of offspring from diabetic mothers.
- DNA methylation of H19 in the offspring sperm was changed by maternal diabetes [61].

We have shown allelic imbalance in the expression and hypomethylation of CpG sites comprising *PEG3* in human pancreatic islets from diabetic donors. Altered methylation could be the cause of allelic imbalance which could in turn influence T2D susceptibility [62].

The expression of *H19* and another diabetes gene, *IGF2*, are closely linked, and they are expressed in the same tissues during fetal development. *H19* is maternally expressed, while *IGF2* is paternally expressed (except in adult liver and central nervous system); both genes control growth and body composition [63]. Studies have shown that SNPs in *IGF2* and *H19* may affect birth weight, with opposite effects depending on parental transmission of the risk alleles, which could eventually impact the parent-of-origin risk of disease [64].

5.5 MOB2 and others

There is emerging evidence for PoO effects from other T2D susceptibility loci, including *MOB2* [48], *TCF7L2*, *THADA* (Prasad, submitted), and possibly many more to be discovered. Studies on PoO effects are hampered by the following main factors:

- Lack of large cohorts with trio data (from patient/control, mother, and father), given that parents heterozygous for the genotype of interest are informative in the analyses.
- Limited availability of fetal tissue.
- Observed disparity in the allelic-specific gene expression during fetal development and adult tissues, as seen for the *KCNQ1* gene.

Taken together, the available data emphasize the significance of PoO effects, and indicate the need for further genetic studies into these effects to clarify whether risk alleles are inherited from the mother or the father.

6. Why parent-of-origin effects should not be overlooked

Identification of markers responsible for PoO effects may have several clinical implications. Firstly, identification of genes regulating fetal growth and development in response to intrauterine environment may aid in unraveling the fetal programming mechanisms underlying increased susceptibility to diabetes and co-morbidities later in life. This, in turn, will enable early intervention strategies during pregnancy aimed at healthy offspring and novel drug targets for the treatment of metabolic diseases in adults to be developed. More precise early preventive diagnostics will improve prevention and prognosis of the diseases later in life.

7. Conclusions

The genetic landscape of T2D is now starting to become more apparent, and novel mechanisms involved in disease pathogenesis are being unraveled. Undoubtedly, recent progress in systematic

and unbiased large-scale genotyping and sequencing methods paves the way to future discoveries and unprecedented findings which would not otherwise be possible. However, much effort is still necessary to reveal the biological mechanisms for many of the genetic variants. Much importance is attached to the main effects on insulin-producing beta-cells, but the genetic effects also involve glucagon-producing alpha-cells and incretin-potentiating insulin secretion [20]. It will be necessary to consider these aspects in future genetic research.

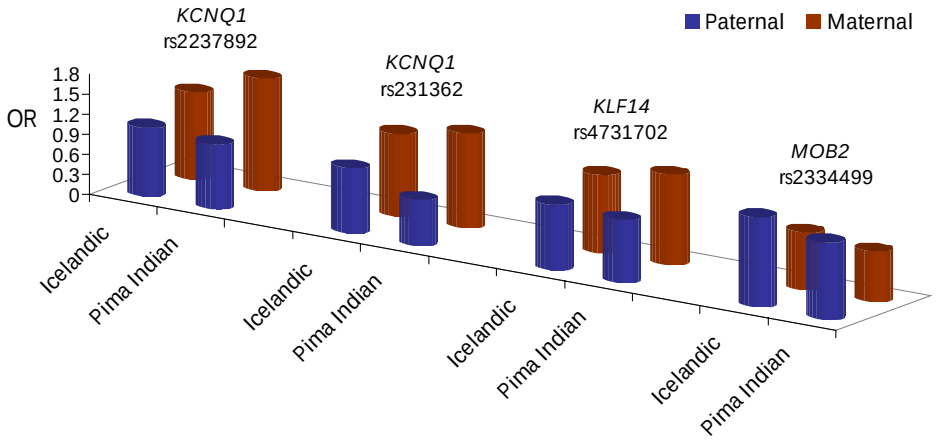

Figure 1. Genetic variants showing parent-of-origin effects for the risk of type 2 diabetes. The risk of T2D was increased for the maternal transmission of the risk alleles in *KCNQ1* ($OR_{Islandic}$ 1.3-1.23; OR_{Pima} 1.69-1.42) and *KLF14* ($OR_{Islandic}$ 1.17; OR_{Pima} 1.36). For the paternal transmission, the risk was increased for the alleles in MOB2 ($OR_{Islandic}$ 1.35; OR_{Pima} 1.15). *Abbreviations*: OR – odds ratio, *KCNQ1* – potassium channel, voltage-gated, KQT-like subfamily, member 1, *KLF14* – Krüppel-like factor 14, *MOB2* – MOB kinase activator 2.

The discovery of genes involved in the regulation of circadian rhythms may explain an established link between different dietary patterns, sleep disturbances, and the risk for T2D, as shown in epidemiological studies [21]. It became clear that PoO effects may constitute an important, so far largely underestimated, aspect of genetic risk assessment for future diabetes risk prediction and family counseling (**Table 1**, **Figure 1**). With this in mind, future studies would certainly benefit from including the parents of subjects with and without diabetes when investigating effects of new environmental exposures. Finally, molecular understanding of the genetic architecture of T2D will lead to better classification of different diabetes subtypes, and will thus pave the way to more precise medical therapy based on the underlying pathophysiologies.

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