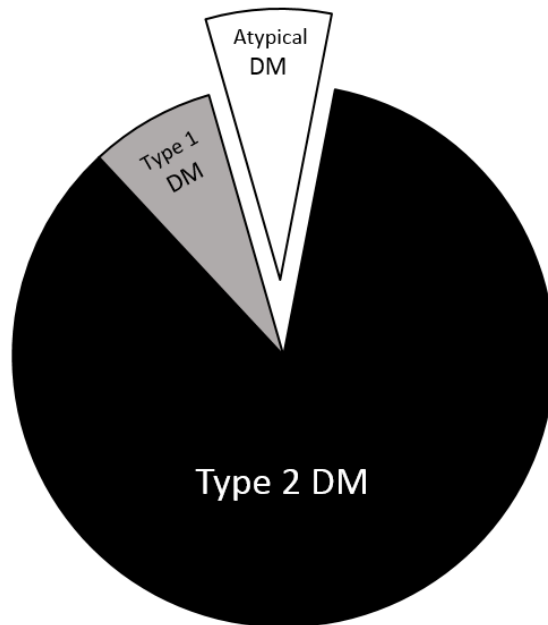


Atypical Diabetes Mellitus: Beginning of Precision Medicine

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This is to acknowledge that Abhimanyu Garg, M.D. has financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Garg will not be discussing “off-label” uses in his presentation.

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Purpose and Overview:

To illustrate the underlying molecular basis of various types of atypical diabetes mellitus and the implications for the precision management of various subtypes.

Educational Objectives:

1. To identify distinct clinical features of different subtypes of atypical diabetes mellitus
2. To understand the underlying molecular mechanisms of various types of monogenic diabetes mellitus
3. To understand the unique therapies (precision medicine) for various subtypes of monogenic diabetes mellitus

Special Interests:

Dr. Garg's group has been interested in studying monogenic syndromes causing diabetes mellitus especially genetic lipodystrophies. His group identified deficiency of AGPAT2 enzyme, which is critical for triglyceride and phospholipid biosynthesis, as the cause of congenital generalized lipodystrophy, type 1. His group also linked peroxisome proliferator-activated receptor- γ (*PPARG*) gene, the key adipocyte differentiation transcription factor, to familial partial lipodystrophy. His team has also identified the second locus for mandibuloacral dysplasia, i.e., zinc metalloproteinase (*ZMPSTE24*), that is responsible for post translational processing of prelamin A to its mature form lamin A. Recently, Garg and his colleagues have discovered mutations in proteasome subunit, beta-type 8 (*PSMB8*), adrenergic receptor alpha 2 A (*ADRA2A*), caveolin 1 (*CAV1*), hormone sensitive lipase (*LIPE*) linked to various syndromes of genetic lipodystrophies. He demonstrated that patients with generalized lipodystrophy have profound leptin deficiency and proposed that leptin deficiency might contribute to the metabolic complications in the disorder. This led him to initiate a collaborative trial with the NIDDK that demonstrated dramatic improvement in hyperglycemia, dyslipidemia, and fatty liver with leptin therapy. Metreleptin is now approved by the FDA for patients with generalized lipodystrophy.

The American Diabetes Association (1) classifies diabetes mellitus into various categories as follows (Table 1). The two main categories being type 1 and 2 DM.

Table 1. ADA Classification of Diabetes Mellitus

- Type 1: due to autoimmune β -cell destruction causing absolute insulin deficiency (estimated prevalence is about 5-10%)
- Type 2: due to progressive loss of β -cell insulin secretion due to insulin resistance (estimated prevalence is about 90-95%)
- Gestational diabetes mellitus (GDM): Diabetes during pregnancy
- Specific diabetes due to other causes (**Atypical**) (estimated prevalence is about 5-10%)

For the purpose of this Grand Rounds, I will label specific diabetes due to other causes (which is not type 1 or type 2 diabetes) as Atypical diabetes. Atypical diabetes can therefore have several causes (Table 2).

Table 2. Causes of Atypical Diabetes Mellitus

- Monogenic Diabetes:
 - Neonatal Diabetes
 - MODY (maturity onset diabetes of youth/young)
 - Maternally-inherited diabetes and deafness (mtDNA mutations)
 - Genetic Lipodystrophies
 - Other rare genetic syndromes
- Exocrine Pancreatic Deficiency:
 - Hemochromatosis
 - Cystic Fibrosis
 - Tropical Calcific Pancreatic Diabetes
 - Alcoholic pancreatitis
 - Others
- Endocrinopathies:
 - Cushing's syndrome
 - Acromegaly
 - Pheochromocytoma
 - Glucagonoma/Somatostatinoma
- Drug-induced:
 - Glucocorticoids
 - Pentamidine
 - Nicotinic acid
 - Psychotropic medications
 - Others

I will discuss some examples of atypical diabetes, especially the genetic syndromes, and highlight how elucidation of the underlying molecular defects have paved the way for specific therapies for these syndromes which serve as leading examples of precision

medicine. Due to time constraints, I would not discuss the Endocrinopathies or Drug-induced atypical diabetes. For these disorders, treatment of the underlying endocrine abnormality, and if possible, avoiding drugs which induce diabetes, are well-recognized therapeutic strategies.

Neonatal Diabetes Mellitus (NDM):

Neonatal diabetes mellitus (NDM) is currently defined as onset of diabetes occurring in the first six months of life (1). This syndrome was recognized as early as 1852 by Kitselle (2) and in 1926 by Ramsey (3). The incidence of NDM is estimated to be ~1:100,000 live births, though in countries with high rates of consanguinity, the incidence has been reported to be as high as 1:21,000 live births (4). Before the elucidation of the genetic basis of NDM, all the infants with NDM were treated with insulin therapy and some of them were considered to have developed type 1 diabetes. It was recognized that NDM could be either transient (TNDM) or permanent (PNDM), and until 2000, little was known about the molecular basis. There were some different clinical features recognized in patients with TNDM and PNDM (Tables 3 and 4).

Table 3. Clinical Features of Neonatal DM

	Temporary NDM	Permanent NDM
Incidence among NDM	50-60%	40-50%
Birth Weight (g)	1987 (510)	2497 (690)
IUGR (%)	74%	35%
Age at diagnosis (d)	6 (1-81)	27 (1-127)
Median Insulin dose (U/kg/d)	0.6	1.4
Median remittance (wk)	12	-
Median relapse (y)	14	-

Modified from Slingerland and Hattersley (5).

Later studies revealed some features that distinguished TNDM and PNDM from patients with T1DM (IDDM at that time) such as:

1. Negative islet cell antibodies
2. Do not express HLA antigens DR3/DR4.
3. Lack of reports of nephropathy or retinopathy
4. Signs of exocrine pancreatic insufficiency in some patients.

Transient NDM: Some patients with TNDM have macroglossia and an umbilical hernia. The pathophysiology of TNDM results from overexpression of the paternally expressed genes with extinction of the maternal genes in a region of chromosome 6q24. A common cause is paternal uniparental disomy or paternal duplication of 6q24. In others, abnormal methylation of the maternal copy of chromosome 6 renders the genes inactive

Table 4. Classification of Neonatal Diabetes Mellitus (NDM)

Transient (TNDM) 45%	Permanent (PNDM) 45%	Syndrome—Rare 10%
TNDM1		
70% of TNDM Involves 6q24. Disturbance of imprinted genes <i>PLAGL</i> (<i>ZAC</i>) and <i>HYMAI</i> caused by:	50% <i>KCNJ11</i> ±DEND syndrome	<i>EIF2AK3</i> —spondyloepiphyseal dysplasia, renal anomalies
(a) Paternal uniparental disomy (sporadic)	15% <i>ABCC8</i> ±DEND syndrome	<i>FOXP3</i> —IPEX: immunodysregulation, polyendocrinopathy, enteropathy, X-linked
(b) Paternal chromosome 6 duplication (dominant transmission)	3% <i>GCK</i> *, homozygous	<i>GLIS3</i> —hypothyroid, hepatic fibrosis, glaucoma, cystic kidneys, developmental delay
(c) Relaxation of imprinting maternal hypomethylation—sporadic or mutation in the transcription factor ZFP57.	2% Others <i>IPF1/PDX1</i> *, homozygous <i>HNF1β</i> *	<i>PTF1A</i> —pancreatic and cerebellar agenesis
TNDM2		
15% of TNDM <i>ABCC8</i> (<i>SUR1</i>) mutations		<i>RFX6</i> —digestive system defects, known as Mitchell-Riley syndrome
10% of TNDM <i>KCNJ11</i> (<i>Kir6.2</i>) mutations		<i>NEUROG3</i> —with congenital malabsorptive diarrhea and enteroendocrine cell dysgenesis
5% of TNDM Mutations in <i>INS</i> , <i>HNF1β</i> , <i>SLC2A2</i>		<i>GATA6</i> and <i>GATA4</i> —with varying degrees of pancreatic agenesis, pancreatic exocrine dysfunction and cardiac malformations
<p>DEND, developmental delay, epilepsy, neonatal diabetes; GCK, glucokinase; HNF, hepatic nuclear factor; INS, insulin gene; Kir, inward rectifying potassium channel; PNDM, permanent neonatal diabetes mellitus; PTF, pancreas transcription factor; RFX6, regulatory factor X, 6; SUR, sulfonylurea receptor; TNDM, transient neonatal diabetes mellitus.</p> <p>*Heterozygous mutations in <i>GCK</i>, <i>IPF1/PDX1</i>, and <i>HNF1β</i> cause MODY2, MODY4, and MODY5, respectively.</p>		
<p>Source: M. A. Sperling, personal communication From Sperling and Garg (4)</p>		

and permits the unopposed action of the paternal genes on this region. The actual genes involved are *ZAC* (zinc finger protein 1 regulating apoptosis and cell cycle arrest), also referred to as *PLAGL1* (pleiomorphic adenoma gene-like 1), and a second gene termed *HYMA1* (hydatidiform mole associated and imprinted gene). While the function of *HYMA1*, a non-coding mRNA, is still unknown, molecular studies show that *ZAC1* overexpression impairs insulin secretion and β cell proliferation. In terms of genetic counseling, those with uniparental disomy of chromosome 6 are sporadic. However, duplications of the 6q24 region in the father cause familial paternal duplications, resulting in a 50% chance of transmission to each of their subsequent children (4). Females who transmit the duplication do not have affected children, but the sons may pass the risk to their subsequent children.

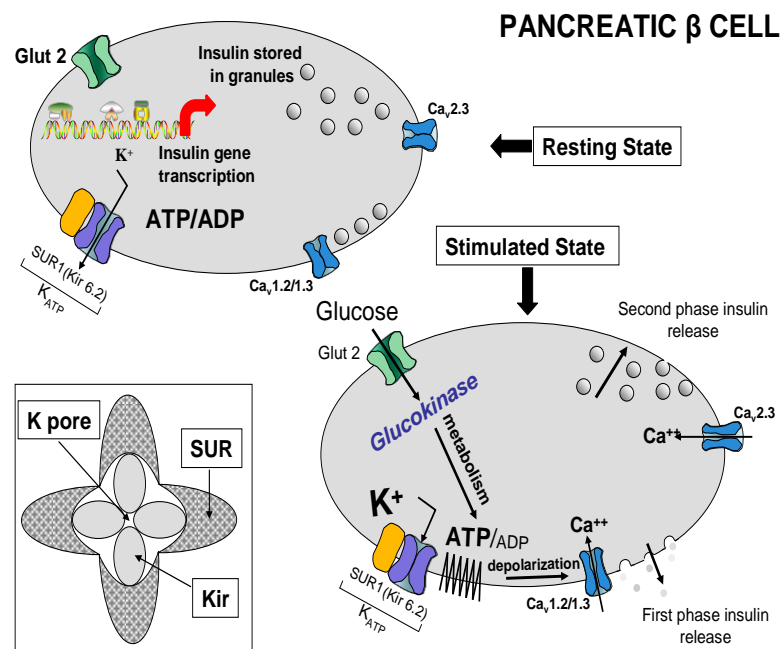


Figure 1 is a simplified cartoon of the beta cell that illustrates the interactions of various proteins in the insulin synthesis/secretion cascade. In the resting state (upper left panel) insulin synthesis and basal secretion are governed by the basal glucose concentration; insulin gene transcription is regulated by a number of regulatory factors that bind to upstream components of the insulin gene on chromosome 11. Also illustrated is one unit of the ATP-regulated potassium channel, governed by the ratio of ATP:ADP. The channel remains open in the basal state, allowing efflux of K from the interior to the exterior of the beta cell and leaving the plasma membrane in a hyperpolarized state. Each K_{ATP} channel consists of 4 subunits of the inward rectifying potassium channel (Kir6.2) encoded by the *KCNJ11* gene, and 4 surrounding regulatory units, the sulfonylurea receptor (SUR1) encoded by the *ABCC8* gene (lower left panel); both genes are located on chromosome 11. Also illustrated are gated voltage calcium channels, designated as Ca_v1.2/1.3 and Ca_v2.3. Stored insulin granules lined up on the cell membrane constitute a quickly releasable pool of insulin granules for the first phase insulin response after glucose is acutely raised. A slower releasable pool of insulin granules is more internal, but can be mobilized to constitute the second phase insulin response when higher glucose is maintained. In the stimulated state (lower right panel), when after a meal blood glucose rises, it enters the beta cell via the Glut 2 glucose transporter, a non-insulin regulated process. The enzyme glucokinase acts as a glucose sensor and phosphorylates glucose to glucose-6-phosphate G6P, permitting its metabolism to produce ATP. The higher ATP:ADP ratio results in closure of the K_{ATP} channel, retention of intracellular K, which leads to membrane depolarization, opening of the voltage-gated Ca channel allowing for influx of calcium

and the secretion of insulin as first and then second phase responses. In this way, the chemical energy of glucose is converted to the electrical activity of the beta cell, creating a “rheostat” effect, with high insulin secretion as glucose is high and a fall in insulin secretion as glucose falls in response to the actions of insulin. Activating mutations of K_{ATP} components will keep the channel open, preventing insulin secretion, i.e. leading to diabetes, the severity of which is proportional to the severity of the defect. In many instances, channel closure with resultant insulin secretion can be restored by sulfonylureas which act on the SUR1 regulatory unit. By contrast, inactivating mutations of these K_{ATP} components, prevent opening of the channel and result in insulin secretion unregulated by glucose concentration and hence hyperinsulinemic hypoglycemia. The drug, diazoxide, acts to open channels and reduce insulin secretion. From Sperling and Garg (4).

Permanent NDM: Most of the patients with PNDM have heterozygous activating mutations in *KCNJ11* or *ABCC8* genes (Table 4). Some patients also have developmental delay and/or epilepsy along with NDM (called DEND). The developmental delay can present as learning and social impairment, delay in motor function, and muscle weakness. Some may have prominent metopic suture, limb contractures, bilateral ptosis and down turned mouth.

Initial studies identified rare causes of PNDM and linked it to *IPF1* (6), *EIF2AK3* (7) genes, followed by glucokinase (*GCK*) gene (8). However, two seminal studies by Gloyn et al. from the Exeter group led by Andrew Hattersley in 2004 (9) and by Babenko et al. from the Paris group led by Michel Polak in 2006 (10) identified the most common causes of PNDM, i.e., activating heterozygous mutations in ATP-sensitive Potassium-channel subunit Kir6.2 encoded by potassium voltage-gated channel subfamily J member 11 (*KCNJ11*) gene and in sulfonylurea receptor (*SUR1*) encoded by ATP-binding cassette transporter sub-family C member 8 (*ABCC8*), respectively.

The main evidence for precision therapy of PNDM with sulfonylureas came from a Brazilian man with heterozygous p.R201H *KCNJ11* mutation who had NDM at age 12 wk and was treated with tolbutamide for 46 years with well controlled DM, fasting plasma glucose 110 mg/dL and detectable C-peptide level of 400 pmol/L (9). Recent data reveal that of a total of 127 patients with PNDM due to *KCNJ11* mutations, 112 (88%) were successfully switched from insulin to sulfonylurea with a glibenclamide dose ~0.8 mg/kg/d. At baseline their HbA1c was 8.2% on insulin therapy and on sulfonylurea therapy it was 5.9% after 4-12 months (11). The authors concluded that in vitro response of the mutation to tolbutamide determined the likelihood of transfer to sulfonylurea. For the mutations where the extent of tolbutamide block was less than 63%, no patients were successfully switched to sulfonylureas (11). Sulfonylurea therapy has been reported to improve psychomotor development and epilepsy in some patients but not others.

Thiamine Responsive Megaloblastic Anemia (TRMA)-associated DM

This rare autosomal recessive syndrome also presents as neonatal or childhood onset DM. It was first reported in 1969 by Rogers et al.(12) in an 11-year-old white girl who developed DM at age 3, hearing loss at 4.5 years and megaloblastic anemia at age 11 which was not responsive to vitamin B12 or folate. Interestingly, the anemia responded to a multivitamin preparation and subsequently, the investigators figured out that it was thiamine to which anemia responded. Thirty years later, TRMA and diabetes

mellitus were reported to be due to biallelic mutations in the thiamine transporter Protein 1 (THTR-1) encoded by the gene, Solute Carrier family 19 member 2 (*SLC19A2*) (13-15). TRMA, also known as Roger's Syndrome, combines megaloblastic anemia, diabetes mellitus and sensorineural deafness which respond by variable degrees to thiamine replacement. Cardiac anomalies and abnormalities of the optic nerves and retina also may occur occasionally in the TRMA syndrome. Markers of autoimmunity are absent in this autosomal recessive form of diabetes mellitus. Most interestingly, pharmacological doses of thiamine may not only reverse anemia but also improve diabetes mellitus early in the course of the disease, however some time during and after puberty, thiamine supplements may become ineffective so that all patients require insulin therapy with regular blood transfusions in adulthood. Recent review from Sun et al.(16) reveal that of a total of 141 patients with TRMA (of which 119 had biallelic mutations in *SLC19A2*), the median age of onset of diabetes was 24 months and diabetes was treatable with high dose thiamine in 50/80 (63%) of the patients, while anemia responded to thiamine in 95% of patients but hearing deficit improved in only 1 out of 50 patients.

The precise role of thiamine in pancreatic β cell biology is not known. However, the gene knock-out, *Slc19a2*^{-/-} mice, have normal islet histology but on thiamine free diet for 14-17 days, they developed hyperglycemia and markedly reduced insulin secretion in response to intravenous glucose (17). Thus, thiamine has an important role in insulin secretion.

Maturity-Onset Diabetes of Youth (or Young; MODY):

MODY is generally referred to as "Maturity-Onset Diabetes of Youth" because when described in the 1970s, the classification of DM consisted of 2 types-a) Juvenile-onset, ketosis-prone DM with onset at ages <20-25 years, severe insulin deficiency and hence dependence on exogenous insulin injections and b) Maturity Onset DM with variable insulin secretion comparable or exceeding levels found in lean (non-obese subjects), onset commonly after age 40 years and often responsive to oral agents such as sulfonylureas. Among these maturity-onset types of diabetes there were adolescents and young adults <30 years of age with a strong family history affecting 2-3 generations suggesting autosomal dominant transmission, and responsive in many instances to oral agents such as sulfonylureas (4). The genetic basis for many of the classic entities have been defined over the past ~15 years and are now known to be transcription factors or enzymes involved in insulin secretion, or formation of the pancreas (Table 5). Hence, these **MODY** entities could equally well be referred to as "**Monogenic Diabetes of Youth**". These syndromes are defined by clinical presentation in pregnancy or early childhood often by asymptomatic discovery of incidental hyperglycemia (MODY2-GCK loss of function mutation), symptomatic diabetes presenting in teens to late twenties (MODY3-HNF1 α mutation), large size at birth with neonatal hypoglycemia but later appearance of diabetes (MODY1-HNF4 α mutation), and diabetes associated with renal anomalies (MODY5-HNF1 β mutation). These four entities constitute close to 90% of all known mutations in MODY. Affected patients typically are negative for autoimmune

markers such as various islet antibodies, have positive family history in 2-3 preceding generations indicative of autosomal dominant transmission, (unless they harbor *de-novo* mutations), and may appear to have low insulin requirements. When measured, C peptide concentrations may be in the normal range or low for the prevailing glucose concentration.

Overall, MODY syndromes represent approximately 2%-3% of all patients diagnosed with diabetes; in the UK, the minimum prevalence of MODY was estimated to be 108 cases per million (18). In the Search for Diabetes in Youth Study (19), of ~5000 newly presenting children with diabetes who had measurements of diabetes autoantibodies (DAA) including GADA and IA2A as well as fasting C-peptide (FCP), 14.5% (730 subjects) were DAA negative and had a FCP \geq 0.8ng/ml. Of these, 586 subjects were tested for MODY (1, 2 and 3) and 48 (8.2%) were MODY positive. Thus, about 1% of the original cohort of children had genetically proven MODY (19). Non-Hispanic White (35%), African-American (24%), Hispanic (26%), Asian-Pacific Islander (13%) were represented in the MODY group and most were considered to have either T1DM and treated with insulin, or T2DM and treated with metformin, or other oral hypoglycemic medications. Therefore, any patient presenting with clinical features of diabetes mellitus before age 25-30 years, who has an apparently mild form or is suspected of having T2DM, is negative when tested for diabetes autoantibodies and is positive for C-peptide, and has a positive family history in 2-3 generations, should be suspected of having MODY. Prompt molecular diagnostics should be performed to confirm the diagnosis. The correct diagnosis permits correct genetic counseling, because the risk of affected offspring is 50%, rather than 5%-10% as in T1DM.

As far as therapy of MODY patients is concerned, the bulk of the clinical evidence suggests that appropriate management for patients with GCK-MODY is observation, exercise and diet which usually suffice to maintain blood glucose within acceptable limits; except during pregnancy, when insulin should be used to control hyperglycemia and avoid the consequence of macrosomia in the fetus. They have only mild hyperglycemia and do not develop long-term complications of diabetes (20).

Patients with HNF1 α -MODY3 and HNF4 α -MODY1 usually respond to sulfonylureas, though about one third may lose this responsiveness in time and progress to require insulin. The increased responsiveness to sulfonylureas in HNF1 α -MODY3 was initially reported anecdotally. Pearson et al. (21) conducted a randomized, cross-over trial of metformin and glicazide in patients with HNF1 α -MODY (n=18) or T2DM (n=18). Patients with HNF1 α -MODY had five fold greater response to glicazide than to metformin and 3.9-fold greater response to glicazide than those with T2DM. Despite reduced insulin response to intravenous glucose, patients with HNF1 α -MODY had a strong insulin secretory response to intravenous tolbutamide. Similar studies have not been conducted in patients with HNF4 α -MODY but clinically they also respond well to sulfonylureas. The early appearance of albuminuria, or a family history of renal cysts or other renal anomalies, should prompt consideration of HNF1 β -MODY5. Subjects with MODY 5 generally require insulin for therapy of diabetes and careful monitoring and management of their renal manifestations.

Table 5. Classification of Maturity-Onset Diabetes of Youth (or Young; MODY).

Syndrome	Defective protein or gene	OMIM number*	Key clinical findings
I.a. Common types of MODY†—autosomal dominant			
MODY3	Hepatic nuclear factor (HNF)1 α	600496	Most common form; present late in first decade to late twenties; islet antibody negative; respond to sulfonylureas initially, but may require insulin later in life.
MODY2	Glucokinase (<i>GCK</i>)	125851	Second most common form, but most common form in children; may be diagnosed as gestational diabetes in lean, healthy young woman; do not need insulin or other drugs, except in pregnancy.
MODY1	HNF4 α	125850	Third most common form; may have macrosomia and hypoglycemia at birth, followed by diabetes later in life; treatment as for MODY3.
MODY5	HNF1 β	189907	Associated with renal cysts, other vesicogenital anomalies, albuminuria, and renal failure unrelated to the control of diabetes.
I.b. Other rarer types of MODY‡			
MODY4	Insulin promoter factor/pancreas duodenal homeobox (<i>IPF1/PDX1</i>)	606392	Heterozygous mutation can cause MODY or type 2 diabetes; homozygous mutation results in pancreas agenesis with severe diabetes and exocrine pancreas insufficiency.
MODY6	NEUROD1/Beta-2, activates transcription of the insulin gene	606394	Presentation similar to MODY3
MODY7	Kruppel-like factor1 (KLF11), regulates <i>PDX1</i>	610508	
MODY8	Carboxyl-ester	609812	Endocrine and exocrine pancreatic

	lipase (<i>CEL</i>)		dysfunction
MODY9	Paired homeobox 4 (<i>PAX4</i>)	612225	Impaired beta cell development
MODY10	Insulin	613370	Mild defect; progressively more severe defects cause type 2 diabetes, type 1 diabetes, and neonatal diabetes mellitus.
MODY X	Unknown		Fit criteria of MODY with young onset, absent islet autoantibodies, and response to oral agents, but gene defect not identified, hence indicated by X.

II. Other single gene defects associated with defective insulin synthesis/secretion and diabetes
HNF, hepatic nuclear factor; MODY, maturity-onset diabetes of youth.

*The Online Mendelian Inheritance in Man (OMIM) is an online catalog of human genes and genetic disorders. OMIM can be accessed at omim.org.

†The common types of MODY (MODY3, MODY2, MODY1, and MODY5 in descending order of frequency) account for almost 90% of all cases of MODY.

‡MODY4-MODY10 account for <1%, and MODY X accounts for ~10% of all cases of MODY.

Source: M. A. Sperling, personal communication

From Sperling and Garg (4).

Maternally Inherited Diabetes and Deafness:

Maternally inherited diabetes and deafness (MIDD) is associated with the 3243A>G mitochondrial DNA point mutation, a condition that may affect up to 1% of patients with diabetes. These gene mutations are nearly always inherited from the mother, since mitochondrial DNA is present in oocytes but not in spermatozoa. Therefore, relatives on the maternal side may also have manifestations of mitochondrial gene defects, of which diabetes is the third most common systemic manifestation after cardiac conduction defects and cardiomyopathy. Other systemic manifestations include short stature, pigmentary retinopathy, lactic acidosis, glomerulopathy with focal segmental glomerulosclerosis, and strokes with cerebellar and cerebral atrophy. Because the 3243A>G mutation results in diminished ATP production, tissues with high energy turnover, such as pancreatic islets and the cochlear stria vascularis, are affected, explaining the presence of deafness and diabetes. The diabetes may be variable in its severity, presenting as diabetic ketoacidosis in young patients and, therefore, being misdiagnosed as type 1 diabetes. Alternatively, milder forms may

present later in life and be diagnosed as type 2 diabetes. Leber's hereditary optic neuropathy (LHON) and Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) may be part of the same familial spectrum and are due to the same gene mutation.

The prognosis for MIDD is determined by the associated systemic manifestations, including cardiac failure and central nervous system dysfunction, and the diabetes requires insulin in those with younger severe onset but may be managed conservatively, at least at first, in older patients presenting with a pattern suggestive of type 2 diabetes. Metformin therapy should be avoided for risk of lactic acidosis in these patients. Genetic counseling is important in clarifying the maternal inheritance of this entity to affected family members.

Genetic Lipodystrophies-associated DM:

Genetic lipodystrophies are heterogeneous disorders characterized by selective loss of body fat (22, 23). About 62 years ago (24), the phenotype of the first genetic variety, congenital generalized lipodystrophy (CGL), was reported. Patients with lipodystrophies are predisposed to develop insulin resistance and its associated complications such as diabetes mellitus, hypertriglyceridemia, hepatic steatosis, polycystic ovarian disease and acanthosis nigricans. The extent of fat loss determines the severity of metabolic and other complications. In my last Internal Medicine Grand Rounds in 2013, I discussed genetic lipodystrophies and therefore, I will only give a brief overview of those subtypes which predispose to DM in Table 6 and Figure 2. Genetic lipodystrophies can be classified into either autosomal recessive or autosomal dominant disorders. Some patients do develop the syndrome as a result of heterozygous *de novo* mutations.

While the phenotype of CGL is so striking that the diagnosis should be apparent at birth, the diagnosis can be delayed in children with familial partial lipodystrophy (FPL) or atypical progeroid syndrome for several years till they see a specialist. Lipodystrophies should be considered in differential diagnosis of patients presenting with early diabetes, severe hypertriglyceridemia, hepatic steatosis, hepatosplenomegaly, acanthosis nigricans and polycystic ovarian syndrome. A thorough physical examination of "lean" patients with these metabolic complications to look for evidence of fat loss should clinch the diagnosis. It is especially important to examine the extremities and hips for signs of fat loss and muscular prominence. Some patients may present with excess sc fat deposition in various anatomic regions and may resemble patients with Cushing's syndrome and truncal obesity. In those suspected to have genetic lipodystrophies, an in depth pedigree analysis should be conducted to understand the mode of inheritance. Parents should be probed for any consanguinity among parents. Careful examination of the male first degree relatives can sometimes reveal previously undiagnosed FPL.

Table 6. Classification, Clinical Features, and Pathogenetic and Molecular Bases of Genetic Lipodystrophies With Predisposition to Diabetes

Syndrome	Subtypes (gene)	OMIM number*	Key clinical features	Molecular basis
I. Autosomal recessive lipodystrophies				
Congenital generalized lipodystrophy (CGL)†	CGL1 (AGPAT2)	608594	Lack of metabolically active adipose tissue since birth.	AGPATs are key enzymes for synthesis of triglyceride and phospholipids. AGPAT2 isoform is highly expressed in adipose tissue.
	CGL2 (BSCL2)	269700	Lack of both metabolically active and mechanical adipose tissue since birth, mild mental retardation, cardiomyopathy.	BSCL2 encodes seipin, which appears to play a role in lipid droplet formation and in adipocyte differentiation.
	CGL3 (CAV1)	612526	Single patient reported. Extreme lack of body fat, short stature, and vitamin D resistance.	Caveolin-1 is an integral component of caveolae, present on adipocyte membranes. Caveolin-1 binds fatty acids and translocates them to lipid droplets.
	CGL4 (PTRF)	613327	Extreme lack of body fat, congenital myopathy, pyloric stenosis, and cardiomyopathy.	PTRF (also known as cavin) is involved in biogenesis of caveolae and regulates expression of caveolin-1 and -3.
Mandibuloacral dysplasia (MAD)†	Type A (LMNA)	248370	Skeletal anomalies, loss of subcutaneous fat from the extremities and trunk.	Defective lamins A and C may disrupt nuclear function, resulting in death of adipocytes and skeletal tissue.
	Type B (ZMPSTE24)	608612	Skeletal anomalies, generalized loss of fat, premature renal failure, progeroid features.	Zinc metalloproteinase is critical for posttranslational processing of prelamin A to its mature form, lamin A. Accumulation of farnesylated prelamin A may be toxic and disrupt nuclear function in several tissues.
Familial partial lipodystrophy (FPLD5)	(CIDEC)	615238	Single patient reported.	Histopathology of subcutaneous fat showed multilocular, small lipid droplets in adipocytes.

II. Autosomal dominant lipodystrophies

FPL	FPLD1, Kobberling variety (unknown)	NA	Loss of subcutaneous fat from the extremities.	Molecular basis is unknown.
	FPLD2, Dunnigan variety (<i>LMNA</i>)	151660	Loss of subcutaneous fat from the extremities and trunk (sparing the face and neck) at puberty.	<i>LMNA</i> encodes nuclear lamina proteins, lamins A and C. Defective lamins A and C may disrupt nuclear function, resulting in death of adipocytes.
	FPLD3 (<i>PPARG</i>)	604367	Loss of subcutaneous fat from the distal extremities.	<i>PPAR</i> γ is essential for adipogenesis. Dominant negative <i>PPAR</i> γ mutations may inhibit adipocyte differentiation.
	FPLD4 (<i>PLIN1</i>)	613877	Loss of subcutaneous fat from the extremities.	Perilipin is an integral component of lipid droplet membranes. Histology revealed small adipocytes with increased fibrosis of adipose tissue.
	FPLD6 (<i>AKT2</i>)	NA	Single family reported with loss of subcutaneous fat from the extremities.	<i>AKT2</i> is involved in adipocyte differentiation and downstream insulin receptor signaling.
Atypical progeroid syndrome	(<i>LMNA</i>)	NA	Variable loss of subcutaneous fat.	Different heterozygous mutations in <i>LMNA</i> cause partial or generalized lipodystrophy.
SHORT syndrome	(<i>PIK3R1</i>)	269880	Short stature, <i>Hyperextensibility</i> or <i>inguinal hernia</i> , <i>Ocular</i> <i>depression</i> , <i>Rieger</i> <i>anomaly</i> , and <i>Teething</i> <i>delay</i>	<i>PIK3R1</i> encodes the p85 α regulatory unit of phosphatidylinositol 3 kinase, which is known to play a role in insulin signaling.

AGPAT, 1-acylglycerol-3-phosphate O-acyltransferase; AKT2, v-AKT murine thymoma oncogene homolog 2; BSCL2, Berardinelli-Seip congenital lipodystrophy 2; CAV1, caveolin-1; CGL, congenital generalized lipodystrophy; CIDEA, cell death-inducing DNA fragmentation factor α -like effector c; FPLD, familial partial lipodystrophy; LMNA, lamin A/C; NA, not applicable; PLIN1, perilipin; PPAR, peroxisome proliferator-activated receptor; PTRF, polymerase I and transcript release factor.

*The Online Mendelian Inheritance in Man (OMIM) is an online catalog of human genes and genetic disorders. OMIM can be accessed at omim.org.

†Additional rare types for which the genetic bases are not known are not included.

From Sperling and Garg (4).

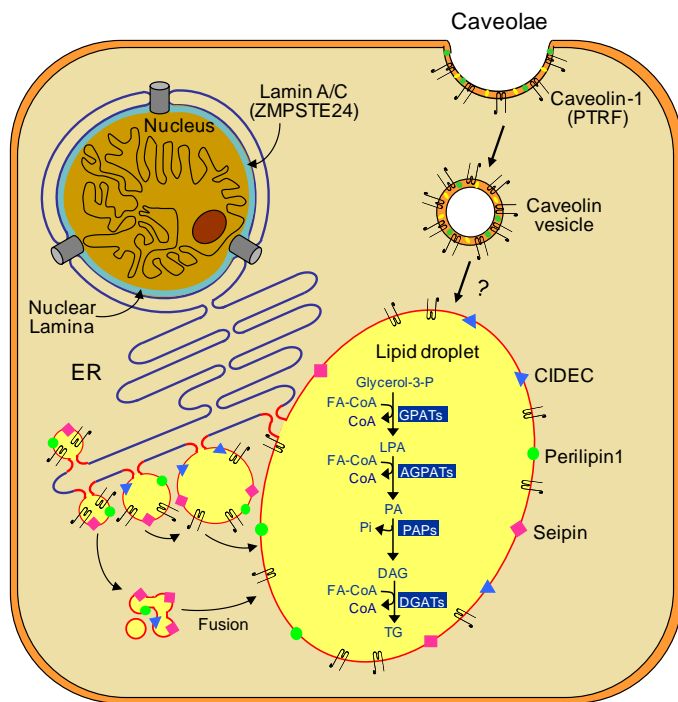


Fig. 2. Role of Lipid droplet formation in adipocytes as it relates to Lipodystrophy genes. Lipid droplets (LD) are organelles that store triglycerides (TG) intracellularly. In the adipocytes, they form as budding vesicles at the endoplasmic reticulum (ER) that fuse together to form one large LD. Many proteins, such as CIDEc (shown in *blue triangles*), seipin (*pink squares*), and perilipin 1 (*green circles*) are present on the LD membrane. CIDEc and seipin may be involved in fusion of LDs to form a larger LD, whereas perilipin 1 is essential for lipid storage and hormone-mediated lipolysis. Caveolae are formed from lipid rafts on the cell surface, which include cholesterol (*yellow symbols*), glycosphingolipids (*green symbols*), and caveolin-1 (*black hairpin-like symbols*). Endocytosis of caveolae forms caveolin vesicles that may directly merge with lipid droplets and thus translocating fatty acids to LDs. PTRF controls expression of caveolin 1 and 3 (data not shown). The classical and alternative pathways involved in the biosynthesis of TG are shown inside the lipid droplet. In the adipose tissue, TG synthesis requires glycerol-3-phosphate as the initial substrate (classical pathway), whereas in the small intestine, synthesis of TG can occur via an alternative pathway using monoacylglycerol

(MAG) as the initial substrate. Acylation of glycerol-3-phosphate using fatty acyl coenzyme A (FA-CoA) at the sn-1 position is catalyzed by glycerol-3-phosphate acyltransferases (GPATs), resulting in the formation of 1-acylglycerol-3-phosphate or lysophosphatidic acid (LPA). LPA is then acylated at the sn-2 position by AGPATs to yield phosphatidic acid (PA). Removal of phosphate group from PA by PA phosphatases (PAP) produces diacylglycerol (DAG). Further acylation of DAG at the sn-3 position by diacylglycerol acyltransferases (DGATs) finally produces TG. Lamin A/C are integral components of nuclear lamina (shown in *blue color*) and interact with nuclear membrane proteins as well as chromatin. Zinc metalloproteinase (ZMPSTE24) is critical for posttranslational processing of prelamin A to its mature form, lamin A. [Modified from A. Garg and A. K. Agarwal: Caveolin-1, a new locus for human lipodystrophy. *J Clin Endocrinol Metab* 93:1183–1185, 2008. © The Endocrine Society. And from A. Garg and A. K. Agarwal: Lipodystrophies: disorders of adipose tissue biology. *Biochem Biophys Acta* 1791:507–513, 2009.

Diabetes control in patients with lipodystrophies can be challenging. A multi-pronged strategy should be used including diet, physical activity and drug therapy. For treatment of diabetes in patients with lipodystrophies, metformin should be the first line therapy for diabetes. There is no hard evidence to show that thiazolidinediones can improve fat deposition in lipodystrophic regions (25). Instead, in patients with partial lipodystrophies, they can potentially increase unwanted fat deposition in nonlipodystrophic regions. Whether thiazolidinediones should be the choice of therapy in FPL patients with *PPARG* mutations is not clear (26). Since many patients with lipodystrophies have extreme insulin resistance, they may require high doses of insulin, including administration of U-500 insulin (500 units of insulin per mL).

Subcutaneous metreleptin replacement in low doses has been reported to dramatically improve diabetes control, hepatic steatosis and hypertriglyceridemia in severely hypoleptinemic patients with generalized lipodystrophies (27-30). Metreleptin

suppresses appetite and patients lose weight on therapy (27, 29). Metreleptin was recently approved by the Food and Drug Administration of the U.S. for improving metabolic complications in patients with generalized lipodystrophies. Metreleptin replacement, however, is only modestly efficacious in patients with FPL (27, 29, 31, 32) and has not been approved for FPL.

In conclusion, elucidation of molecular basis of many patients with atypical diabetes has led to unique therapies for many subtypes, such as, neonatal diabetes, TRMA-DM, MODY and genetic lipodystrophies. It is hoped that as we learn more about the genetic predisposition to T2DM, similar precision medicine approach may be adopted for various genetically heterogeneous subtypes of T2DM.

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