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REVIEW ARTICLE

Genes, Genetics, and Environment in Type 2 Diabetes: Implication in Personalized Medicine

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Type 2 diabetes (T2D) is a multifactorial anomaly involving 57 genes located on 16 different chromosomes and 136 single nucleotide polymorphisms (SNPs). Ten genes are located on chromosome 1, followed by seven genes on chromosome 11 and six genes on chromosomes 3. Remaining chromosomes harbor two to five genes. Significantly, chromosomes 13, 14, 16, 18, 21, 22, X, and Y do not have any associated diabetogenic gene. Genetic components have their own pathways encompassing insulin secretion, resistance, signaling, and β-cell dysfunction. Environmental factors include epigenetic changes, nutrition, intrauterine surroundings, and obesity. In addition, ethnicity plays a role in conferring susceptibility to T2D. This scenario poses a challenge toward the development of biomarker for quick disease diagnosis or for generating a consensus to delineate different categories of T2D patients. We believe, before prescribing a generic drug, detailed genotypic information with the background of ethnicity and environmental factors may be taken into consideration. This nonconventional approach is envisaged to be more robust in the context of personalized medicine and perhaps would cause lot less burden on the patient ensuring better management of T2D.

Introduction

Type 2 diabetes (T2D) is a complex multifactorial disorder involving genetics and environmental factors (American Diabetes Association, 2011). T2D include genes from various pathways such as insulin secretion, its resistance, signaling, and pancreatic β-cell (PBC) dysfunction. Environmental factors include epigenetic changes, adverse nutrition, intrauterine environment, and obesity. In addition, ethnicity also has a role in conferring susceptibility to T2D. Earlier studies have genotyped the common variants associated with T2D in different populations of the world. However, the efforts to understand the underlying pathways have remained limited. In this study, we have listed the candidate genes involved in the main pathways and have discussed their involvement in the light of environmental factors having implication in personalized medicine. Literature on T2D showed involvement of about 57 genes located on 16 different chromosomes having 136 single nucleotide polymorphisms (SNPs). This includes 63 SNPs from 18 genes related to insulin secretion pathway, 37 SNPs from 21 genes related to insulin signaling and PBC dysfunction pathway, and finally 36 SNPs from 18 genes related to insulin resistance (IR) pathway.

Insulin Secretory Pathway

Glucose-stimulated insulin secretion (GSIS) starts as glucose molecules enter into PBC by GLUT2. Glucose gets phosphorylated by glucokinase (GCK) enzyme leading to ATP generation through glycolysis pathway. This step is termed as the rate-limiting step of GSIS. For complete oxidation of glucose, pyruvate undergoes oxidative phosphorylation through electron transport chain (ETC) in mitochondria. It begins as electrons within the carbon bonds are transferred to dinucleotide electron carriers, NADH, and $FADH_2$. They donate electrons to ETC, a multiprotein unit grouped into four complexes (I–IV). Complexes I, III, and IV are reduction and oxidation-driven proton pumps. Ultimately, electrons cause reduction of oxygen to water. ETC utilizes electrons to obtrude the protons out of the matrix. This creates an electrochemical potential gradient across the mitochondrial inner membrane. Energy stored in this gradient is utilized by ATP synthase to generate ATP from ADP (Lowell and Shulman, 2005) causing an increase in ATP/ADP ratio and thus closure of ATP-sensitive potassium (K^+) channel. This closure depolarizes the PBC membrane, which opens the voltage-dependent Ca^{++} channel. Opening of calcium (Ca) channel initiates incoming of Ca ions and stimulates secretion of stored insulin granules from PBCs through exocytosis (Guyton and Hall, 2010). The detailed pathway is shown as a diagrammatic illustration highlighting the potent candidate genes involved in insulin secretion (Fig. 1).

Candidate Genes and Variants Associated with Insulin Secretion and T2D

Insulin secretion is an important pathway in pathogenesis of T2D. Literature showed 63 SNPs in 18 genes from this pathway in T2D (Table 1).

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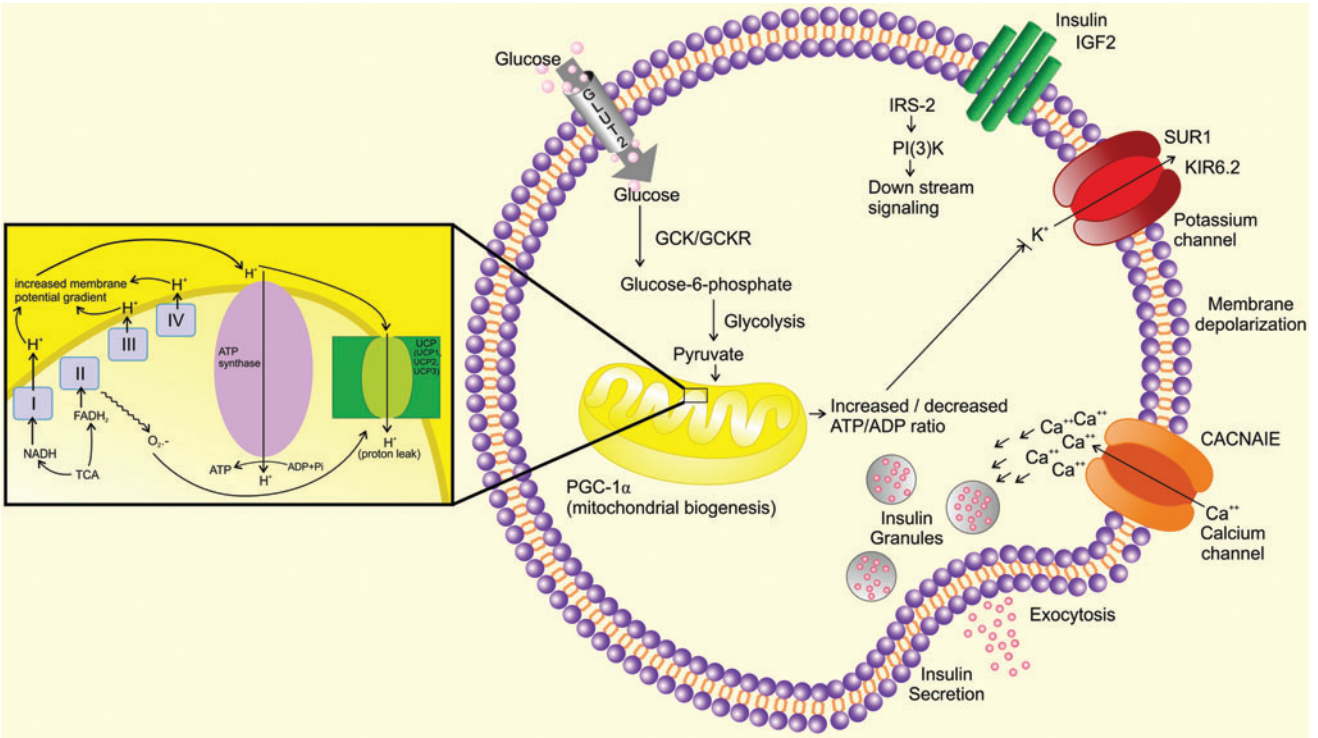

FIG. 1. Diagrammatic illustration highlighting insulin secretion pathways encompassing some potent genes and their involvement in type 2 diabetes (T2D) pathophysiology. Glucose molecules enter pancreatic β-cell (PBC) by GLUT2 and undergo glycolysis. Pyruvate (substrate of glycolysis) enters electron transport chain (ETC) in mitochondria for complete oxidation. This leads to increase in the ATP/ADP ratio, which is sensed by $K_{(ATP)}$ channel, and leads to membrane depolarization causing Ca channel to open. Influx of Ca ions initiates secretion of insulin from PBC through exocytosis. In addition to this, the name of the genes, which are involved at various steps in the pathways, have also been mentioned along side. Ca, calcium. Color images available online at www.liebertpub.com/dna

Sixteen SNPs are associated with *SUR1* and four with *Kir6.2*. The ATP-sensitive potassium channel is the key component of GSIS. $K_{(ATP)}$ channels are the heterooctameric complexes consisting of pore and ATP-sensitive regulatory subunit. Pore is formed by *Kir6.1/Kir6.2* genes and regulatory subunit is formed by *SUR1/SUR2A/SUR2B* genes. $K_{(ATP)}$ channel couples metabolic changes to membrane electric signals leading to GSIS. Given the vital role of $K_{(ATP)}$ channel in GSIS, polymorphisms in these genes are found associated with causation of T2D (Qin *et al.*, 2013; Haghverdizadeh *et al.*, 2014). However, mitochondrial inner membrane anion carrier protein acts as uncoupling proteins (UCP), which regulate ATP production by oxidative phosphorylation. *UCP2* mediates proton leak across mitochondrial membrane and hence decreased insulin secretion. −866 G>A polymorphism of *UCP2* is the most extensively studied variant of this gene. Positive association of this gene has been reported in Bavarians, Austro-Germans, Caucasians, Japanese, Hispanics, Africans, and Asian Americans. Besides, another variant Ala55Val of *UCP2* is also associated with T2D as a haplotype (Crispim *et al.*, 2010).

Another set of genes significantly associated with T2D were the pancreatic membrane transporters (*SLC2A2*-rs5406, rs5404, rs5400, rs5398, *SLC2A1*-rs841853, and *SLC30A8*-rs13266634). *SLC2A2* encodes GLUT2 and *SLC2A1* encodes GLUT1, which are the facilitative glucose transporters of PBC. Polymorphisms in *SLC2A2* play a role in the conversion of impaired glucose intolerance (IGT) into T2D in Finnish, Japanese, and Caucasian populations (Kilpelainen *et al.*, 2007). However, *SLC2A1* polymorphism rs841853 has been found to be associated only in Asians (Du *et al.*, 2013). *SLC30A8* encodes pancreas-restricted zinc transporter ZnT8. Zinc is required for insulin biosynthesis and maturation of insulin secretory granules (Wijesekara *et al.*, 2009). *SLC30A8*-rs13266634 is a nonsynonymous variant encoding tryptophan to arginine change at position 325 of the carboxyl terminal domain. This SNP associates reduced zinc transport activity, reduced zinc levels in β-cells, and diminished insulin secretion (Rutter and Chimienti, 2014). Another variant of this gene rs7480010 was also associated with T2D in Tunisians comprising 734 subjects (Kifagi *et al.*, 2011).

Glucose metabolism starts with glycolysis involving GCK enzyme. The activity of *GCK* is inhibited by *GCKR*. *GCK* is selectively expressed in liver and PBC. Given its function in glycolysis, the variants in these two genes (*GCK*-rs199884 and *GCKR*-rs3757840) are associated with fasting plasma glucose (FPG) and hence T2D in Caucasians, Whites, Chinese, and South Asians (Wang *et al.*, 2013). Another variant of *GCK*-rs3757840 is also associated with FPG and birth weight (Weedon *et al.*, 2006).

Similarly, *CDK2A/B* and *CDKAL1* are shown to have regulatory effects on glucose metabolism and insulin secretion. Two variants in *CDK2A/B* gene rs10811661 and rs564398 and three variants in *CDKAL1* gene—rs7754840, rs7756992, and rs10946398 are widely associated with T2D in different populations. Recent meta-analysis across

Table 1. List of Candidate Genes and Variants Associated with Insulin Secretion and Type 2 Diabetes

Gene name	*Full gene name*	*Chromosome number*	*SNP common name*	*db SNP*	*Position*	*References*
SLC2A2	Solute carrier family 2 (facilitated glucose transporter), member 2	3		rs5406	Intron	Kilpelainen *et al.* (2007)
				rs5404	Synonymous	Kilpelainen *et al.* (2007)
				rs5400	Missense	Kilpelainen *et al.* (2007)
				rs5398	Synonymous	Kilpelainen *et al.* (2007)
GCK	Glucokinase	7		rs1799884		Wang *et al.* (2013)
				rs3757840		Weedon *et al.* (2006)
GCKR	Glucokinase regulator	2		rs780094	Intron	Wang *et al.* (2013)
SUR1	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	11	IV38 + 54	rs4148646	Intron	Haghverdizadeh *et al.* (2014)
			IV18-36	rs4148628	Intron	Haghverdizadeh *et al.* (2014)
			IVS11-74	rs2074308	Intron	Haghverdizadeh *et al.* (2014)
			K649	rs1799858	Exon	Haghverdizadeh *et al.* (2014)
				rs2237984	Intron	Haghverdizadeh *et al.* (2014)
				rs2188966	Intron	Haghverdizadeh *et al.* (2014)
				rs59852838	Exon	Haghverdizadeh *et al.* (2014)
				rs358953	5′UTR	Haghverdizadeh *et al.* (2014)
				rs3758947	Intron	Haghverdizadeh *et al.* (2014)
				rs1799859	Exon	Haghverdizadeh *et al.* (2014)
			S1369A	rs757110	Exon	Haghverdizadeh *et al.* (2014)
			IVS19 + 123	rs8192692	Intron	Haghverdizadeh *et al.* (2014)
			IMS-JST032704	rs2283257	Intron	Haghverdizadeh *et al.* (2014)
			Syn T759T	rs1801261	Exon	Haghverdizadeh *et al.* (2014)
			Intron 24 T/C	rs1799854	Intron	Haghverdizadeh *et al.* (2014)
			Syn R1273R	rs4148643	Intron	Haghverdizadeh *et al.* (2014)
Kir6.2	Potassium inwardly rectifying channel, subfamily J, member 11	11	E23K	rs5219	Intron	Qin *et al.* (2013)
			A190	rs5218	Synonymous codon	Qin *et al.* (2013)
			3p+215	rs5210	3′UTR	Qin *et al.* (2013)
				rs5215	Missense	Qin *et al.* (2013)
CACNA1E	Calcium channel, voltage dependent, R type, alpha 1E subunit	1	−1039G/T	rs10797728	Intron	Trombetta *et al.* (2012)
			+8130G/A	rs3753737	Intron	Trombetta *et al.* (2012)
				rs175338	Intron	Trombetta *et al.* (2012)
				rs2184945	Intron	Trombetta *et al.* (2012)
				rs3905011	Intron	Trombetta *et al.* (2012)
				rs4652679	Intron	Trombetta *et al.* (2012)
CAPN10	Calpain 10	2	SNP 19	rs3842570	Intron	Sharma *et al.* (2013)
			SNP 43 Intron 3	rs3792267	Intron	Sharma *et al.* (2013)
			SNP 63	rs5030952		Sharma *et al.* (2013)
			SNP 44 C/T or T504A	rs2975760	Intron	Sharma *et al.* (2013)
HHEX	Hematopoietically expressed homeobox	10		rs7923837		Cai *et al.* (2011)
				rs1111875		Cai *et al.* (2011)
				rs5015480		Klimentidis *et al.* (2014)
IDE	Insulin-degrading enzyme	19		rs2209772		Zee *et al.* (2008)
				rs1887922	Intron	Karamohamed *et al.* (2003)
				rs2149632	Intron	Rudovich *et al.* (2009)
PPARGC1A	Peroxisome proliferative activated receptor, gamma, coactivator 1	4	G482S	rs8192678	Exon	Franks *et al.* (2014)
			T528T	rs3755863	Exon	Franks *et al.* (2014)
SLC30A8	Solute carrier family 30, class A, member 2	8	T325A	rs13266634	Missense	Rutter and Chimienti (2014)
			R325W	rs7480010	Intron	Kifagi *et al.* (2011)
WFS1	Wolfram syndrome 1	4		rs6446482	Intron	Mita *et al.* (2008)
				rs1251142	Intron	Mita *et al.* (2008)
			R456H	rs1801208	Missense	Mita *et al.* (2008)
			H611R	rs734312	Missense	Mita *et al.* (2008)
UCP2	Uncoupling protein 2	11	Ala55Val	rs660339	Exon	Crispim *et al.* (2010)
				rs659366	Promoter	Crispim *et al.* (2010)
PTGS2	Prostaglandin-synthase 2	1		rs2066826	Intron	Konheim and Wolford (2003)
				rs20417	Promoter	Konheim and Wolford (2003)
			Arg298His	rs13283456	Promoter	Nitz *et al.* (2007)
CDKN2A/B	Cyclin-dependent kinase inhibitor-2A/B	9		rs10811661		Peng *et al.* (2013)
				rs564398	Intron	Peng *et al.* (2013)
CDKAL1	Cyclin-dependent kinase-5 regulatory subunit-associated protein-like-1	6		rs7754840	Intron	Peng *et al.* (2013)
				rs7756992	Intron	Peng *et al.* (2013)
				rs10946398	Intron	Peng *et al.* (2013)
SLC2A1	Solute carrier family 2 (facilitated glucose transporter, member 1)	1		rs841853	Intron	Du *et al.* (2013)
MTNR1B	Melatonin receptor 1B	11		rs10830963	Intron	Ren *et al.* (2014)

SNP, single nucleotide polymorphism.

populations confirmed the associations of rs10811661, rs7756992, and rs10946398 variants with T2D (Peng *et al.*, 2013).

For secretion of insulin from PBCs, calcium influx is critical. *CACNA1E* is member of voltage-gated Ca^{2+} channel family. It mediates entry of Ca^{2+} ions into the cells upon membrane depolarization initiating insulin release. The variants in this gene have been associated with insulin secretion and sensitivity in Pima Indians and Swedish population. Revalidation in Italians confirmed that *CACNA1E* tag SNPs (rs10797728, rs3753737, rs175338, rs2184945, rs3905011, and rs4652679) were associated with different aspects of PBC functions leading to T2D (Trombetta *et al.*, 2012).

CACNA1E gene is located on chromosome 1 similar to *PTGS2*. *PTGS2* generates prostaglandins, which is a negative regulator of GSIS and also causes insulin insensitivity. It lies in the region (1q25.2) closely associated with early onset of T2D. Similarly, *PTGS2* (rs20417 and rs2066826) polymorphisms were found to be associated with T2D in Pima Indians comprising 1000 subjects. SNP rs20417 was found to decrease the activity of promoter emphasizing its functional relevance (Konheim and Wolford, 2003). Variant rs13283456 has a protective role against T2D in two German cohorts with odds ratio of 0.63 and *p*-value 0.04 (Nitz *et al.*, 2007).

CAPN10 gene on chromosome 2 encodes Calpain 10 enzyme, which is a cysteine protease. SNPs-43 (rs3792267), 63 (rs5030952), and 19 (rs3842570) are individually as well as in combination with haplotype are associated with different phenotypes of T2D. This includes insulin secretion, IR, and IGT. Association of these SNP has been replicated in several populations belonging to different ethnicities (Sharma *et al.*, 2013).

PGC-1α and *WFS1* are the two genes present on chromosome 4. *PGC-1α* integrates with metabolic pathways, which include increased hepatic gluconeogenesis and β-oxidation and mitochondrial biogenesis. Further, insulin-independent uptake of glucose and metabolism, reduced insulin secretion providing more glucose for brain and kidney during starvation has been well documented. Positive association of Gly482Ser has been documented in Danish and Slovene Caucasians. Positive association of both Thr394Thr and Gly482Ser variants has been seen in Japanese population. Recently Gly482Ser has been reported to be associated with accumulation of subcutaneous adiposity and Thr394Thr is reportedly associated with modified effects of metformin on triacylglycerol level in diabetic patients (Franks *et al.*, 2014).

Wolfram syndrome is caused by mutations in *WFS1* gene. It is a rare autosomal recessive disorder characterized by juvenile diabetes mellitus and diabetes insipidus. *WFS1* encodes for a gene product, which is involved in β-cell loss, increased apoptosis and diminished insulin secretion. The variants (WFS1-rs6446482, rs12511742, rs1801208, and rs734312) were found to be associated with T2D through genome-wide association studies (GWAS) carried out on 9533 cases and 11,389 controls. Same variants were found to be associated in the Japanese population as well (Mita *et al.*, 2008).

HHEX gene located on chromosome 10 encodes for a transcription factor involved in WNT signaling pathway. It is expressed during early stages and required for the development of ventral pancreas and liver. SNPs rs7923837 and rs1111875 are associated with impaired insulin secretion and T2D in several populations. However, a large meta-analysis of 88,495 samples showed significant association with odds ratio of 1.19 and 1.23, respectively, in Caucasians and Asians only (Cai *et al.*, 2011). Another variant in *HHEX* gene, rs5015480 showed association with lower prevalence of T2D in native population of Alaska ($n = 1144$) with *p*-value of 0.00046 (Klimentidis *et al.*, 2014).

IDE located on chromosome 11 can degrade the number of peptides, including insulin-like growth factor (IGF)-I, IGF-II, transforming growth factor, and proteins damaged oxidatively. *IDE* is implicated with fasting glucose plasma (FGP) levels and glycated hemoglobin A1c (HBA1C). Positive association of these *IDE* (rs2209772 and rs1887922) variants in men has been reported in Framingham Heart study (Karamohamed *et al.*, 2003). Another variant, rs2149632, was also associated with decreased insulin secretion in German cohort comprising 3049 subjects (Rudovich *et al.*, 2009).

Another gene present on chromosome 11 is MTNR1B, which encodes for 7-transmembrane melatonin receptor secreted by pineal gland. MTNR1B (rs10830963) variant was found to be associated with FGP, T2D, and insulin secretion uncovered by recent GWAS in Mexican Americans (Ren *et al.*, 2014). This variant was also found to be associated with South Indians (Mohammed *et al.*, 2015), Caucasians, and Hispanics (Zheng *et al.*, 2015).

Insulin Signaling Pathway, Candidate Genes, and Polymorphisms Implicated with T2D

Insulin signaling involves major pathways in T2D pathophysiology and its signaling and resistance goes hand in hand to cause overt T2D. Insulin signaling cascade begins with *IRS1/PI3K/AKT* genes. Glucose uptake activates *IRS-2/PI3K* complex, which targets Akt and protein kinase C zeta to begin downstream signaling (Rudovich *et al.*, 2009). Mutations and polymorphisms involved with insulin signaling include 21 genes and 37 SNPs (Table 2). Few genes may not be playing a direct role in insulin signaling, instead participating indirectly. However, such details are not available.

The *STK11-AMPK-CRTC2* complex forms a signaling pathway which controls glucose homeostasis in the liver. This complex is a target for antidiabetes drugs. SNPs in these genes (*STK11*-rs741765, *AMPK*-rs1418442, and *CRTC2*-6909C>T) were found to be associated with moderate risk of developing T2D in the Japanese population comprising 1787 subjects. *AMPK* (rs1418442) is also associated with serum cholesterol levels in Caucasian females (Keshavarz *et al.*, 2008).

Maximum number of candidate genes associated with insulin signaling is present on chromosome 1, which includes *PRKCZ*, *IL6*, *CRP*, *CASQ1*, and *ATF6*. *PRKCZ* is a member of PKC serine/threonine kinase family and plays a role in cell differentiation, proliferation, and secretion. This gene mapped to 1p36.33-1p36.23 region of chromosome 1 and is reported to be associated with T2D in Han Chinese showing association with rs436045 variant (Li *et al.*, 2003). Another gene present on chromosome 1 is *CASQ1* that codes for Calsequestrin protein. It is involved in intracellular storage and release of calcium. Two polymorphisms

Table 2. List of Genes and Their Variants Associated with Insulin Signaling and Miscellaneous Pathways

Gene name	*Full gene name*	*Chromosome number*	*SNP common name*	*db SNP*	*Position*	*References*
STK11	Serine/threonine kinase 11	19		rs741765	Intron	Keshavarz *et al.* (2008)
CRTC2	CREB-regulated transcription factor coactivator 2	3	6909 C>T			Keshavarz *et al.* (2008)
AMPK	Protein kinase AMP-activated, alpha catalytic subunit	5		rs1418442	Intron	Keshavarz *et al.* (2008)
WNTB5	Wolfram syndrome 5	4	IVS3C>G	rs2270031	Intron	Salpea *et al.* (2009)
PRKCZ	Protein kinase C, zeta	1		rs436045	Intron	Li *et al.* (2003)
RPTP,S	Receptor protein tyrosine phosphatase sigma	19		rs1978237	Intron	Langberg *et al.* (2007)
				rs1143699	Exon	Langberg *et al.* (2007)
				rs4807015	Intron	Langberg *et al.* (2007)
GNB3	G protein beta3 subunit	12	C825T	rs5443	Exon	Daimon *et al.* (2008)
				rs5446	3′UTR	Daimon *et al.* (2008)
				rs2301339	Intron	Daimon *et al.* (2008)
SREBF1	Sterol regulatory element binding transcription factor 1	17		rs11868035	Exon	Liu *et al.* (2012)
				rs2297508	Exon	Liu *et al.* (2012)
				rs1889018	5′UTR	Grarup *et al.* (2008)
				rs6502618	5′UTR	Grarup *et al.* (2008)
				rs2236513	5′UTR	Harding *et al.* (2006)
IL6	Interlukin 6	7	−174G>C	rs1800797	Promoter	Saxena *et al*. (2014)
				rs1800795	Promoter	Saxena *et al.* (2014)
BCAT1	Branched-chain amino acid transaminase-1, cytosolic	12		rs2242400	Intron	Rampersaud *et al.* (2007)
ENDOGL1	Endonuclease G-like 1 gene	3	A375G	rs2051211	Intron	Moritani *et al*. (2007)
EXT2	Exostosin glycosyltransferase 2	11		rs1113132	Intron	Liu *et al.* (2013)
				rs3740878	Intron	Liu *et al.* (2013)
				rs11037909	Intron	Liu *et al.* (2013)
GRB10	Growth factor receptor-bound protein 10	11		rs2237457	Intron	Rampersaud *et al.* (2007)
PCK1	Phosphoenolpyruvate carboxykinase, 1	2	−232C>G	rs2071023	Promoter	Rees *et al.* (2009)
FXN	Friedreich's ataxia	9		rs2498429		Holmkvist *et al.* (2005)
IL6R	Interlukin 6 receptor	1	Asp358Ala	rs8192284	Exon	Qi *et al.* (2007)
CRP	C-reactive protein gene	1		rs3093059	Promoter	Zee *et al.* (2008)
				rs2794521	Promoter	Zee *et al.* (2008)
CASQ1	Calsequestrin-1	1		rs2275703	Intron	Fu *et al.* (2004)
				rs617698	Intron	Fu *et al.* (2004)
ATF6	Activating transcription factor 6	1	M67V	rs1058405	Exon	Chu *et al.* (2007)
				rs11579627	3′UTR	Chu *et al.* (2007)
IGF2BP2	Insulin-like growth factor 2 m-RNA-binding protein 2	3		rs4402960	Intron	Omori *et al.* (2008)
				rs1470579	Intron	Omori *et al.* (2008)
IRS1	Insulin receptor substrate 1	2		rs1801278	Missense	Alharbi *et al.* (2014)
				rs2943641		Sun *et al.* (2014)
TCF7L2	Transcription factor 7-like 2	10		rs7903146	Intron	Pradas-Juni *et al.* (2014)
ENPP1	Ectonucleotide pyrophosphatase 1	6		rs1044498		de Lorenzo *et al.* (2013)

(rs2275703 and rs617698) of this gene were significantly associated with T2D in Amish population comprising 651 subjects (Fu *et al.*, 2004). In addition, *ATF6* is also located in the same region associated with T2D. *ATF6* gene plays a role in endoplasmic reticulum stress response. Two variants of this gene have been shown to be associated with T2D in Utah Caucasians comprising 544 subjects (Chu *et al.*, 2007). *IL6R,* which is the receptor for *IL6* gene, is also located on chromosome 1. A polymorphism (*IL6R*-rs8192284) was associated with T2D in women from United States in a study comprising of 1730 subjects (Qi *et al.*, 2007). *CRP* gene present on chromosome 1, encodes for a protein that belongs to pentaxim family and has a major role in host defense mechanisms. The level of protein increases in response to injury, infection, or inflammation. Two variants (rs3093059 and rs2794521) of this gene have been originally associated

with T2D in European populations (Carlson *et al.*, 2005). However, only rs3093059 ($p=0.03$, OR: 7.01) could be well replicated in different populations, including Caucasians (Zee *et al.*, 2008).

Two genes *PCK1* and *IRS1* present on chromosome 2 have been implicated with insulin signaling. *PCK1* encodes for cytosolic, phosphoenolpyruvate carboxykinase, which is a known candidate gene for T2D. Variant rs2071023 was found to be associated (OR: 1.21, $p=0.019$) with T2D in a South Asian population residing in United Kingdom. The study consisted on 1374 subjects from Mirpur, Pakistan (Rees *et al.*, 2009). However, *IRS1* plays a crucial role in insulin signaling pathway. The protein encoded by *IRS1* is phosphorylated by insulin receptor tyrosine kinase leading to downstream signaling. Glysine972Arginine (rs18011278) is associated ($p=0.04$, OR: 1.7) with T2D in populations worldwide (Alharbi *et al.*, 2014). Another variant of this gene, rs2943641 was found implicated with IR, hyperinsulinemia, and reduced basal IRS-1 protein level in Europeans (Sun *et al.*, 2014).

Two genes present on chromosome 3 are *ENDOGL1* and *IGF2BP2*. *ENDOGL1* encodes for 5′-3′ endonuclease enzyme. This gene plays a role in apoptosis. However, the role in T2D is unclear. A polymorphism of this gene rs2051211 was found to be significantly associated ($p=0.000046$, OR: 1.33) with T2D in Japanese population (Moritani *et al.*, 2007). While, *IGF2BP2* is an mRNA-binding protein, which regulates IGF2 by binding to its 5′UTR. It also plays a role in growth and insulin signaling pathways influencing insulin secretion. Two variants (rs4402960 and rs1470579) in *IGF2BP2* gene have been associated with T2D in different populations of the world, including Asian and Caucasian. Carriers of these variants were found to have decreased first phase of insulin secretion. Recently these variants were also associated (OR: 1.87 and OR: 2) with Pioglitazone drug response in T2D patients acting as a potential biomarker (Omori *et al.*, 2008).

The only gene present on chromosome 4 is *WNTB5*. It belongs to the Wnt signaling pathway and regulates adiposeness and insulin secretion. *WNTB5* gene variant IVS3C>G was found to provide risk of T2D in absence of obesity in Japanese and Caucasian populations (Salpea *et al.*, 2009).

Chromosome 6 harbors *ENPP1* gene, which is a transmembrane glycoprotein. It interacts with insulin receptor inhibiting downstream signaling. rs1044498 is a gain of function mutation, which causes inhibited autophosphorylation of insulin receptor and hence decreased tissue-specific insulin action affecting glucose uptake and glycogen synthesis (de Lorenzo *et al.*, 2013).

Chromosome 7 harbors *IL6* gene, which encodes for a proinflammatory hormone. As insulin has an anti-inflammatory role, it is believed that *IL6* interferes with insulin and hinders the downstream signaling leading to T2D. Two *IL6* polymorphisms rs1800797 and rs1800795 were associated with T2D in populations from Boston, American, and Spanish Caucasians. However, in North Indian population only rs1800795 showed association with T2D (Saxena *et al.*, 2014).

A gene *FXN* present on chromosome 9 causes Friedreich's ataxia (FRDA), which is a neurodegenerative disease involving GAA repeat. More than 20% of the patients develop T2D in their later parts of life. A SNP in X25 gene (rs2498429) was found to be associated with causation of T2D in FRDA patients (220 trios) with p-value of 0.02. However, the exact pathway leading to T2D in the context of this gene is unknown (Holmkvist *et al.*, 2005).

TCF7L2 gene is present on chromosome 10. *TCF7L2* harbors the most replicated and implicated genetic variant (rs7903146) associated with T2D till date. Studies carried out on mice models and cell lines have suggested that *TC7L2* mRNA levels are upregulated and protein levels are downregulated in PBC. For this, splice variants are mainly responsible for its regulation. However, the exact pathway is still unknown (Pradas-Juni *et al.*, 2014).

Chromosome 11 harbors two important insulin-signaling genes, *EXT2* and *GRB10*. *EXT2* encodes exostocin 2, which is required during early pancreatic development and insulin synthesis. Three variants (rs3740878: OR: 1.07, $p=0.038$; rs11037909: OR: 1.05, $p=0.008$; rs1113132: OR: 1.04, $p=0.005$) of this gene showed marginal association with Han Chinese population consisting of 2533 cases and 2643 controls (Liu *et al.*, 2013). *GRB10* encodes for growth factor protein 10, which binds to activated insulin receptor and hence negatively regulate insulin signaling and glucose uptake. Highly significant association ($p=1.07\times10^{-5}$) of rs2237457 has been reported with T2D (Rampersaud *et al.*, 2007).

Chromosome 12 has *GNB3* and *BCAT1* genes implicated in insulin signaling. G proteins relay information from one cell to another through G protein–coupled receptors. *GNB3* gene encodes for G protein β3 subunit. Given its pivotal role in ion channels and signaling, the polymorphisms in this gene were analyzed in Japanese population comprising 2956 subjects. rs5443 was associated with T2D along with flanking SNPs rs5446 and rs2301339. *BCAT1* encodes for cytosolic branched chain amino acid transaminase, which is essential for cell growth. *BCAT1* variant rs2242400 was associated with decreased risk of T2D in Amish (OR: 0.71, $p=0.004$), Pima Indians (OR: 0.66, $p=0.019$), and Mexican Americans (OR: 0.78, $p=0.034$) (Daimon *et al.*, 2008).

SREBF1 gene present on chromosome 17 is a transcription factor regulating lipid and glucose metabolism by downregulating genes like *PGC-1α*. Based on three different studies, five variants of this gene have been reported to be associated with T2D (Harding *et al.*, 2006; Grarup *et al.*, 2008; Liu *et al.*, 2012). rs2297508 and rs11868035 are associated in Han and Dongxiang populations, whereas rs1889018 is associated with Danish Caucasians. Variants rs2236513 and rs6502618 are associated with population from United Kingdom.

RPTP,S gene present on chromosome 19 encodes for a phosphatase enzyme associated with the maintenance of glucose homeostasis and insulin signaling. Polymorphisms (rs1143699, rs4807015, and rs1978237) of this gene were also found to be associated with T2D in Swedish Caucasian population in a study conducted on 497 participants (Langberg *et al.*, 2007).

Genes Involved in IR Pathway

IR marks the beginning of pathophysiology of T2D. At the molecular level, IR correlates with impaired insulin signaling. Due to the progressive demand of insulin, PBC are stressed to secrete more insulin to compensate for the IR. This phenomenon is known as compensatory mechanism. This leads to a condition called as hyperinsulinemia. Burden

on PBC initiates insulin secretory defects and pancreas are no longer able to compensate for the IR. Extensive stress, calcium influx, and effects of cytokines graduate the process of PBC apoptosis leading to overt T2D form of prediabetes. Genes like PPAR-γ play a crucial role in IR by its effects on adiponectin, obesity, and free fatty acids (Porter and Barrett, 2005). Along with PPAR-γ, defects in insulin receptor also lead to IR. Genes implicated in IR and T2D are given in the Table 3.

The candidate genes associated with IR and T2D are spread all across the genome. Two genes present on chromosome 1 are *PRKAA2* and *HSD11B1*. *PRKAA2* gene encodes alpha 2 isoform of catalytic subunit of *AMPK*, which is involved in glucose and lipid metabolism, IR and T2D. Moreover, *PRKAA2* is located at the highly susceptible loci on chromosome 1 (1p36-32), which is associated with T2D in populations worldwide. SNP rs2051040 is independently and as a haplotype have been associated with IR in Japanese population ($p = 0.009$) in a sample set of 1205 cases and 824 controls (Horikoshi *et al.*, 2006). *HSD11B1* is an enzyme, which converts cortisol to cortisone. Changes in enzymatic action have been associated with metabolic syndrome, IR, and T2D. Two variants of this gene (rs846910, $p = 0.03$ and rs12086634, $p = 0.03$) have been reported in the context of IR, dyslipidemia, and T2D (Gandhi *et al.*, 2013).

Two genes *PPARG* and *ADIPOQ* present on chromosome 3 are implicated with IR. *LPN2* encodes for protein Lipin required for normal adipose tissue differentiation and triglyceride (TG) metabolism. Lipin2 binds upstream to *PPARG* to carry out this process. Owing to its role, the SNP in its 3′UTR was associated ($p = 0.03$, OR: 1.96) with IR in the Dutch population comprising 3506 subjects (Aulchenko

Table 3. List of the Candidate Genes and Their Variants Associated with Insulin Resistance Causing Type 2 Diabetes

Gene symbol	*Full name of the genes*	*Chromosomal location*	*SNP common name*	*db SNP*	*Position*	*References*
LPIN2	Lipin 2	17		rs3745012	3′UTR	Aulchenko *et al.* (2007)
PPARG	Peroxisome proliferator-activated receptor gamma	3	Pro12Ala	rs1801282	Intron	Li *et al.* (2014)
HNF4A	Hepatocyte nuclear factor 4, alpha	20		rs4810424	Promoter	Saif-Ali *et al.* (2011)
				rs1884613	Promoter	Saif-Ali *et al.* (2011)
				rs1884614	Promoter	Saif-Ali *et al.* (2011)
PTPN1	Protein tyrosine phosphatase, nonreceptor type 1	20		rs941798	5′UTR	Cheyssac *et al.* (2006)
				rs2426159	Intron	Cheyssac *et al.* (2006)
				rs914458	Intron	Cheyssac *et al.* (2006)
PRKAA2	Protein kinase, AMP-activated, alpha 2, catalytic subunit	1		rs2051040	Intron	Horikoshi *et al.* (2006)
UCP3	Uncoupling protein 3	11		rs1800849	5′UTR	Salopuro *et al.* (2009)
				rs3781907	5′UTR	Salopuro *et al.* (2009)
SOCS3	Suppressor of cytokine signaling 3	17		rs12953258	5′UTR	Meng *et al.* (2014)
				rs4969168	3′UTR	Meng *et al.* (2014)
				rs9914220	Intron	Meng *et al.* (2014)
CAV2	Calveolin 2	7		rs2270188	Intron	Fisher *et al.* (2011)
UCP1	Uncoupling protein 1	8	−112A>C	rs10011540	Promoter	Salopuro *et al.* (2009)
ADRB2	Adrenoceptor beta 2, surface	5		rs1042711	5′UTR	Tellechea *et al.* (2013)
				rs1801704	5′UTR	Tellechea *et al.* (2013)
				rs1042713	5′UTR	Tellechea *et al.* (2013)
				rs1042714	5′UTR	Tellechea *et al.* (2013)
HSD11B1	Hydroxysteroid (11-beta) dehydrogenase 1	1		rs846910	Intron	Gandhi *et al.* (2013)
				rs12086634	Intron	Gandhi *et al.* (2013)
ADIPOQ	Adiponectin	3	−11391G/A	rs17300539	Promoter	Foucan *et al.* (2014)
			45T>G	rs2241766	Exon	Foucan *et al.* (2014)
			276G>T	rs1501299	Intron	Foucan *et al.* (2014)
			G(−10069)A	rs182052	Intron	Foucan *et al.* (2014)
ESR1	Estrogen recceptor-alpha gene	6		rs2431260	Intron	Gallagher *et al.* (2007)
				rs1709183	Intron	Gallagher *et al.* (2007)
NRF1	Nuclear respiratory factor 1	7	−24833A>G	rs6969098	Intron	Liu *et al.* (2008)
			G141T	rs1882094	5′UTR	Liu *et al.* (2008)
NOS3	Nitric oxide synthase	7	G894T	rs1799983	Missense	Jia *et al.* (2013)
LTA	Lymphotoxin-alpha	6		rs2229094	Missense	Mahajan *et al.* (2010)
RACE	Receptor for advanced glycation end product	5		rs3134945	Intron	Gaens *et al.* (2008)
TNF	Tumor necrosis factor	6	−857C>T	rs1799724	Promoter	Xu *et al.* (2013)
			−803 A>C	rs1800630	Promoter	Xu *et al.* (2013)
			−1031T>C	rs1799964	Promoter	Xu *et al.* (2013)

et al., 2007). Pro12Ala variant of *PPARG*, which has been found associated with IR and obesity leading to T2D in various populations of the world, including Caucasians, Americans, and Japanese (Li *et al.*, 2014). *ADIPOQ* (Adiponectin) is a protein peptide secreted by adipose cells, which has anti-inflammatory effects. Decreased concentration of adiponectin in plasma is associated with T2D, IR, and obesity. Four major SNPs (rs17300539, rs2241766, rs1501299, and 182052) related to this gene are implicated with T2D in Han Chinese, Japanese, Caucasian, and Asian populations (Foucan *et al.*, 2014).

Chromosome 5 also harbors two genes *ADRB2* and *RACE*. *ADRB2* is a beta adrenergic G protein coupled receptor, which is directly associated with the calcium channel for fast transport. Haplotype analysis of 5′UTR SNPs (rs1042711, rs1801704, rs1042713, rs1042714) of this gene revealed its protective role ($p = 0.018$) against IR (Tellechea *et al.*, 2013). RAGE is a cell surface receptor implicated in the development of T2D. One variant (rs3134945) has been associated ($p < 0.05$) with IR in T2D patients from the Netherlands (Gaens *et al.*, 2008).

ESR1, *LTA*, and *TNF*-α are the three genes present on chromosome 6. *ESR1* encodes for sex steroids. Treatments with sex steroids are known to cause IR. Two SNPs (rs2431260 and rs1709183) in these genes are found to cause IR in European American cohort with 300 cases and 310 controls with *p*-value of $p = 0.015$ and $p = 0.019$, respectively (Gallagher *et al.*, 2007). *TNF*-α encodes for a proinflammatory cytokine, secreted by macrophages. TNFα plays a role in the regulation of cell proliferation, apoptosis, lipid metabolism, and cancer. Being part of lipid metabolism regulation, it has been associated with IR. Haplotype analysis of three SNPs (rs179964, rs1800630, rs1799724) in this gene revealed significant association (OR: 2.7 and $p < 0.05$) in T2D patients on insulin therapy (Xu *et al.*, 2013). *LTA* encodes for lymphotoxin alpha protein. A study conducted on North Indians comprising of 1073 cases and 1042 controls showed significant association (OR: 0.86, $p = 0.02$) of this gene with decreased body mass index (BMI) and waist circumference (WC) in diabetic subjects (Mahajan *et al.*, 2010).

Chromosome 7 harbors three genes *CAV2*, *NRF1*, and *NOS3*. *CAV* is a protein present on the inner surface of plasma membrane involved in lipid metabolism and cancer. SNP in this gene (rs2270188) is reported to be associated with dietary fat intake ($p = 0.004$) in a European population (Fisher *et al.*, 2011). *NRF1*, a nuclear respiratory factor-1 gene, downregulates mitochondrial respiratory genes during oxidative phosphorylation. Two SNPs (rs1882094 and rs6969098) of this gene were found to be associated with T2D in Han Chinese population comprising 1027 subjects. GG carriers of rs1882094 were found to have low plasma glucose levels ($p = 0.0002$) and rs6969098 was associated with this polymorphism as a risk-conferring haplotype. These SNPs were also associated in Korean population (Liu *et al.*, 2008). *NO* is encoded by nitric oxide synthase (*NOS*) isoenzyme gene and is known to cause IR and glucose intolerance especially in Asian populations. Based on meta analysis, rs1799983 correlated with the risk of T2D in Chinese diabetic subjects ($n = 8600$, OR: 1.14) (Jia *et al.*, 2013).

UCP1 present on chromosome 8 and *UCP3* on chromosome 11 are the metabolite transporters belonging to the subfamily of the mitochondrial anion carrier. *UCP1* is involved in adaptive thermogenesis and decrease in reactive oxygen species (ROS) production, whereas *UCP3* is believed to be involved in free fatty acids (FFA) metabolism and transport (Lim *et al.*, 2012). A promoter polymorphism (rs10011540) in *UCP1* gene has been associated ($p = 0.0089$) with IR and accumulation of hepatic lipid in the Japanese population. Two variants (rs1800849 and 3781907) in *UCP3* gene have been found to be associated with high lipid levels and waist hip ratio (WHR) reported from Finnish population. These SNPs have also been well associated with T2D, obesity indices, and cholesterol levels in Caucasians, Japanese, South Indians and Asian populations (Salopuro *et al.*, 2009).

SOCS3 gene is present on chromosome 17. *SOCS3* expression is induced by *IL6*. Haplotype of three SNPS (rs12953258, rs4969168, and rs9914220) was found to be associated with IR ($p = 0.023$) in Uygur males and rs12953258 with IR in Uygur females (Meng *et al.*, 2014).

Chromosome 20 harbors two genes. *HNF4A* gene encodes for a nuclear transcription factor involved in the development of kidneys, liver, and intestine. Mutations in this gene have been associated with monogenic form of diabetes called MODY. Three promoter variants (rs4810424, $p = 0.017$; rs1884613, $p = 0.037$; rs1884616, $p = 0.024$) in this gene have been associated with IR in Malaysian population (Saif-Ali *et al.*, 2011). *PTPN1* is a negative regulator of insulin and leptin signaling, which modulates glucose homeostasis and IR. In a French cohort comprising 2264 subjects, three variants (rs914458, $p = 0.02$; rs941798, $p = 0.04$; rs2426159, $p = 0.02$) of this gene were reportedly associated with IR (Cheyssac *et al.*, 2006).

Epigenetics in T2D

Epigenetics is implicated in control of gene expression and epigenetic changes can be endogenously programmed or may occur in response to exogenous factors. Endogenous factors comprise changes during early developmental stages, diverse cell lineage, stem cell variation, and age-related modifications. Exogenous factors are of two types, which include physical and chemical ones. Physical factors include exposure to radiations, hypoxia, calorie restriction, and excessive cold and heat. Bisphenol-A, herbicides, emulsifiers, surfactants, and arsenic are some of the chemicals leading to epigenetic changes.

DNA methylation of the CpG sites in promoters of the candidate genes was noticed in T2D. About 70% of the SNPs in the promoter region are associated with T2D through DNA methylation. Most of the genes, such as *IL6*, *IL6R*, and *TNF*, were proinflammatory (Wren and Garner, 2005). Ageing apparently could cause errors in methylation. It leads to production of short-chain fatty acids accompanied by hypomethylation resulting in dysregulation of the proinflammatory cytokines. Patients with T2D reported with enhanced methylation display aging, hyperglycemia, and obesity (Gilbert and Liu, 2012).

The number of mi-RNA is altered in various tissues in T2D. Hyperglycemia and lipotoxicity are the key modulators of miRNA expression in response to environmental damage. miRNA plays a role in PBC development, maturity, and function. Increase in mi-RNA expression leads to altered fat metabolism, chronic hyperglycemia, increase in proinflammatory cytokine signaling, and finally β-cell apoptosis.

PGC-1α, *GCK*, *PDX-1, PPAR-γ, GLUT-4, TCF7L2* genes have shown altered expression in response to DNA methylation. Increased methylation of insulin gene promoter causes decreased *PGC-1α* expression leading to decreased insulin secretion. Hypermethylation of DNA causes decreased expression of *GCK*. Increased methylation leads to decreased expression of *PDX1* in β-cells and histone modifications impairing β-cell development and function (Yang *et al.*, 2012). *TCF7L2* promoter was found 50% more methylated in patients with T2D without medication (Canivell *et al.*, 2014).

Intrauterine environment also initiates epigenetic changes such as PPAR-γ coactivator gene promoter hyperacetylation observed in the liver of intrauterine growth restriction rat models (IUGR). Similarly, in skeletal muscle of female IUGR, *GLUT-4* genes were found to be regulated by methylation and deacetylation (Fu *et al.*, 2004). Human studies were carried out using blood, where CpG hypomethylation of *IGF-II* gene in response to periconceptional famine was reported (Heijmans *et al.*, 2008). Similarly, nonCpG hypermethylation of *PPAR-γ* coactivator was observed when incubated with *TNF-α*, free fatty acids, insulin, and glucose (Barres *et al.*, 2009). In skeletal muscle, the *PPAR-γ* coactivator gene CpGs was hypermethylated in response to a high-fat diet (Brons *et al.*, 2010).

Obesity in T2D

The changing environmental and economic growth owing to green and white revolutions leads to improved socioeconomic status contributing to obesity and diabetes (Sharma *et al.*, 2013). Studies for Asian Indian populations have also indicated that central obesity poses a greater risk than general obesity toward T2D and associated complications. WC and WHR are the commonly used parameter to assess central obesity and may act as a risk factor for T2D. Central obesity reflects enhanced abdominal fat, visceral adipose tissue, and hepatic fat cells contributing to increased values of WC and WHR (Lear *et al.*, 2002). However, in western countries, BMI is more associated with T2D.

The biological reason is that the central fat deposits have direct access to liver through portal vain circulation. When more energy is required, central fat deposits mobilize first as compared to other subcutaneous and gluteofemoral fat. Central obesity results in the overload of abdominal adipocytes with TG, reducing the capacity of fat depots to utilize dietary fat. Central adipocytes have high basal lipolysis and are very sensitive to fat mobilizing hormones like catecholamines (Arner, 1997), but they respond poorly to insulin. The enlarged central adipocytes flood the portal circulation with FFA exposing nonadipose tissue to excess of fat. This leads to accumulation of TG in muscles, liver, and PBCs, resulting in IR and β-cell dysfunction. Therefore, to reduce the ectopic fat deposition in insulin-sensitive tissues and to reduce excessive outflow of fat, it is recommended to decrease central fat reserves (Raz *et al.*, 2005). Thus, obesity is the reason behind the epidemic rise of T2D, either measured by WC or by BMI. Obesity disrupts many pathways interlinked with T2D such as IR, and increased FFA circulation, which makes it even more dangerous as a risk factor for T2D.

Gene Environment Interactions

Interactions between genes and environmental factors contribute toward causation of T2D. The detrimental effects of genetic factors are elevated in the presence of environmental triggers. During the last few years, several studies have documented gene environment interaction showing associations with SNP markers. Diet and excessive intake of calories have been identified as the major force escalating the prevalence of T2D in the populations worldwide (Qi *et al.*, 2008).

Most of the genetic variants associated with T2D in Caucasian population have been successfully replicated in Asians. Regardless of the heterogeneity, the number of risk variants seems to be similar across populations. Each variant increases the risk of developing T2D by 10–20%. However, increased T2D susceptibility can be better investigated in presence of the environmental factors (Murcray *et al.*, 2008). In Caucasians, inflammatory genes were found to aggrandize the risk in the presence of western diet, which included sugar-sweetened beverages, refined/white grains, red/processed meat. Along with diet, other anthropometric measures like BMI were also found to aggravate the risk of T2D in Caucasian populations (Hu, 2011). On the other hand, in Asian populations the presence of thrifty genes is believed to play an important role in T2D. Due to the exposure of Asian populations to feast and famine cycle, they are believed to have inherited thrifty genes which are supposed to release more energy even with small amount of food intake (Neel, 1962). However, now with industrial and green revolutions, accompanied with sedentary lifestyles, have led to an increased prevalence of T2D in these populations. Besides thrifty genes, low birth weight and intrauterine nutrition are also the important factors deciding the risk for T2D in Asians populations. Asians are also found to have greater risk of obesity and T2D even at lower BMI values. WC and WHR are some of the important parameters implicated with T2D in Asians (Lear *et al.*, 2007).

Thus, for the management of T2D, the genetic factors, environmental factors, ethnic differences, and dietary intake should be taken into consideration before attempting to develop a possible biomarker.

Ethnicity, T2D, and Prospect of Personalized Medicine

Ethnicity is an inevitable factor contributing toward T2D (Kaul *et al.*, 2015). Different populations are susceptible toward T2D due to different environmental conditions, which modulate genetic backgrounds. The climatic conditions and dietary pattern in Western and European countries are entirely different from Asian countries. Moreover, the level of physical activity is more in Western and European countries than East Asian countries. In addition, the level of physical activity is highly reduced in South Asian countries because of cheap labor options, lack of awareness, and hectic job timing schedules. The thrifty genes are adapted to produce more energy even with less amount of food intake in cases of T2D. These environmental factors, climatic conditions, dietary pattern, and physical activity affect different populations in a different manner giving rise to varying genotype.

There are about 47 genetic loci responsible for T2D in the European population. However, genetic loci in East Asians included few loci common from European and some new loci like *KCNQ1* (rs2237892), *ZFAND3* (rs659470794), and

MAEA (rs6815464) etc. Most of the GWAS were carried out on Europeans. After 2008, GWAS were also carried out in other populations like East Asians, South Asians, Mexican Americans, and African Americans. The differential association of variants was noticed in different populations, which included some variants that were common in all the populations (*PPAR-γ, KCNJ11, TCF7L2* etc) to some variants that were specific to one population, such as *MEAE* and *ZFAND3* in East Asians, and TMEM163 and MAP3K1 in Indians (Tabassum *et al.*, 2013).

These reports suggest that in case of T2D, there are several genes having their own variants correlated with a given ethnic group. Thus, the only consensus in the present scenario is that there is no consensus whatsoever nor would there be any in the future. What all has gone wrong in a T2D patient in one population compared to those in another T2D patient of another population would always be different. Therefore, genotypically, each patient from a population is expected to be unique and thus, the response of the medicament given to such a patient would also be different. With respect to personalized medicine, all these factors qualify to be taken seriously. One possibility is that the T2D patients from across the world may be systematically classified based on their lifestyle and food intake coupled with ancestral history. This would provide some semblance on the category-wise genotypic variation across the population. The information on the intake of food habit would help in developing more efficient personalized medicine in tune with recognized genotype encompassing all the chromosomes and SNPs implicated with T2D.

Conclusion

T2D has become a threat to mankind globally. Unfortunately, there seem to be no respite from this or similar such burdens. Thus, before prescribing a generic drug, the complete knowledge of a person's genetic makeup, ethnicity, and the environmental factors that he has been exposed to should be considered. Till now, the drugs and medication provided to a diabetic person is more or less similar, irrespective of the abovementioned factors. This means that a personalized drug for T2D patient is nowhere in sight. This surely requires concerted efforts on the part of researchers, scientists, and clinicians and able all drug discoverers to join hands and move forward to meet the challenge.

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References

Alharbi, K.K., Khan, I.A., *et al.* (2014). Association of the genetic variants of insulin receptor substrate 1 (IRS-1) with type 2 diabetes mellitus in a Saudi population. Endocrine **47,** 472–477.

American Diabetes Association. (2011). Diagnosis and classification of diabetes mellitus. Diabetes Care **29,** S43–S48.

Arner, P. (1997). Regional adipocity in man. J Endocrinol **155,** 191–192.

Aulchenko, Y.S., Pullen, J., *et al.* (2007). LPIN2 is associated with type 2 diabetes, glucose metabolism, and body composition. Diabetes **56,** 3020–3026.

Barres, R., Osler, M.E., *et al.* (2009). Non-CpG methylation of the PGC-1alpha promoter through DNMT3B controls mitochondrial density. Cell Metab **10,** 189–198.

Brons, C., Jacobsen, S., *et al.* (2010). Deoxyribonucleic acid methylation and gene expression of PPARGC1A in human muscle is influenced by high-fat overfeeding in a birth-weight-dependent manner. J Clin Endocrinol Metab **95,** 3048–3056.

Cai, Y., Yi, J., Ma, Y., and Fu, D. (2011). Meta-analysis of the effect of HHEX gene polymorphism on the risk of type 2 diabetes. Mutagenesis **26,** 309–314.

Canivell, S., Ruano, E.G., *et al.* (2014). Differential methylation of TCF7L2 promoter in peripheral blood DNA in newly diagnosed, drug-naive patients with type 2 diabetes. PLoS One **9,** e99310.

Carlson, C.S., Aldred S.F, *et al.* (2005). Polymorphisms within the C-reactive protein (CRP) promoter region are associated with plasma CRP levels. Am J Hum Genet **77,** 64–77.

Cheyssac, C., Lecoeur, C., *et al.* (2006). Analysis of common PTPN1 gene variants in type 2 diabetes, obesity and associated phenotypes in the French population. BMC Med Genet **7,** 44.

Chu, W.S., Das, S.K., *et al.* (2007). Activating transcription factor 6 (ATF6) sequence polymorphisms in type 2 diabetes and pre-diabetic traits. Diabetes **56,** 856–862.

Crispim, D., Fagundes, N.J., *et al.* (2010). Polymorphisms of the UCP2 gene are associated with proliferative diabetic retinopathy in patients with diabetes mellitus. Clin Endocrinol (Oxf) **72,** 612–619.

Daimon, M., Sato, H., *et al.* (2008). Salt consumption-dependent association of the GNB3 gene polymorphism with type 2 DM. Biochem Biophys Res Commun **374,** 576–580.

de Lorenzo, C., Greco, A., *et al.* (2013). Variants of insulin-signaling inhibitor genes in type 2 diabetes and related metabolic abnormalities. Int J Genomics **2013,** 376454.

Du, B., Liu, S., *et al.* (2013). Association between glucose transporter 1 rs841853 polymorphism and type 2 diabetes mellitus risk may be population specific (1rs8418532). J Diabetes **5,** 291–299.

Fisher, E., Schreiber, S., *et al.* (2011). A two-step association study identifies CAV2 rs2270188 single nucleotide polymorphism interaction with fat intake in type 2 diabetes risk. J Nutr **141,** 177–181.

Foucan, L., Maimaitiming, S., *et al.* (2014). Adiponectin gene variants, adiponectin isoforms and cardiometabolic risk in type 2 diabetic patients. J Diabetes Investig **5,** 192–198.

Franks, P.W., Christophi, C.A., *et al.* (2014). Common variation at PPARGC1A/B and change in body composition and metabolic traits following preventive interventions: the Diabetes Prevention Program. Diabetologia **57,** 485–490.

Fu, M., Damcott, C.M., *et al.* (2004). Polymorphism in the calsequestrin 1 (CASQ1) gene on chromosome 1q21 is associated with type 2 diabetes in the old order Amish. Diabetes **53,** 3292–3299.

Gaens, K.H., van Der Kallen, C.J., *et al.* (2008). Receptor for advanced glycation end product polymorphisms and type 2 diabetes: the CODAM study. Ann N Y Acad Sci **1126,** 162–165.

Gallagher, C.J., Keene, K.L., *et al.* (2007). Investigation of the estrogen receptor-alpha gene with type 2 diabetes and/or nephropathy in African-American and European-American populations. Diabetes **56,** 675–684.

Gandhi, K., Adhikari, P., Basu, A., and Achappa, B. (2013). Association between a 11beta-hydroxysteroid dehydrogenase type 1 gene polymorphism and metabolic syndrome in a South Indian population. Metab Syndr Relat Disord **11,** 397–402.

Gilbert, E.R., and Liu, D. (2012). Epigenetics: the missing link to understanding beta-cell dysfunction in the pathogenesis of type 2 diabetes. Epigenetics **7,** 841–852.

Grarup, N., Stender-Petersen, K.L., *et al.* (2008). Association of variants in the sterol regulatory element-binding factor 1 (SREBF1) gene with type 2 diabetes, glycemia, and insulin resistance: a study of 15,734 Danish subjects. Diabetes **57,** 1136–1142.

Guyton, C., and Hall, J.E. (2010). *Text Book of Medical Physiology: Insulin, Glucagon and Diabetes Mellitus*, 11th ed. (Saunders, Elsevier, Philadelphia), pp. 939–950.

Haghverdizadeh, P., Sadat Haerian, M., and Sadat Haerian, B. (2014). ABCC8 genetic variants and risk of diabetes mellitus. Gene **545,** 198–204.

Harding, A.H., Loos, R.J., *et al.* (2006). Polymorphisms in the gene encoding sterol regulatory element-binding factor-1c are associated with type 2 diabetes. Diabetologia **49,** 2642–2648.

Heijmans, B.T., Tobi, E.W., *et al.* (2008). Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A **105,** 17046–17049.

Holmkvist, J., Almgren, P., *et al.* (2005). Haplotype construction of the FRDA gene and evaluation of its role in type II diabetes. Eur J Hum Genet **13,** 849–855.

Horikoshi, M., Hara, K., *et al.* (2006). A polymorphism in the AMPKalpha2 subunit gene is associated with insulin resistance and type 2 diabetes in the Japanese population. Diabetes **55,** 919–923.

Hu, F.B. (2011). Globalization of diabetes—the role of diet, lifestyle, and gene. Diabetes Care **34,** 1249–1257.

Jia, Z., Zhang, X., Kang, S., and Wu, Y. (2013). Association of endothelial nitric oxide synthase gene polymorphisms with type 2 diabetes mellitus: a meta-analysis. Endocr J **60,** 893–901.

Karamohamed, S., Demissie, S., *et al.* (2003). Polymorphisms in the insulin-degrading enzyme gene are associated with type 2 diabetes in men from the NHLBI Framingham Heart Study. Diabetes **52,** 1562–1567.

Kaul, N., Singh, Y.P., and Bhanwer, A.J.S. (2015). Influence of ethnicity in association of WC, WHR, hypertension and *PGC-1α* (Gly482Ser), *UCP2*-866 G/A and *SIRT1*-1400 T/C polymorphisms with T2D in population of Punjab. Gene **563,** 150–154.

Keshavarz, P., Inoue, H., *et al.* (2008). Single nucleotide polymorphisms in genes encoding LKB1 (STK11), TORC2 (CRTC2) and AMPK alpha2-subunit (PRKAA2) and risk of type 2 diabetes. Mol Genet Metab **93,** 200–209.

Kifagi, C., Makni, K., *et al.* (2011). Association of genetic variations in TCF7L2, SLC30A8, HHEX, LOC387761, and EXT2 with Type 2 diabetes mellitus in Tunisia. Genet Test Mol Biomarkers **15,** 399–405.

Kilpelainen, T.O., Lakka, T.A., *et al.* (2007). Physical activity modifies the effect of SNPs in the SLC2A2 (GLUT2) and ABCC8 (SUR1) genes on the risk of developing type 2 diabetes. Physiol Genomics **31,** 264–272.

Klimentidis, Y.C., Lemas, D.J., *et al.* (2014). CDKAL1 and HHEX are associated with type 2 diabetes-related traits among Yup'ik people. J Diabetes **6,** 251–259.

Konheim, Y.L., and Wolford, J.K. (2003). Association of a promoter variant in the inducible cyclooxygenase-2 gene (PTGS2) with type 2 diabetes mellitus in Pima Indians. Hum Genet **113,** 377–381.

Langberg, E.C., Gu, H.F., *et al.* (2007). Genetic variation in receptor protein tyrosine phosphatase sigma is associated with type 2 diabetes in Swedish Caucasians. Eur J Endocrinol **157,** 459–464.

Lear, S.A., Chen, M.M., *et al.* (2002). The relationship between waist circumference and metabolic risk factors: cohorts of European and Chinese descent. Metabolism **51,** 1427–1432.

Lear, S.A., Humphries, K.H., *et al.* (2007). Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). Am J Clin Nutr **86,** 353–359.

Li, T., Shi, Y., Yin, J., *et al.* (2014). The association between lipid metabolism gene polymorphisms and nephropathy in type 2 diabetes: a meta-analysis. Int Urol Nephrol **47,** 117–130.

Li, Y.F., Sun, H.X., *et al.* (2003). Protein kinase C/zeta (PRKCZ) gene is associated with type 2 diabetes in Han population of North China and analysis of its haplotypes. World J Gastroenterol **9,** 2078–2082.

Lim, J.H., Ko, M., *et al.* (2012). Differential association of uncoupling protein 2 polymorphisms with pattern identification among korean stroke patients: a diagnostic system in traditional Korean medicine. Evid Based Complement Alternate Med **2012,** 532078.

Liu, J.X., Liu, J., *et al.* (2012). Association of sterol regulatory element binding protein-1c genetic polymorphisms rs2297508 and rs11868035 with type 2 diabetes mellitus in Gansu Han and Dongxiang population. Zhonghua Yi Xue Yi Chuan Xue Za Zhi **29,** 328–333.

Liu, L., Yang, X., *et al.* (2013). Association between variants of EXT2 and type 2 diabetes: a replication and meta-analysis. Hum Genet **132,** 139–145.

Liu, Y., Niu, N., *et al.* (2008). Genetic variation and association analyses of the nuclear respiratory factor 1 (nRF1) gene in Chinese patients with type 2 diabetes. Diabetes **57,** 777–782.

Lowell, B.B., and Shulman, G.I. (2005). Mitochondrial dysfunction and type 2 diabetes. Science **307,** 384–387.

Mahajan, A., Tabassum, R., *et al.* (2010). Obesity-dependent association of TNF-LTA locus with type 2 diabetes in North Indians. J Mol Med (Berl) **88,** 515–522.

Meng, J., Li, N.F., *et al.* (2014). Relationship between female dyslipidemia and polymorphism of suppressor of cytokine signaling-3 in Xinjiang Uygur population. Zhongguo Yi Xue Ke Xue Yuan Xue Bao **36,** 5–11.

Mita, M., Miyake, K., *et al.* (2008). Association study of the effect of WFS1 polymorphisms on risk of type 2 diabetes in Japanese population. Kobe J Med Sci **54,** E192–E199.

Mohammed, S., Dasgupta, S., *et al.* (2015). MTNR1B gene polymorphisms and susceptibility to type 2 diabetes: a pilot study in South India. Gene **566,** 189–193.

Moritani, M., Nomura, K., *et al.* (2007). Genetic association of single nucleotide polymorphisms in endonuclease G-like 1 gene with type 2 diabetes in a Japanese population. Diabetologia **50,** 1218–1227.

Murcray, C.E., Lewinger, J.P., and Gauderman, W.J. (2008). Gene-environment interaction in genome wide association studies. Am J Epidemiol **169,** 219–226.

Neel, J.V. (1962). Diabetes mellitus: a ''Thrifty'' genotype rendered detrimental by ''Progress''? Am J Hum Genet **14,** 353–362.

Nitz, I., Fisher, E., *et al.* (2007). Association of prostaglandin E synthase 2 (PTGES2) Arg298His polymorphism with type 2 diabetes in two German study populations. J Clin Endocrinol Metab **92,** 3183–3188.

Omori, S., Tanaka, Y., *et al.* (2008). Association of CDKAL1, IGF2BP2, CDKN2A/B, HHEX, SLC30A8, and KCNJ11 with susceptibility to type 2 diabetes in a Japanese population. Diabetes **57,** 791–795.

Peng, F., Hu, D., *et al.* (2013). The relationship between five widely-evaluated variants in CDKN2A/B and CDKAL1 genes and the risk of type 2 diabetes: a meta-analysis. Gene **531,** 435–443.

Porter, J.R., and Barrett, T.G. (2005). Monogenic syndromes of abnormal glucose homeostasis: clinical review and relevance to the understanding of the pathology of insulin resistance and beta cell failure. J Med Genet **42,** 893–902.

Pradas-Juni, M., Nicod, N., *et al.* (2014). Differential transcriptional and posttranslational transcription factor 7-like regulation among nondiabetic individuals and type 2 diabetic patients. Mol Endocrinol **28,** 1558–1570.

Qi, L., Hu, F.B., and Hu, F.B. (2008). Genes, environment, and interactions in prevention of type 2 diabetes: a focus on physical activity and lifestyle changes. Curr Mol Med **8,** 519–532.

Qi, L., Rifai, N., and Hu, F.B. (2007). Interleukin-6 receptor gene variations, plasma interleukin-6 levels, and type 2 diabetes in U.S. Women. Diabetes **56,** 3075–3081.

Qin, L.J., Lv, Y., and Huang, Q.Y. (2013). Meta-analysis of association of common variants in the KCNJ11-ABCC8 region with type 2 diabetes. Genet Mol Res **12,** 2990–3002.

Rampersaud, E., Damcott, C.M., Fu, M., *et al.* (2007). Identification of novel candidate genes for type 2 diabetes from a genome-wide association scan in the Old Order Amish: evidence for replication from diabetes-related quantitative traits and from independent populations. Diabetes **56,** 3053–3062.

Raz, I., Eldor, R., *et al.* (2005). Diabetes: insulin resistance and derangements in lipid metabolism. Cure through intervention in fat transport and storage. Diabetes Metab Res Rev **21,** 3–14.

Rees, S.D., Britten, A.C., *et al.* (2009). The promoter polymorphism −232C/G of the PCK1 gene is associated with type 2 diabetes in a UK-resident South Asian population. BMC Med Genet **10,** 83.

Ren, J., Xiang, A.H., *et al.* (2014). Genetic variation in *MTNR1B* is associated with gestational diabetes mellitus and contributes only to the absolute level of beta cell compensation in Mexican Americans. Diabetologia **57,** 1391–1399.

Rudovich, N., Pivovarova, O., *et al.* (2009). Polymorphisms within insulin-degrading enzyme (IDE) gene determine insulin metabolism and risk of type 2 diabetes. J Mol Med (Berl) **87,** 1145–1151.

Rutter, G.A., and Chimienti, F. (2014). SLC30A8 mutations in type 2 diabetes. Diabetologia **57,** 485–490.

Saif-Ali, R., Harun, R., *et al.* (2011). Hepatocyte nuclear factor 4 alpha P2 promoter variants associate with insulin resistance. Acta Biochim Pol **58,** 179–186.

Salopuro, T., Pulkkinen, L., *et al.* (2009). Variation in the UCP2 and UCP3 genes associates with abdominal obesity and serum lipids: the Finnish Diabetes Prevention Study. BMC Med Genet **10,** 94.

Salpea, K.D., Gable, D.R., *et al.* (2009). The effect of WNT5B IVS3C>G on the susceptibility to type 2 diabetes in UK Caucasian subjects. Nutr Metab Cardiovasc Dis **19,** 140–145.

Saxena, M., Agrawal, C.G., *et al.* (2014). Interleukin-6 (IL-6)-597 A/G (rs1800797) & −174 G/C (rs1800795) gene polymorphisms in type 2 diabetes. Indian J Med Res **140,** 60–68.

Sharma, R., Matharoo, K., *et al.* (2013). Ethnic differences in CAPN10 SNP-19 in type 2 diabetes: a North-West Indian case control study and evidence from meta-analysis. Genet Res (Camb) **95,** 146–155.

Sun, X., Yu, W., and Hu, C. (2014). Genetics of type 2 diabetes: insights into the pathogenesis and its clinical application. Biomed Res Int **2014,** 926713.

Tabassum, R., Chauhan, G., *et al.* (2013). Genome-wide association study for type 2 diabetes in Indians identifies a new susceptibility locus at 2q21. Diabetes **62,** 977–986.

Tellechea, M.L., Muzzio, D.O., *et al.* (2013). Association between beta2-adrenoceptor (ADRB2) haplotypes and insulin resistance in PCOS. Clin Endocrinol (Oxf) **78,** 600–606.

Trombetta, M., Bonetti, S., *et al.* (2012). CACNA1E variants affect beta cell function in patients with newly diagnosed type 2 diabetes. The Verona newly diagnosed type 2 diabetes study (VNDS) 3. PLoS One **7,** e32755.

Wang, H., Liu, L., *et al.* (2013). Large scale meta-analyses of fasting plasma glucose raising variants in GCK, GCKR, MTNR1B and G6PC2 and their impacts on type 2 diabetes mellitus risk. PLoS One **8,** e67665.

Weedon, M.N., Clark, V.J., *et al.* (2006). A common haplotype of the glucokinase gene alters fasting glucose and birth weight: association in six studies and population-genetics analyses. Am J Hum Genet **79,** 991–1001.

Wijesekara, N., Chimienti, F., and Wheeler, M.B. (2009). Zinc, a regulator of islet function and glucose homeostasis. Diabetes Obes Metab **11,** 202–214.

Wren, J.D., and Garner, H.R. (2005). Data-mining analysis suggests an epigenetic pathogenesis for type 2 diabetes. J Biomed Biotechnol **2005,** 104–112.

Xu, H.X., Xu, W., *et al.* (2013). Association of TNF-1031T/C and clinical efficacy of insulin therapy in newly diagnosed type 2 diabetics. Zhonghua Yi Xue Za Zhi **93,** 3197–3201.

Yang, B.T., Dayeh, T.A., *et al.* (2012). Increased DNA methylation and decreased expression of PDX-1 in pancreatic islets from patients with type 2 diabetes. Mol Endocrinol **26,** 1203–1212.

Zee, R.Y., Germer, S., *et al.* (2008). C-reactive protein gene variation and type 2 diabetes mellitus: a case-control study. Atherosclerosis **197,** 931–936.

Zheng, C., Dalla Man, C., *et al.* (2015). A common variant in the MTNR1b gene is associated with increased risk of impaired fasting glucose (IFG) in youth with obesity. Obesity (Silver Spring) **23,** 1022–1029.

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