

# New insights from monogenic diabetes for “common” type 2 diabetes

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Boundaries between monogenic and complex genetic diseases are becoming increasingly blurred, as a result of better understanding of phenotypes and their genetic determinants. This had a large impact on the way complex disease genetics is now being investigated. Starting with conventional approaches like familial linkage, positional cloning and candidate genes strategies, the scope of complex disease genetics has grown exponentially with scientific and technological advances in recent times. Despite identification of multiple loci harboring common and rare variants associated with complex diseases, interpreting and evaluating their functional role has proven to be difficult. Information from monogenic diseases, especially related to the intermediate traits associated with complex diseases comes handy. The significant overlap between traits and phenotypes of monogenic diseases with related complex diseases provides a platform to understand the disease biology better. In this review, we would discuss about one such complex disease, type 2 diabetes, which shares marked similarity of intermediate traits with different forms of monogenic diabetes.

**Keywords:** simple/Mendelian diseases, complex diseases, type 2 diabetes, monogenic diabetes, maturity onset diabetes of the young

## Introduction

Genetic diseases have been historically categorized into simple, monogenic and complex, polygenic diseases. This straight forward classification of inherited diseases based on the number of genes involved in precipitating a diseased state proved to be useful in the identification and development of effective diagnostic, genetic counseling strategies, and drug target genes. Studies on single gene- Mendelian disorders have greatly benefitted our understanding of disease causing variants, gene functions and various regulatory mechanisms involved in the normal physiological functioning of the body (Weatherall, 2000). However, this distinction between rare monogenic and common complex diseases is now unclear with blurring boundaries defining these categories (Cooper et al., 2013). One of the best examples driving this point is sickle cell anemia which is caused by single base substitution that replaces glutamic acid with valine in the  $\beta$ -globin (Ingram, 1957). However, marked clinical heterogeneity cannot be explained by this single global mutation but to an extent by different haplotype background in the gamma-globin gene (Steinberg, 2005). Interestingly, the differences among different gamma-globin haplotypes correlate with differences in mean levels of fetal hemoglobin (HbF), which is known to influence the disease severity. Early linkage studies identified *Xmn1-HBG2* and *HBS1L-MYB* loci and genome-wide association studies (GWAS) identified polymorphisms at *BCL11A* locus, which

predict higher HbF levels and a milder disease course in sickle cell anemia patients (Lettre et al., 2008; Sedgewick et al., 2008; Uda et al., 2008). Together, they account for 20–50% of the variance in HbF levels, illustrating the importance of other genetic loci in modifying disease severity (Menzel and Thein, 2009; Thein et al., 2009). Thus, sickle cell anemia, which was once considered as the simplest of all Mendelian diseases, now strikes as an example of complex disease where multiple factors influence a particular patient's clinical outcome. The story of sickle cell anemia highlighting limitations in the age-old classification of inherited diseases doesn't stand in isolation. This example can now be extrapolated to other Mendelian disorders like phenylketonuria, cystic fibrosis etc. where mutations in one primary gene are present in most of the cases but the phenotype is influenced by allelic heterogeneity and/or mutations at multiple modifier genes (Dipple and McCabe, 2000a).

In today's world, genetic diseases represent a continuum where the phenotype is influenced by the number of loci involved and the extent of environmental participation. This also has direct relation to the methods used for understanding genetic diseases (Dipple and McCabe, 2000b). Techniques utilized for investigating single gene disorders may be applied to identification of genes influencing intermediate traits related to complex diseases. Similarly, methodologies typically used for complex trait analysis like GWAS and next-generation sequencing (NGS) technologies may be applied for identification of modifier genes that influence the phenotypes in monogenic disorders. In this review, we will discuss about one such disease, where defects in single gene are known to cause relatively rare, monogenic forms of diabetes and polymorphisms at several loci are associated with polygenic forms of diabetes. Significant overlap of phenotypes between monogenic diabetes and commonly occurring type 2 diabetes (T2D) provide a great platform to investigate pathophysiological mechanisms underlying development of T2D.

## Diabetes: A Complex, Chronic Metabolic Disease

Diabetes is the most prevalent metabolic disease characterized by hyperglycemia due to primary defects in insulin secretion and/or insulin function. Diabetes has reached pandemic proportions with 347 million people affected worldwide which can be traced back to rapid rise in obesity and life style changes like physical inactivity (American Diabetes Association, 2014). Inadequate treatment is potentially devastating due to micro- and macrovascular complications. Total deaths due to diabetes is expected to rise by 50% in the coming decade projecting it to be the 7th leading global cause of death by 2030 (Mathers and Loncar, 2006). High rate of morbidity and mortality in diabetes is due to the direct and indirect effects of hyperglycemia on the vasculature which include retinopathy causing loss of vision, nephropathy causing renal failure, peripheral neuropathy and autonomic neuropathy and macrovascular complications such as stroke and atherosclerosis (Forbes and Cooper, 2013).

Majority of diabetic cases are broadly classified into two etiological categories: type 1 diabetes (T1D) where lack of insulin secretion due to auto-immune mediated destruction of beta cells causes hyperglycemia and T2D where insulin resistance and inadequate insulin secretory response result in raised circulating glucose levels (American Diabetes Association, 2014). T1D represents around 5–10% (Atkinson et al., 2014) and T2D accounts for about 90% of the diabetic cases worldwide (Wild et al., 2004). Autoimmune destruction of beta cells has multiple genetic predispositions (Onengut-Gumuscu et al., 2015) and effect of environmental factors is still being understood in T1D (Knip et al., 2005; Vaarala et al., 2008). However, markers of immune destruction like islet cell auto-antibodies, auto-antibodies to insulin, GAD65, and tyrosine phosphatases IA-2 and IA-2b and rise in circulating levels of C-peptide help in reasonably accurate diagnosis of T1D and determine their clinical course (Arvan et al., 2012; American Diabetes Association, 2014; Atkinson et al., 2014). In the latter case, decreased insulin secretion and insulin resistance frequently co-exist in patients. T2D, on the other hand is characterized by resistance to insulin action in tissues like liver, skeletal muscle and adipose tissue, which leads to other features such as dyslipidaemia and central obesity (Thomas and Philipson, 2015). Impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) can provide indications of derangements in glucose metabolism (American Diabetes Association, 2014). Patients spend a long asymptomatic period characterized by hyperglycemia, which is undetectable but sufficient to cause pathological changes.

T1D and T2D are polygenic in nature and caused due to interaction between genetic and environmental factors. Monogenic diabetes, on the other hand represents rare, heterogeneous group of disorders due to genetic defects in single genes causing pancreatic beta cell dysfunction and marked hyperglycemia (Thomas and Philipson, 2015). Around 2–5% of global cases correspond to monogenic diabetes. Maturity onset diabetes of the young (MODY) and neonatal diabetes mellitus (NDM) represent two different classes of monogenic diabetes where hyperglycemia is either due to defects in insulin secretion, decrease in beta cell mass or both (Schwitzgebel, 2014). MODY is characterized by features like autosomal dominant inheritance pattern, positive familial history, early age of onset, absence of auto-immune antibodies and insulin resistance (Owen, 2013). Its shared features (**Table 1**) with other forms of diabetes often results in misdiagnosis of MODY patients as T1D or T2D patients (van der Zwaag et al., 2015). NDM on the other hand is characterized by onset of hyperglycemia in the first few weeks of life and can be either transient neonatal diabetes mellitus (TNDM) or permanent neonatal diabetes mellitus (PNDM). TNDM is a mild form and usually resolves by 18 weeks of age but the patients are at risk of developing diabetes in the adult stages of life where as PNDM requires life-long treatment and can result in isolated hyperglycemia or may present with extra-pancreatic features depending on the gene mutated (Greeley et al., 2011).

In addition to these categories, few monogenic forms of insulin resistance such as primary lipodystrophic syndromes and insulin receptor defects leading to Donahue syndrome, Rabson–Mendenhall syndrome or Type-A insulin resistance display

**TABLE 1 | Characteristic features of different types of diabetes.**

Features	Type 1 diabetes (T1D)	Type 2 diabetes (T2D)	Maturity onset diabetes of the young (MODY)
Age of onset	Any age/more frequent childhood and adolescence	More frequent in adults and obese children	Usually before the age of 25 years
Parents affected	Rarely multigenerational	Rarely multigenerational	Usually minimum three generations affected
Inheritance	Polygenic	Polygenic	Monogenic, autosomal dominant/recessive
Beta cell autoantibodies	Present	Absent	Absent
C-peptide	Undetectable/low	Normal/high	Normal
Insulin production	Absent	Present	Present*
Obesity	Usually absent	Frequent (>80%)	Very rare
Diabetic ketoacidosis	Common	Rare	Rare
First line treatment	Insulin	Oral hypoglycemic agents (Metformin)	Depends on sub-type of MODY

\*Low levels when pancreatic agenesis occurs due to gene mutations.

features of metabolic syndrome and are associated with insulin resistant T2D (Hegele, 2003).

## Genetics of Monogenic Diabetes: A Success Story

Linkage studies in families with above diagnostic criteria identified mutations in several genes leading to MODY. Mutations in hepatocyte nuclear factor 4 alpha, (*HNF4A*, MODY1), glucokinase (*GCK*, MODY2), hepatocyte nuclear factor 1 alpha (*HNF1A*, MODY3) result in most common forms of MODY (Shields et al., 2010; Pihoker et al., 2013). Mutations in genes like pancreatic and duodenal homeobox 1 (*PDX1*, MODY4), hepatocyte nuclear factor 1 beta (*HNF1B*, MODY5) neurogenic differentiation 1 (*NEUROD1*, MODY6) and insulin (*INS*, MODY10) cause relatively rare forms of MODY (Naylor and Philipson, 2011). Fine mapping studies and the advent of NGS technologies like whole-exome sequencing, not only rapidly increased the mutational spectrum of causal genes but also helped in the identification of novel MODY genes (Bamshad et al., 2011; Ku et al., 2011; Bonnefond et al., 2012; Johansson et al., 2012). Currently, Online Mendelian Inheritance in Man (OMIM) lists 13 different causal genes that result in distinct sub-phenotypes of MODY as described in **Table 2**.

TNDM is most commonly caused due to over-expression of imprinted genes, *PLAGL1* and *HYMAI* at 6q24 due to paternal uniparental disomy of chromosome 6 or duplication of 6q24 on the paternally inherited allele or hypomethylation of the maternally inherited 6q24 allele (Temple and Shield, 2002). Other rarer causes of TNDM include heterozygous mutations in genes encoding sub-units of ATP-sensitive potassium channel: potassium channel, inwardly rectifying subfamily J, member 11 (*KCNJ11*) (Flanagan et al., 2007), ATP-binding cassette, sub-family C, member 8 (*ABCC8*) (Patch et al., 2007) and bi-allelic mutations in zinc finger protein 57 (*ZFP57*) (Mackay et al., 2008). In addition, rare mutations in *INS* may also cause a phenotype which can be described as TNDM (Stoy et al., 2007). More than 50% of PNDM cases are due to activating mutations in *KCNJ11* and *ABCC8*, while majority of mutations genes

associated with PNDM are de novo in origin (Gloyn et al., 2004; Babenko et al., 2006; Edghill et al., 2010). Approximately 20% of PNDM is attributed to mutations of *INS* (Stoy et al., 2007). Rarely PNDM is caused by inactivating mutations of *PDX1* and glucose transporter2 (*SLC2A2*) (Nicolino et al., 2010). As of date, mutations in close to 20 genes are known to cause diabetes in the first year of life (**Table 2**).

Hyperglycemia is a common consequence of mutations in these genes; nevertheless, they are associated with distinct phenotype and characteristic clinical presentation. For instance, mutations in *HNF4A* are associated with increase in birth weight, macrosomia, hypoglycemia at birth and adolescent onset of diabetes (Pearson et al., 2007). Patients exhibit progressive beta cell failure and long term treatment with low dose sulphonylureas is proven to be more effective than insulin treatment (Fajans and Brown, 1993). In addition to the above features, patients carrying *HNF-1A* mutations present with severe dysfunction of hepatocytes and renal tubular cells resulting in glycosuria with high incidence of vascular complications. Patients with *HNF1A* mutations are also extremely sensitive to low doses of sulphonylureas (Pearson et al., 2000). Mutations in *HNF1B* are associated with renal defects with cystic renal disease, pancreatic agenesis and genitor-urinary abnormalities. But these patients are insensitive to treatment with insulin sensitizers and require early treatment with insulin (Edghill et al., 2006). In contrast to the mutations in various *HNF* genes, glucokinase mutations result in mild, stable, fasting hyperglycemia from birth and small elevations in post-prandial glucose levels. Insulin secretion remains intact and vascular complications are not commonly observed in these patients and hence they do not require any pharmacological intervention and dietary intervention is usually sufficient to maintain stable glycosylated hemoglobin levels (HbA1c) levels (Stride et al., 2002; Murphy et al., 2008). Activating *KCNJ11* mutations are associated with a number of clinical features ranging from isolated diabetes to more severe phenotypes such as developmental delay-epilepsy-neonatal diabetes syndrome (Gloyn et al., 2006). Neonatal patients identified with *KCNJ11* and *ABCC8* mutations show little endogenous insulin secretion and non-detectable C-peptide levels and hence used to be put on long-term insulin

TABLE 2 | Genes/loci associated with different forms of monogenic diabetes and insulin resistance.

Disease	Genes/loci	Gene name	Chromosome	Inheritance pattern	Characteristic clinical features
<b>MATURITY-ONSET DIABETES OF THE YOUNG (MODY)</b>					
MODY-1	<i>HNF-4A</i>	Hepatocyte nuclear factor 4 alpha	20q13.12	AD	Familial, early-onset diabetes. Responds well to sulphonylurea pills
MODY-2	<i>GCK</i>	Glucokinase (hexokinase 4)	7p15.3-p15.1	AD/AR	Mild and long-lasting stable hyperglycemia; <b>mutations can cause PNDM</b>
MODY-3	<i>HNF1A</i>	HNF1 homeobox A	12q24.2	AD	Normoglycemic in childhood, develop progressive beta-cell dysfunction
MODY-4	<i>PDX1</i>	Pancreatic and duodenal homeobox 1	13q12.1	AR	Pancreatic agenesis
MODY-5	<i>HNF1B</i>	HNF1 homeobox B	17q12	AD/Spontaneous	Exocrine pancreatic insufficiency, renal cysts, genitourinary abnormalities; <b>mutations can cause TNDM</b>
MODY-6	<i>NEUROD1</i>	Neurogenic differentiation 1	2q82	AR	Very rare, adult onset diabetes with reduced insulin production and associated with obesity; <b>mutations can cause PNDM</b>
MODY-7	<i>KLF11</i>	Kruppel-like factor 11	2p25	AD	None other than diabetes mellitus
MODY-8	<i>CEL</i>	Carboxy ester lipase	9q34.3	AD	Marked exocrine pancreatic is noticed
MODY-9	<i>PAX4</i>	Paired box 4	7q82	AD	Adult onset diabetes
MODY-10	<i>INS</i>	Insulin	11p15.5	AD	Growth retardation; <b>mutations can cause PNDM and TNDM</b>
MODY-11	<i>BLK</i>	BLK, proto-oncogene, Src family tyrosine kinase	8p23-p22	AD	Adult onset diabetes
MODY-12	<i>ABCC8</i>	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	11p15.1	AD	Can cause developmental delay and epilepsy; <b>mutations can cause PNDM and TNDM</b>
MODY-13	<i>KCNJ11</i>	Potassium channel, inwardly rectifying subfamily J, member 11.	11p15.1	AD	Developmental delay and epilepsy; <b>mutations can cause PNDM and TNDM</b>
Mitochondrial mutations	-	Mitochondrial m.3243A>G mutation	-	Mitochondrial	Deafness, short stature, pigmentary retinopathy
<b>NEONATAL DIABETES MELLITUS (NDM)</b>					
Permanent neonatal diabetes mellitus (PNDM)	<i>CISD2</i>	CDGSH iron sulfur domain 2	4q24	AR	Sensorineural hearing loss, optic atrophy or neuropathy and defective platelet aggregation
	<i>EIF2AK3/PERK</i>	Eukaryotic translation initiation factor 2-alpha kinase 3	2p12	AR	Epiphyseal dysplasia, osteoporosis, and growth retardation at later age
	<i>FOXP3</i>	Forkhead box P3	Xp11.23	X-linked	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
	<i>GATA6</i>	GATA binding protein 6	18q11.1-q11.2	AD	Pancreatic agenesis, congenital heart abnormalities
	<i>GLIS3</i>	GLIS family zinc finger 3	9p24.2	AR	Congenital hypothyroidism, glaucoma, liver fibrosis and cystic kidney disease

(Continued)

TABLE 2 | Continued

Disease	Genes/loci	Gene name	Chromosome	Inheritance pattern	Characteristic clinical features
	<i>IER3IP1</i>	Immediate early response 3 interacting protein 1	18q12	AR	Microcephaly, infantile seizures
	<i>MX1</i>	Motor neuron and pancreas homeobox 1	7q36	AD	Partial absence of the sacrum, anorectal anomalies and presacral mass
	<i>NEUROG3</i>	Neurogenin 3	10q21.3	AR	Diabetes and chronic intractable malabsorptive diarrhea starting soon after birth
	<i>NKX2-2</i>	NK2 homeobox 2	20p11.22	NR	Developmental delay with impaired motor and intellectual functions
	<i>PCBD1</i>	Pterin-4 Alpha-Carbinolamine Dehydratase/Dimerization Cofactor of HNF-1a	10q22	AR	Early onset diabetes similar to MODY-3; new born screening for phenylketonuria
	<i>PLAGL1-HYMAI</i>	Pleiomorphic adenoma gene-like 1; Hydatidiform mole associated and imprinted	6q24	Sporadic	Macroglossia, umbilical hernia, cardiac and brain developmental defects
	<i>PTF1A</i>	Pancreas specific transcription factor, 1a	10p12.2	AR	Pancreatic and cerebellar hypoplasia without exocrine dysfunction
	<i>RFX6</i>	Regulatory factor X, 6	6q22.1	AR	Intestinal atresia, gall bladder hypoplasia, diarrhea, exocrine pancreatic insufficiency
	<i>TRMT10A</i>	TRNA Methyltransferase 10 Homolog A	4q23	NR	Microcephaly with mental retardation, short stature, and early-onset diabetes.
	<i>WFS1</i>	Wolframin	4p16.1	AR	Optic atrophy, diabetes insipidus, deafness, renal tract abnormalities, neurological abnormalities
Temporary neonatal diabetes mellitus (TNDM)	<i>ZFP57</i>	Zinc finger protein 57	17	AR	Intrauterine growth restriction
	<i>SLC2A2</i>	Solute carrier family 2 (facilitated glucose transporter), member 2	3q26.1-q26.2	AR	Hepatomegaly, proximal tubular nephropathy, hypergalactosemia
Permanent/temporary neonatal diabetes mellitus (FNDM/TNDM)	<i>GATA4</i>	GATA binding protein 4	8p23.1-p22	AD/De novo	Pancreatic agenesis, congenital heart abnormalities
	<i>SLC19A2</i>	Solute carrier family 19 (thiamine transporter), member 2	1q23.3	AR	Megaloblastic anemia, deafness, cardiac and neurological abnormalities
<b>MONOGENIC FORMS OF INSULIN RESISTANCE</b>					
CGL type 1	<i>AGPAT2</i>	Acylglycerol-3-phosphate O -acyltransferase 2	12q14.1	AR	Very low adiponectin levels, acanthosis nigricans and hypertrophic cardiomyopathy
CGL type 2	<i>BSCL2</i>	Berardinelli-Seip congenital lipodystrophy 2 (Seïgin)	11q13	AR	Loss of adipose tissue from mechanical fat pads such as the palms, soles, orbits, scalp and periauticular regions
CGL type 3	<i>CAV1</i>	Caveolin-1	7q31.1	AR	Short stature
CGL type 4	<i>PTRF</i>	Cavin	17q21.2	AR	Muscular dystrophy
FPLD-type 2 (FPLD2)	<i>LMNA</i>	Lamin A	1q22	AD	Preserved/Excess facial and neck fat

(Continued)

TABLE 2 | Continued

Disease	Genes/loci	Gene name	Chromosome	Inheritance pattern	Characteristic clinical features
FPLD-type 3 (FPLD3)	PPARG	Peroxisome proliferator-activated receptor gamma,	3p25	AD	Excess abdominal fat and hypertension
FPLD-type 4 (FPLD4)	PLIN1	Perilipin 1	15q26	AD	Loss of subcutaneous adipose tissue primarily affecting lower limbs
Partial lipodystrophy	TBCD14	TBC1 domain family, member 4	13q22.2	AD	Acanthosisnigricans and extreme postprandial hyperinsulinemia
	ZMPSTE24	Zinc metalloproteinase STE24	1p34	AR	Mandibuloacral dysplasia
	AKT2	v-akt murine thymoma viral oncogene homolog 2	19q13.2	AD	Hypoinsulinemic hypoglycemia with hemihypertrophy, dyslipidemia and hepatic steatosis
Leprechaunism (Donahue syndrome), Rabson-Mendenhall syndrome, Type-A insulin resistance	CIDEc	Cell death-inducing DFFA-like effector c	3p25.3	AR	Preserved facial and neck fat, multifoliated lipid droplets
	INSR	Insulin receptor	19p13.3-p13.2	AD	Acanthosisnigricans, extreme hyperinsulinemia but normal lipid profile, preserved adiponectin levels

AD, Autosomal dominant; AR, Autosomal recessive; PNDM, permanent neonatal diabetes mellitus; TNDM, temporary neonatal diabetes mellitus; CGL, Congenital Lipodystrophy (Berardinelli-Seip syndrome); FPLD, Familial partial lipodystrophy.

treatment. However, understanding of mechanism of action of sulphonylureas led to shift of therapeutic regimen from insulin injections to high sulphonylureas with improved glycemic control, lower costs of treatment and better quality of life (Sagen et al., 2004; Pearson et al., 2006; Mlynarski et al., 2007; Rafiq et al., 2008). This stands as a classical example of application of genetic information for personalized medicine.

The success in the field of monogenic diabetes can largely be attributed to a distinct phenotype associated with each subclass, and strong genotype-phenotype correlation that allowed room for better diagnostic- and genotype- based management options. Genetic dissection of different forms of monogenic diabetes sheds light on beta cell physiology and improved understanding of insulin secretion and its regulation. With rapid advances and decreased cost of the NGS technologies, it is expected that screening of people affected with monogenic diabetes would unravel novel genetic etiologies of pancreatic beta cell dysfunction (Bamshad et al., 2011; Ellard et al., 2013).

## Type 2 Diabetes Is a Syndrome, Not a Single Disease

From the above section, it is evident that monogenic diabetes has a clear genetic basis and a reasonably distinct phenotypic presentation for each sub-class. T1D also has clear autoimmune origin leading to absolute insulin deficiency in vast proportion of cases. These facts have guided benefits of early intensive glycemic control (HbA1c below 6%) compared to conventional approach (HbA1c between 7 and 7.9%) in T1D patients as demonstrated in Diabetes Control and Complications Trial (DCCT) and follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) clinical trials which showed significant reduction in the risk of developing both micro and macrovascular complications associated with chronic hyperglycemia (Diabetes Control and Complications Trial, 2005).

In a sharp contrast, T2D does not have a known directly identifiable cause. It is characterized by progressive insulin resistance in insulin responsive tissues, dyslipidaemia, abdominal obesity, and rise in pro-coagulant and pro-inflammatory factors (Thomas and Philipson, 2015). Multitude of studies have revealed the confounding effects of risk factors like age, sex, physical inactivity, smoking, diet, ethnicity, family history, and gestation. Adding to the complexity, chronic exposure to stress, low socio-economic status and psycho-social factors are also shown to be risk factors for T2D from recent environment-wide association studies. The diagnosis of T2D can rather be considered “waste basket diagnosis”—not because there is *no-cause*, but because there is *no-one-cause*. The rate of disease progression and advent of long-term complications is not similar in all patients and hence treatment regimen needs individual tailoring based on suitable assessment of risk factors involved. While follow-up of United Kingdom Prospective Diabetes Study (UKPDS) showed that tight glycemic control decreases macrovascular end points in patients with T2D (Group UKPDS, 1998), other studies like Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease (ADVANCE) trials

did not provide consistent results. Type 2 diabetics with intensive blood glucose-lowering treatment arm had an increased risk of cardiovascular death in ACCORD trial compared to those in the conventional treatment arm (Ismail-Beigi et al., 2011). Although the ADVANCE trial did not exhibit increased mortality, it did not reveal any significant benefit on macrovascular outcome (Zoungas et al., 2009). All these observations strongly indicate that T2D is not a single disease, but, a conglomeration of metabolic disorders characterized by a combination of multiple intermediate traits like increased IFG, IGT, body mass index (BMI), waist-hip-ratio (WHR), dyslipidemia and hypertension. This very reason led to a paradigm shift in the field of genetics of T2D, which is discussed in detail in the next section.

## Genetics of Type 2 Diabetes: An Unexpected Failure or a Missed Opportunity

Several lines of evidence support the principle of inherited genetic susceptibility as an important risk factor for T2D. Offspring of a parent with T2D face a 40% lifetime risk of developing T2D, which increases to 70% when both parents have T2D. High concordance rate obtained in monozygotic twins (96%) suggests a strong genetic component of this multifactorial disease (Barnett et al., 1981). Furthermore, 40% of first-degree relatives of T2D patients develop diabetes as compared to 6% in the general population (Kobberling and Tillil, 1982). Its substantial genetic component propelled geneticists from all over the globe to devote huge efforts for the hunt of T2D susceptibility genes.

Initial attempts were through genome-wide familial linkage-based approaches using multi-generational pedigrees and/or affected sib-pairs studies where the analysis relies on shared chromosomal regions inherited from common ancestors to identify familial genetic variants with large consequences. While this method largely helped in genetic studies of monogenic diabetes, its application to common T2D has been a limited success. Several chromosomal regions showed evidence of linkage, but positional cloning of the putative causative genes has not been successful for most of the regions except few like *HNF4A*, calpain 10 (*CAPN10*), ectonucleotidepyrophosphatase/phosphodiesterase 1 (*ENPP1*), adiponectin, C1Q and collagen domain containing (*ADIPOQ*) and transcription factor 7 like 2 (*TCF7L2*) (Florez et al., 2003). Parallel to linkage studies, candidate gene approach was employed by researchers to identify T2D risk associated genes. Selection of candidate genes was typically based on hypothesis about biological mechanisms that are putatively involved in T2D pathogenesis, hence, it was plausible to conceive that variants in these genes could predispose to disease or related phenotype. Genes influencing pancreatic beta cell function, like *ABCC8*, *KCNJ11*, *SLC2A2*, *HNF4A*, *INS*, and genes influencing insulin action like *PPARG*, *INSR*, *PIK3R1*, *IRS1*, *IRS2*, and *SOS1* were among the initially identified candidate genes that significantly alter disease susceptibility (McCarthy, 2004). Despite many positive reports, associations could be replicated rarely in other

studies mainly because of the small sample sizes used in these studies. Furthermore, poor functional characterization of much of the genome made it impossible to make fully informed decisions while selecting candidate genes for association studies.

At this instance, completion of the Human Genome and International HapMap Projects came as a major boon to the then growing field of T2D genetics. Identifying genetic associations in a genomic fashion i.e., GWAS became a reality. Based on the “common variant- common disease (CVCD) hypothesis” that the genetic risk for common complex diseases is often due to disease producing alleles found at relatively high frequencies (>1%), GWA studies were designed to pick up multiple common variants associated with disease risk (Reich and Lander, 2001). The first wave of GWAS was conducted in Europeans and identified a dozen loci, of which 8 T2D susceptibility loci have been replicated across multiple ethnic groups: *TCF7L2*, *SLC30A8*, *HHEX*, *CDKAL1*, *IGF2BP2*, *CDKN2A/B*, *PPARG*, and *KCNJ11* (Cauchi et al., 2007; Lee et al., 2008; Ng et al., 2008; Wu et al., 2008; Hu et al., 2009; Rong et al., 2009; Chauhan et al., 2010; Han et al., 2010). In parallel, strong association between *FTO* variants and T2D was replicated in three independent studies, but the association signal weakened after adjustment for BMI, suggesting that variants mediate risk partly through increased adiposity (Dina et al., 2007; Frayling et al., 2007; Scuteri et al., 2007). While the first wave of studies employed logistic analyses and investigated T2D as a dichotomous phenotype in cases and controls, the second wave of GWAS loci were identified from linear analysis of continuous glycemic traits and anthropometric traits in participants without diabetes. Different consortia were formed to increase the sample size, which facilitated detection of low-effect common variants associated with T2D risk. One of the early consortiums was the DIAbetes Genetics Replication And Meta-analysis consortium (DIAGRAM) aimed at characterizing genetic basis of T2D, mainly in individuals of European descent and identified 31 novel loci associated with increased T2D risk (Saxena et al., 2007; Sladek et al., 2007; Zeggini et al., 2008; Voight et al., 2010; Morris et al., 2012; Scott et al., 2012). Another major collaborative effort to dissect loci that impact glycemic and metabolic traits was the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC). Several loci influencing traits like fasting plasma glucose (FPG), fasting insulin, 2h glucose and HbA1c were identified and many of them like *ADCY5*, *PROX1*, *GCK*, *GCKR*, and *DGKB-TMEM195* also influenced risk of T2D (Dupuis et al., 2010; Soranzo et al., 2010; Strawbridge et al., 2010; Manning et al., 2012; Scott et al., 2012). The Genetic Investigation of ANthropometric Traits (GIANT) consortium dedicated efforts to identify genetic loci that modulate obesity related traits like height, BMI, WHR, WHR adjusted for BMI and waist and hip circumference. So far, common genetic variants at hundreds of loci associated with above anthropometric traits have been identified (Berndt et al., 2013; Randall et al., 2013; Locke et al., 2015; Shungin et al., 2015).

In parallel to these studies, GWAS and meta-analyses of GWAS performed in other ethnicities (i.e., East Asians, South Asians, and African Americans) revealed multiple new T2D-associated genes (Billings and Florez, 2010). For example, six novel signals *GRB14*, *ST6GAL1*, *VPS26A*, *HMG20A*, *AP3S2*, and

*HNF4A* loci were identified from a meta-analysis of GWAS in South Asian population (Kooner et al., 2011). Interestingly, many, but not all of the variants identified in Europeans have been replicated in non-Europeans and amongst the replicated loci, differences in allelic frequencies and effect sizes have been observed (Yajnik et al., 2009). Put together, these results highlight similarity in genetic susceptibility as well as ethnic differences indicating that genetic variability strongly influences magnitude of the effect of GWAS risk loci in different populations. Adding to the complexity, amongst close to 80 loci associated with T2D risk (Data Sheet 3 in Supplementary Material), other than *TCF7L2*, there is absence of any large single-gene effects (Billings and Florez, 2010). Together these loci account for less than 20% of the T2D heritability due to their small effect sizes and point to reasons for the “missing heritability” in T2D (Manolio et al., 2009). Furthermore, resolving functional mechanism of the genetic association and establishing causality has proven to be extremely challenging, primarily because of the fact that large percentage of associations are determined by non-coding variants. This hugely supported the notion that high-penetrant rare-variants (minor allele frequency <1%) could be the primary players in common diseases and may have a strong impact on disease risk (Pritchard and Cox, 2002; Carlson et al., 2004).

While GWAS have implicated previously unknown genes and pathways in T2D pathogenesis, next generation sequencing studies like whole genome and exome sequencing aimed at identifying variants of low frequency with large effect size and likely elucidate disease causing mechanisms (Cirulli and Goldstein, 2010; Steinthorsdottir et al., 2014). Whole genome sequencing of Icelanders has identified low-frequency and rare sequence variants in *CCDN2*, *PAM* and *PDX1* that are associated with altered T2D risk (Flannick et al., 2014). Similarly, genotyping of ~150,000 individuals across 5 ancestry groups has identified 12 loss of function mutations in *SLC30A8* which decrease risk of T2D (Majithia et al., 2014). Exome sequencing of *PPARG* in 19,752 T2D cases and controls from multiple studies and ethnic groups identified rare variants which are associated with decreased activity in adipocyte differentiation and increased T2D risk (Claussnitzer et al., 2014). While these technologies identify additional genetic changes that contribute to risk of T2D, obtaining a huge sample size for the detection of low frequency variants remains a huge challenge.

## **MODY and T2D: Common Loci-Common Mechanisms**

The GWAS and post-GWAS era witnessed tremendous advancements made on the technological front and parallel developments in statistical methodology and inference, analytical frameworks, and computational tools, yet translation of the research findings for accurate risk prediction and subsequent disease prevention, discovery of new drug targets, personalization of medicine remains an unsolved challenge. Increasing efforts are now being devoted to understand the functional mechanisms underlying genetic association of loci with T2D risk and associated quantitative glycemic and/or

anthropometric traits. Owing to the large number of associations found with genetic variants in the non-protein coding region or gene desert regions, special focus is laid on decoding the nature of these non-coding variants (Fogarty et al., 2014). Recent fine mapping and functional characterization of GWAS variants provide several evidences where *cis*-regulation is a common mechanism underlying these associations and most frequently affected elements include transcriptional enhancers and silencers (Winckler et al., 2007; Fogarty et al., 2013, 2014). Thus, identification of target genes of *cis*-regulatory variants is necessary to understand the functional mechanisms by which these variants act.

As these efforts continue, gaining novel insights from the molecular genetics of monogenic forms of diabetes would help propel research in the field of common T2D genetics toward a translational level. From the research efforts in identifying genes responsible for monogenic forms of diabetes and findings from GWAS for T2D, strong evidence has emerged that several loci implicated in monogenic diabetes are also involved in mediating risk of polygenic T2D. As a matter of fact, most of the T2D susceptibility genes identified in the pre-GWAS era are key players in the development of some forms of monogenic diabetes; *KCNJ11*, *HNF4A*, *SLC2A2*, *PPARG*, and *INSR*. Recent studies identified few other monogenic diabetes loci like *HNF1A*, *HNF1B*, *GCK*, *PDX1*, *GLIS3*, *WFS1*, *PAX4*, and *LMNA* which harbor variants associated with T2D risk (Sidransky, 2006; Sandhu et al., 2007; Wegner et al., 2007; Voight et al., 2010; Rees et al., 2011; Cho et al., 2012). Interestingly, several variants in these loci influence intermediate glycemic and anthropometric traits associated with T2D like FPG, insulin related traits, lipid related traits, Hb1Ac levels, C-reactive protein, homocysteine and waist circumference. Complete list of loci common between T2D and monogenic diabetes and associated phenotypes is presented in **Table 3**.

It is interesting to observe that loci common/shared between monogenic diabetes and T2D affect physiological processes like pancreatic beta cell development and function, glucose sensing mechanisms and their coupling with insulin release/secretion and endoplasmic reticulum (ER) stress. Most of the common loci are transcription factors, which play key role in beta cell development. For example, *PDX1* directs the early embryonic development of pancreas and differentiation of insulin-producing islet  $\beta$  cells in endocrine pancreas by forming cross-regulatory transcriptional networks where *FOXA2* and *HNF1B*, other T2D associated genes are also key players (Oliver-Krasinski et al., 2009; Arda et al., 2013). It also promotes expression of *INS*, *SLC2A2*, and *GCK*, which are essential for insulin synthesis and glucose sensing. *HNF1A* also controls beta cell function by regulating target genes like *SLC2A2*, *HNF4A*, pyruvate kinase, and hepatocyte growth factor activator (Servitja et al., 2009). Genes encoding ATP-sensitive potassium channel sub-units *KCNJ11* and *ABCC8* couple cell metabolism with membrane potential and play a central role in regulation of insulin secretion in pancreatic beta cells. Mutations in these genes form high-risk haplotype which affect progression from IGT to T2D (Laukkanen et al., 2004). *WFS1* forms component of unfolded protein response and maintains homeostasis of the



**TABLE 3 | Genes/loci common between monogenic diabetes and type 2 diabetes and related intermediate traits.**

Genes/loci	Trait	SNP(s)	Nature of variant	PubMed IDs
<i>GLIS3</i>	FPG and FPG levels adjusted for BMI	rs7034200	Intronic	22581228, 20081858
	HOMA-B	rs7034200	Intronic	20081858
<i>HNF1A</i>	Cholesterol, total	rs1169288, rs1800961	Missense	20686565
	LDL cholesterol	rs1169288, rs2650000	Missense	24097068, 19060906
	Homocysteine levels	rs2251468	Intronic	23824729
	C-reactive protein	rs1183910, rs7979473, rs7310409, rs2393791, rs2259816, rs7305618	Intronic	23844046, 22939635, 21647738, 21196492, 19567438, 18439548, 24763700
		rs1169310	3' UTR	18439552
<i>HNF4A</i>	Cholesterol, total	rs1800961	Missense	24097068, 20686565
	HDL cholesterol	rs1800961	Missense	24097068, 19060906, 24097068
<i>GCK</i>	C-reactive protein	rs1800961	Missense	21300955, 22939635
	FPG	rs4607517, rs1799884, rs3757840	Intronic	19060907, 20081858, 23575436, 22399527
	FPG adjusted for BMI	rs4607517, rs2293941	Intronic	22581228
	1-h plasma glucose and 2-h plasma glucose	rs1799884	Intronic	23575436
	Glycated hemoglobin levels	rs1799884, rs730497, rs4607517	Intronic	24647736, 24244560, 20858683, 19096518
	HOMA-B	rs4607517	Intronic	20081858
		rs1801282	Missense	22581228
<i>PPARG</i>	Fasting insulin adjusted for BMI	rs1801282	Missense	22581228
<i>LMNA</i>	WHR adjusted for BMI in women	rs4684854	Intergenic	23754948
	Cholesterol, total	rs577492	Intronic	17327437
<i>SLC2A2</i>	Waist circumference	rs11578696, rs955383	Intronic	17327437
	FPG and FPG levels adjusted for BMI	rs11920090	Intronic	20081858, 22581228
<i>INSR</i>	HOMA-B	rs11920090	Intronic	20081858
	Triglycerides	rs7248104	Intronic	24097068

SNP, single nucleotide polymorphism; FPG, Fasting plasma glucose; PG, plasma glucose; BMI, body mass index; HOMA-B, homeostasis model assessment of beta cell function; LDL, low density lipoprotein; HDL, high density lipoprotein; UTR, untranslated region; WHR, waist-hip ratio.

ER in pancreatic beta cells. Inactivating mutations in *WFS1* result in ER stress causing beta cell dysfunction and recently *HNF4A* is also shown to regulate beta cell susceptibility to ER stress (Fonseca et al., 2005; Takei et al., 2006).

Deciphering a role for genes implicated in monogenic diabetes to T2D has the advantage of carrying the benefits along with. For example, *GCK* gene product, hexokinase 4 catalyzes the first step of glycolysis and is expressed in both hepatocytes and pancreatic beta cells. The beta cell isoform is a glucose sensor and plays an important role in glucose stimulated insulin secretion (Matschinsky, 1990, 2002). Common variants in *GCK* predict T2D risk by influencing various T2D intermediate phenotypes like FPG, HbA1c levels, and HOMA-B (Dupuis et al., 2010; Soranzo et al., 2010; Manning et al., 2012; Chen et al., 2013). A recent study has revealed that patients harboring *GCK* mutations reportedly have a low prevalence of vascular complications highlighting the probable limited role of isolated, mild hyperglycemia in mediating diabetic vascular complications (Steele et al., 2014). In this scenario, it may not be unreasonable to surmise a possible role for variants in *GCK* or other monogenic diabetes associated genes modifying the T2D disease course in presence of other precipitating factors. However, it is important to note that these common loci are causal in case of monogenic

diabetes, yet they contribute merely to T2D pathogenesis and this discrepancy is largely explained by mutational heterogeneity and the nature of variants at these loci (Sidransky, 2006). While mostly, coding and rare variants cause monogenic diabetes, non-coding and regulatory variants at the same loci are associated with T2D and related intermediate traits. This, in turn, also accounts for differences in the effect sizes of associated variants and phenotypic heterogeneity between monogenic diabetes and T2D. Regulatory nature of variants associated with T2D and intermediate traits also entails gene-gene and gene-environment interactions, of which the later mainly results in modulation of variant effects with various factors like physical activity, nutrition, stress, etc. (Buil et al., 2015). Thus, in contrast to the monogenic diabetes, screening for the common variants in these loci to decide the clinical course of T2D is still a long sought dream.

## Role of Environmental Factors: Epigenetic Regulation of Candidate Genes

Epigenetic mechanisms like DNA methylation, covalent histone modifications, non-coding RNAs, microRNAs are plausible means by which environmental factors integrate their effects with

genetic variants to mediate T2D risk (Ling and Groop, 2009; Waki et al., 2012). Of all, the most thoroughly studied epigenetic modification is the methylation of cytosine-phosphatidyl-guanine (CpG) sites which is associated with post-translational histone modifications and results in altered chromatin structure and consequent differences in gene expression (Jaenisch and Bird, 2003). The loci shared between monogenic diabetes and T2D serve as good example to study these interactions. Mutations in transcription factors like *HNF1A*, *HNF1B*, *HNF4A*, *PDX1*, and *NEUROD1* modulate their affinity for both histone modifying enzymes and DNA leading to disruption of regulatory interactions (Ling and Groop, 2009). Several T2D associated variants either introduce or remove a CpG site, which results in differential DNA methylation and altered expression of associated or near-by genes. Tissue specific DNA methylation of common loci like *PPARG*, *WFS1*, *IRS1*, *PDX1*, and *INS* have been reported in independent studies (Dayeh et al., 2013; Nilsson et al., 2014). For example, differential methylation has been observed in common loci like *PPARG* and *IRS1* in adipose tissue from unrelated T2D patients compared with control individuals and expression of *PDX1* and *INS* was decreased in pancreatic islets from diabetics compared to non-diabetic donors (Yang et al., 2011, 2012). Interestingly, quantitative DNA methylation analysis also shows consistent differences in DNA methylation patterns between populations of different ethnicities at common loci *KCNJ11* along with other loci like *ADCY5* and *FTO* which are attributed to genetic and/or region-specific environmental factors (Elliott et al., 2013).

In addition, epigenetic modifications are proposed as key mechanisms in mediating effect of nutritional disturbances that result in fetal programming and/or metabolic programming for future risk of cardio-metabolic disorders and is current topic of scientific probity. The fetal environment is influenced by several factors and maternal under and/or over nutrition, and interaction between fetal and maternal environment were found as major determinants mediating metabolic programming (Aagaard-Tillery et al., 2008; Yajnik and Deshmukh, 2012). Several epidemiological and animal studies provide evidence for impact of suboptimal uterine environment and early neonatal life on the offspring susceptibility to chronic diseases like T2D in adult life (Snoeck et al., 1990; Breier et al., 2001; Ozanne and Hales, 2002). Epigenetic mechanisms, especially changes in DNA methylation have been shown to modulate effect of these determinants on the altered expression of key genes involved in fetal metabolism and development (Burdge et al., 2007; Gonzalez-Bulnes and Ovilo, 2011). The critical issue is that fetal programming is even transmitted to the next generations highlighting the possibility of transgenerational epigenetic inheritance of disease susceptibility (Waki et al., 2012). Studies on human cord blood samples from neonates with intrauterine growth restriction due to maternal low protein diet has shown dysregulation of *HNF4A* methylation and other loci encoding *HNF4A*-interacting proteins (Sandovici et al., 2011). Similarly, maternal and paternal high fat diet consumption is associated with global methylation changes and induces glucose intolerance and insulin resistance in offspring (Aagaard-Tillery et al., 2008; Gallou-Kabani et al., 2010; Ng et al., 2010). Effect

of maternal micronutrients like folic acid (FA) and vitamin B12 (B12) on fetal development and increased obesity risk is already established (Yajnik et al., 2008). Maternal micronutrient deficiency (FA and vitamin B12) results in global methylation changes in livers of pups leading to decrease in expression of *PPAR $\alpha$*  and *PPAR $\gamma$*  genes and supplementation of omega-3 fatty acid to these pups reduced the global DNA methylation and restored the expression of these transcription factors highlighting the role of poly unsaturated fatty acids and their interaction with one-carbon metabolism (Kulkarni et al., 2011). All the above results indicate strong role of epigenetic modifications not only in mediating the effects of common variants in shared loci but also in programming fetus for future risk of metabolic disturbances.

## Future Perspectives

Developments in the field of T2D genetics have undoubtedly led to identification of new loci like *GLIS3* (Cho et al., 2012), *PAX4* (Ma et al., 2013), and *GCK* (Muller et al., 2014) that are common between monogenic diabetes and T2D. However, expanding mutational spectrum of these common loci using techniques like whole exome sequencing has now reached a point of saturation. At this point, understanding intricate mechanisms of interaction of these common variants with environmental factors in manifesting a syndrome like T2D would help us expand basis of phenotypic heterogeneity in the background of mutational heterogeneity. A recent study provides experimental evidence for a new functional approach to investigate epigenetics of T2D (Fogarty et al., 2014). Epigenetic conservation of dysregulated loci in high fat diet fed mice and obese humans as observed in this study substantiates usage of animal models to understand effect of various environmental factors in modifying disease risk. Moreover, overlap between epigenetically regulated regions with nominally associated T2D risk loci suggests that present approach can complement human genetic studies to assess clinical risk of such loci. Besides mediating epigenetic changes, variants in these common loci also explain significant proportion of variance in response to treatment options currently available for T2D. *KCNJ11* and *PPARG* variants provide evidence of a successful pharmacogenetic approach for treatment of T2D (Gloyn et al., 2001; Bluher et al., 2003). Several common polymorphisms in genes like *KCNJ11*, *ABCC8*, *WFS1*, *GLIS3*, *HNF4A*, *HNF1B* and *GCK* that have common antecedents in monogenic diabetes and T2D have influence on the glycemic outcomes of metformin treatment (Jablonski et al., 2010). Common variants in *KCNJ11*, *ABCC8*, *NEUROD1* and *PAX4* predict response to repaglinide for glycemic outcomes like glycated hemoglobin, fasting glucose and post-prandial glucose (He et al., 2008; Florez et al., 2012; Gong et al., 2012). Though, these examples foster the potential for utilization of these variants in common loci to personalize medicine, understanding diversity of drug responders, metabolic and signaling pathways associated with a drug's action supported by clinical observations is required for tailoring therapeutic needs. In addition, exploring new avenues like brain centered glucose regulation and investigating the role of common loci

in central regulation of glucose metabolism would help us expand our horizons and improve our understanding of disease biology.

## Conclusions

To conclude, no genetic disease is monogenetic now, thanks to better understanding of the clinical phenotype and to the various technological advances that allow the whole “OME” to be investigated. Understanding and utilization of single gene effects on specific traits that conglomerate into a complex phenotype is currently the best way to understand the genetic basis at functional level and be of any use for disease prevention and management. However, lot of factors such as mutational

heterogeneity, nature of variants, ethnic differences etc. need to be understood before this becomes a practical reality.

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## Supplementary Material

The Supplementary Material for this article can be found online at: <http://journal.frontiersin.org/article/10.3389/fgene.2015.00251>

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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