CHAPTER 7

MONOGENIC FORMS OF DIABETES

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SUMMARY

Types 1 and 2 diabetes have multiple and complex genetic influences that interact with environmental triggers, such as viral infections or nutritional excesses, to result in their respective phenotypes: young, lean, and insulin-dependence for type 1 diabetes patients or older, overweight, and often manageable by lifestyle interventions and oral medications for type 2 diabetes patients. A small subset of patients, comprising ~2%–3% of all those diagnosed with diabetes, may have characteristics of either type 1 or type 2 diabetes but have single gene defects that interfere with insulin production, secretion, or action, resulting in clinical diabetes. These types of diabetes are known as MODY, originally defined as maturity-onset diabetes of youth, and severe early-onset forms, such as neonatal diabetes mellitus (NDM). Defects in genes involved in adipocyte development, differentiation, and death pathways cause lipodystrophy syndromes, which are also associated with insulin resistance and diabetes. Although these syndromes are considered rare, more awareness of these disorders and increased availability of genetic testing in clinical and research laboratories, as well as growing use of next generation, whole genome, or exome sequencing for clinically challenging phenotypes, are resulting in increased recognition. A correct diagnosis of MODY, NDM, or lipodystrophy syndromes has profound implications for treatment, genetic counseling, and prognosis. This chapter summarizes the clinical findings, genetic basis, and prognosis for the more common forms of these entities.

MODY typically appears before age 25–35 years, in those with a strong family history affecting two to three successive generations, occurs in all races, affects both males and females, and is often misdiagnosed as type 1 or type 2 diabetes. Autoantibodies to islet components are absent, whereas residual insulin secretion is retained, as demonstrated by the concentration of C-peptide in serum at diagnosis. Patients who present with these features should be considered for genetic testing. Three genetic defects (MODY3, MODY2, and MODY1, in order of frequency) comprise ≥85% of all known forms of these entities. MODY3 (more so) and MODY1 patients often respond to oral sulfonylureas, especially at younger ages, and may not require insulin injections. MODY2 patients generally do not require any medication, except during pregnancy to protect the fetus from hyperglycemia, which may cause either macrosomia or small birth weight depending on whether both mother and child have the mutation or not. A correct molecular diagnosis is cost-effective in savings from avoiding insulin, offers precise genetic counseling for a 50% chance of occurrence in each offspring of an affected individual, and generally has a substantially better prognosis for avoidance of the long-term complications of type 1 or type 2 diabetes.

NDM presents as transient or permanent diabetes in the newborn, may be corrected by sulfonylurea medication in specific gene mutations, or may be associated with specific syndromes of congenital malformations. Some forms represent familial inheritance, with less severe defects in the same genes masquerading as type 2 diabetes in first-degree relatives, while many represent spontaneous new mutations. NDM is rare, with an estimated incidence of ~1:100,000 live births; the incidence of NDM is significantly higher in populations with high rates of consanguinity.

MODY and NDM gene defects have been associated with "typical" type 1 and type 2 diabetes clinical presentation; thus, these single gene defects play an important role in the global burden of diabetes.

The autosomal recessive congenital generalized lipodystrophy (CGL) and autosomal dominant familial partial lipodystrophy (FPL) are the two most common types of genetic lipodystrophies. Patients with CGL present with near total lack of body fat, while those with FPL have variable loss of fat, mainly from the extremities. Both disorders present with severe insulin resistance, premature diabetes, hypertriglyceridemia, and hepatic steatosis. Mutations in *AGPAT2*, *BSCL2*, *CAV1,* and *PTRF* have been reported in CGL and in *LMNA*, *PPARG*, *AKT2,* and *PLIN1* in FPL. Management of diabetes in patients with genetic lipodystrophies involves low-fat diet and high doses of insulin and other antihyperglycemic agents. Metreleptin replacement therapy improves glycemic control, especially in patients with generalized lipodystrophies, and is approved for this specific use in the United States.

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INTRODUCTION

Diabetes, a syndrome characterized by hyperglycemia and other metabolic abnormalities, occurs when there is a critical degree of deficiency of insulin secretion or insulin action or combinations of insulin secretion inadequate to overcome moderate degrees of insulin resistance. Because insulin synthesis, secretion, and action are under complex genetic controls, type 1 and type 2 diabetes are considered to be multifactorial diseases. Type 1 diabetes refers to severe insulin deficiency as the primary abnormality and is most often due to autoimmune destruction of insulin-producing beta cells in the pancreas in the context of clear insulinopenia and ketosis; this autoimmune form is sometimes, and for the purposes of this chapter, specified as type 1a diabetes. Some patients have a clinical picture that is consistent with type 1 diabetes, but the cause of beta cell failure is not known and no autoantibodies are detected; this form of diabetes is sometimes, and for the purposes of this chapter, specified as type 1b (or idiopathic) diabetes. It is not known whether these patients have a different underlying pathology or if they have autoantibodies that are not measured by common assays. Type 2 diabetes is associated with insulin resistance and variable degrees of insulin deficiency. However, mutations in single genes, either inherited or as *de novo* mutations, may result in various forms of *monogenic diabetes* that mimic type 1 diabetes, type 2 diabetes, and other distinct types. Variants in the same genes that cause maturity-onset diabetes of youth (MODY) and various forms of neonatal diabetes mellitus (NDM) or other syndromes have been increasingly identified in the more common forms, especially type 2 diabetes, where the severity of the gene defects are milder and, hence, manifest later in life. Thus, the importance of understanding these less common entities far outweighs their incidence or prevalence.

All monogenic forms of diabetes, including MODY, NDM, and lipodystrophies, are rare. However, more awareness of these disorders and increased availability of genetic testing in clinical and research laboratories, as well as growing use of next generation sequencing, whole genome sequencing, or exome sequencing for clinically challenging phenotypes, are increasing recognition of these conditions.

This chapter focuses on common patterns of clinical presentation as occurs with MODY, NDM, and the lipodystrophy syndromes. The presentation, incidence, and prevalence of the more common forms of each entity are highlighted, and the more rare forms are briefly described. Specific genetic defects for all syndromes that fulfill the clinical criteria of MODY, NDM or lipodystrophy syndromes are still not completely defined.

MONOGENIC FORMS OF DIABETES

Table 7.1 summarizes the monogenic forms of diabetes, including syndrome names, associated genes, and key clinical findings.

MODY: GENERAL CONSIDERATIONS

MODY is generally referred to as "maturity-onset diabetes of youth" because when described in the 1970s, the classification of diabetes consisted of two types: (a) juvenile ketosis-prone diabetes with onset at ages <20–25 years, severe insulin deficiency, and hence, dependence on exogenous insulin injections; and (b) maturity-onset diabetes 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 patients with maturity-onset types of diabetes were adolescents and young adults age <30 years with a strong family history affecting two to three generations, suggesting autosomal dominant transmission, who were responsive in many instances to oral agents, such as sulfonylureas (1).

The genetic bases for many of the classic forms of monogenic diabetes are known to be transcription factors or enzymes involved in insulin secretion or formation of the pancreas and its endocrine

TABLE 7.1. Monogenic Forms of Diabetes

SYNDROME	DEFECTIVE PROTEIN OR GENE	OMIM NUMBER*	KEY CLINICAL FINDINGS
I. Transcription factors and enzymes affecting insulin synthesis/secretion (MODY)			
I.a. Common types of MODY†—autosomal dominant			
MODY3	Hepatocyte nuclear factor (HNF)1α	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 (*GCK*)	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	HNF4α	125850	Third most common form; may have macrosomia and hypoglycemia at birth, followed by diabetes later in life; treatment as for MODY3.
MODY5	HNF1β	189907	Associated with renal cysts, other vesicogenital anomalies, albuminuria, and renal failure unrelated to the control of diabetes.

Table 7.1 continues on the next page.

TABLE 7.1. (continued)

SYNDROME	DEFECTIVE PROTEIN OR GENE	OMIM NUMBER*	KEY CLINICAL FINDINGS
I.b. Other rarer types of MODY‡			
MODY4	Insulin promoter factor 1/ pancreatic and duodenal homeobox 1 (*IPF1/PDX1*)	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 factor 1 (KLF11), regulates *PDX1*	610508	
MODY8	Carboxyl-ester lipase (*CEL*)	609812	Endocrine and exocrine pancreatic dysfunction
MODY9	Paired box 4 (*PAX4*)	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			
Wolfram syndrome/DIDMOAD	Wolframin 1 (*WFS1*)	606201	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness
Wolfram syndrome/DIDMOAD	Wolframin 2 (*WFS2*)	604928	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness
Mitochondrial form of Wolfram syndrome		598500	As above
Thiamine-responsive megaloblastic anemia (TRMA)/ Rogers syndrome	Thiamine transporter 1 *SLC19A2*	249270	Thiamine-responsive megaloblastic anemia, deafness, and diabetes
Pigmented hypertrichosis and insulin-dependent diabetes (PHID)	Nucleoside transporter 3 *SLC29A3*	612373	Multiple associated anomalies
Mitochondrial inherited diabetes and deafness (MIDD)	3243A>G mitochondrial gene mutation	520000	Same mutation as involved in Leber's hereditary optic neuropathy (LHON) and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); may be associated with Wolf-Parkinson-White syndrome, deafness, maternal inheritance.
III. Genetic defects of insulin			
Transient or permanent neonatal diabetes mellitus (NDM); type1 diabetes; type 2 diabetes presenting later in life	Insulin gene (*INS*)	176730	Diabetes without any distinguishing features; see text and Table 7.2 for details.
IV. Genetic defects of insulin processing			
	Prohormone convertase 1/3 (*PCSK-1*)	600955	Obesity, low cortisol, high proinsulin, hypogonadotropic hypogonadism
	Prohormone convertase 2 (*PCSK-2*)	162151	High proinsulin and diabetes
V. Genetic defects in insulin action: insulin receptor and postreceptor defects			
Donohue syndrome (Leprechaunism)	Insulin receptor *(INSR)*	246200	Intrauterine growth retardation, minimal subcutaneous fat, low glycogen content in liver, fasting hypoglycemia, and postprandial hyperglycemia
Rabson-Mendenhall syndrome	Insulin receptor *(INSR)*	262190	Similar to Donohue syndrome with skeletal/bony deformities
Insulin resistance syndrome type A	Insulin receptor *(INSR)*	610549	May not be a specific syndrome distinct from obesity, diabetes, and acanthosis nigricans.
VI. Abnormal function of cilia			
Alstrom syndrome	*ALMS1*	203800	Obesity, type 2 diabetes, blindness, hearing loss, cardiomyopathy
Bardet-Biedl syndrome			Obesity, type 2 diabetes, blindness, hearing loss, cardiomyopathy

HNF, hepatocyte 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 (see also Figure 7.1).
‡ MODY4–MODY10 account for <1%, and MODY X accounts for ~10% of all cases of MODY.

SOURCE: M. A. Sperling, personal communication

function (Figure 7.1) (1,2,3,4,5,6). 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 (i.e., MODY2, glucokinase [*GCK*] loss of function mutation), symptomatic diabetes usually presenting in teens (although a patient as young as age 8 years has been reported) to late twenties (but patients have been diagnosed in their forties) (i.e., MODY3, hepatocyte nuclear factor (HNF) 1α mutation), large size at birth with neonatal hypoglycemia but later appearance of diabetes (i.e., MODY1, HNF4α mutation), and diabetes associated with renal anomalies (i.e., MODY5, HNF1β mutation). These four entities constitute close to 90% of all known mutations in MODY (Figure 7.1). Affected patients typically are negative for autoimmune markers, such as various islet antibodies, have positive family history indicative of autosomal dominant transmission, unless they harbor *de novo* mutations, and may appear to have low insulin requirements. When measured, insulin levels may be normal or low for the prevailing glucose concentration.

FIGURE 7.1. Classification of Maturity-Onset Diabetes of Youth (MODY)

TYPE	GENE	CHROMOSOME	TREATMENT	RELATIVE FREQUENCY (%)
MODY1	HNF4α	20q12-q13.1	Insulin/SU	5
MODY2	Glucokinase	7p15-p13	Exercise/diet	22
MODY3	HNF1α	12q24.2	Insulin/SU	58
MODY4	IPF1/PDX1	13q12.2	Insulin	<1
MODY5	HNF1β	17q12	Insulin/SU	2
MODY6	NEUROD1/Beta-2	2q32	Insulin	<1
MODY7	KLF11	2p25	Insulin	<1
MODY8	CEL	9q34.3	Insulin	<1
MODY9	PAX4	7q32	Insulin	<1
MODY10	Insulin	11p15.5	Insulin	<1

MODY1, 2, and 3 together constitute 85% of all known MODY syndromes; if MODY5 is included, almost 90% of all MODY syndromes are defined.

MODY2 is stable, rarely requires insulin treatment except during pregnancy to protect the fetus from hyperglycemia, and has an excellent prognosis for avoidance of vascular complications.

MODY1 and 3 frequently respond to sulfonylurea drugs (SU) initially but may progress to insulin dependence and risk for development of vascular complications dependent on metabolic control.

MODY constitutes about 1.5%–2.5% of new-onset childhood diabetes and should be suspected in those with: a family history of multiple affected members in two to three generations, with onset before age 35 years; absence of markers of autoimmunity; "mild diabetes" requiring <0.5 U/kg insulin from the outset or unusually prolonged "honeymoon" phase.

CEL, carboxyl-ester lipase; HNF, hepatocyte nuclear factor; IPF/PDX, insulin promoter factor/pancreatic and duodenal homeobox; KLF, Kruppel-like factor; MODY, maturity-onset diabetes of youth; PAX, paired homeobox; SU, sulfonylurea drugs.

SOURCE: M. A. Sperling, personal communication; the clinical manifestations, pathophysiology, and treatment of MODY are reviewed in Reference 2.

Epidemiology

Overall, MODY syndromes represent approximately 2%–3% of all patients diagnosed with diabetes; in the United Kingdom, the minimum prevalence of MODY was estimated to be 108 cases per million (5). In the Search for Diabetes in Youth Study (6), of ~5,000 newly presenting children with diabetes with measurement of diabetes autoantibodies and fasting C-peptide, 14.5% (730 subjects) were diabetes autoantibodies negative and fasting C-peptide positive. Of these, 586 subjects were tested for MODY (MODY1, 2, and 3), and 48 (8.2%) were MODY positive. Thus, about 1.2% of the original cohort of children had genetically proven MODY. Non-Hispanic white (35%), African American (24%), Hispanic (26%), and Asian and Pacific Islander (13%) individuals were represented in the MODY group, and most were considered to have either type 1 diabetes and treated with insulin or type 2 diabetes and treated with metformin and other oral hypoglycemic medications.

A clinical presentation before age 25–30 years of apparent mild type 1 diabetes or type 2 diabetes with negative diabetes autoantibodies and positive C-peptide, as well as a positive family history in two to three generations should prompt consideration of a diagnosis of MODY and referral for molecular diagnostics 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 type 1 diabetes.

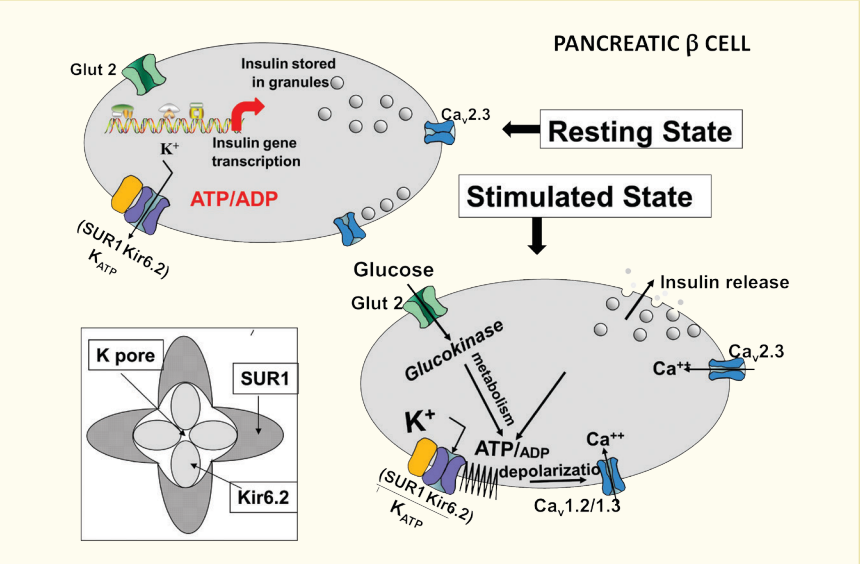
Appropriate management for patients with MODY2 is exercise and diet, which usually suffice to control blood glucose, except in pregnancy when insulin may be required to control blood glucose to avoid the consequences of hyperglycemia in the fetus. Patients with MODY3 and MODY1 usually respond to sulfonylureas, though about one-third may lose this responsiveness in time and progress to require insulin (1,2,3,4). The response to sulfonylureas is much more pronounced in MODY3 patients, such that hypoglycemia may ensue. Rather than transfer to insulin or other agents, the best approach is smaller doses, down to 1.25 mg per day or even less to achieve very reasonable glycemic control in hyper-responsive MODY3 patients. The early appearance of albuminuria, or a family history of renal cysts or other renal anomalies, should prompt consideration of MODY5. Subjects with MODY5 generally require insulin for therapy and careful management of their renal manifestations.

Common Forms of MODY

As shown in Figure 7.1, MODY3, MODY2, MODY1, and MODY5 together constitute ~90% of all forms of MODY and almost 98% of all known MODY mutations. Two forms, MODY3 and MODY1, are caused by heterozygous mutations in the transcription factors HNF1α and HNF4α, respectively, whereas MODY2 is caused by a heterozygous inactivating mutation in the enzyme glucokinase, which acts as the sensing apparatus of glucose concentration within the beta cell (Figure 7.2) (1,2,3,4). MODY5 is similar to MODY1 or MODY3 in clinical presentation but is associated with renal anomalies, predominantly cystic changes.

Figure 7.2 is a simplified cartoon of the beta cell that illustrates the interactions of these proteins in the insulin synthesis/secretion cascade (6,7). In the resting state (upper left quadrant of the figure), insulin synthesis and basal secretion are governed by the basal glucose concentration; insulin gene (*INS*) transcription is regulated by a number of regulatory factors that bind to upstream components of *INS* on chromosome 11. Also illustrated is one unit of the ATP-regulated potassium channel (K_{ATP}), governed by the ratio of ATP:ADP. The channel remains open in the basal state, allowing efflux of potassium 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 four subunits of the inward rectifying potassium channel (Kir6.2), encoded by the *KCNJ11* gene, and four surrounding regulatory units, the sulfonylurea receptor (SUR1), encoded by the *ABCC8* gene (lower left quadrant); both genes are located on chromosome 11. Also illustrated are voltage-gated calcium channels, designated as Ca_v 1.2/1.3 and Ca_v2.3. Stored insulin granules lined up on the cell membrane constitute a quickly releasable pool of insulin responsible 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 quadrant), when blood glucose rises after a meal, it enters the beta cell via the GLUT2 glucose transporter, a non-insulin regulated process. Glucokinase acts as a glucose sensor and phosphorylates glucose to glucose-6-phosphate (G6P), permitting its metabolism to produce ATP. The higher ATP:ADP results in closure of the K_{ATP} channel, retention of intracellular K^+, which leads to membrane depolarization, opening of the voltage-gated Ca^{2+} 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

FIGURE 7.2. Schematic Representation of a Beta (β) Cell



Please see text for detailed explanation of insulin synthesis and secretion. ATP/ADP, adenosine triphosphate/adenosine diphosphate; Cav, voltage-gated calcium channel; Glut 2, glucose transporter 2; K_{ATP}, ATP-regulated potassium channel; Kir, inward rectifying potassium channel; SUR, sulfonylurea receptor.

SOURCE: M. A. Sperling, personal communication

insulin secretion when 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 keep the channel open, preventing insulin secretion, i.e., leading to neonatal 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 that act on the SUR1 regulatory unit even though the mutation is in the Kir6.2 channel unit encoded by *KCNJ11*. 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 may reduce insulin secretion, although it has many other side effects, including hypertension and edema (6,7).

Heterozygous inactivating mutations in *GCK* create a rightward shift in the ability of the enzyme to phosphorylate glucose, resulting in normal insulin secretion but at higher than normal glucose concentrations. Thus, the set point of glucose is on the order of 90–120 mg/dL (5.00–6.66 mmol/L) in the basal state and briefly in the range of diabetes after a meal, but it returns to normal as adequate insulin secretion occurs at the higher glucose concentrations (Figure 7.3). The result is "mild" diabetes, as seen in MODY2. Homozygous inactivating mutations of *GCK* result in the virtual absence of phosphorylating activity and, hence, NDM. By contrast, activating mutations in *GCK* cause inappropriately high insulin secretion at lower glucose concentrations, causing hyperinsulinemic hypoglycemia of infancy and a milder adult form of familial hypoglycemia, the severity of which will be proportional to the degree of activation of *GCK* (1,2,3,4,6,7).

MODY3. MODY3 is due to mutations in the transcription factor HNF1α gene, located on chromosome 12q24.2 and expressed in liver and beta cells. The gene is regulated to some extent by HNF4α, providing a link between MODY1 and MODY3. In most series, this entity is the most common form of MODY (Figure 7.1), with over 120 known mutations, though MODY2 is as, or more, common when assessed in younger subjects (age <20 years). Birth weight is normal in MODY3 patients, and symptoms of diabetes usually appear towards the end of the first decade or in the second to third decades; some patients are entirely asymptomatic despite glucose values in the low-mid

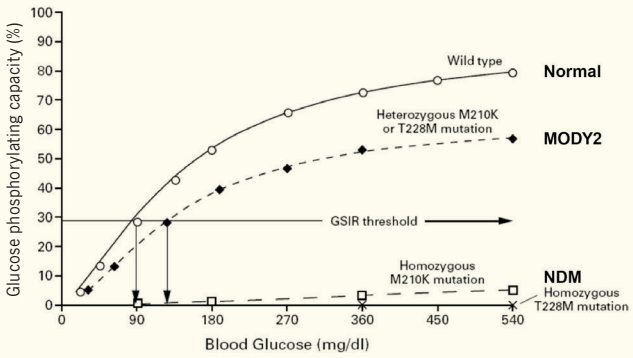
200 mg/dL (11.10 mmol/L) range and glycosylated hemoglobin (A1c) in the 7.5%–8.5% (58–69 mmol/mol) range at diagnosis. Others present with diabetic ketoacidosis. Females may be diagnosed with gestational diabetes; a lean young woman with a family history of diabetes in her parents, grandparents, or siblings, who is found to have gestational diabetes, should be tested for MODY2 and, if negative, for MODY3.

Most patients with MODY3 (and MODY1) are initially responsive to sulfonylureas, which promote endogenous insulin secretion and correct hyperglycemia, but about one-third to one-half of affected subjects may have progressive insulinopenia with increasing age, ultimately requiring insulin for treatment. However, newer agents combined with sulfonylureas may prove useful for good glycemic control in the absence of exogenous insulin.

Once the mutation is confirmed, genetic counseling must emphasize that these mutations are dominant, so statistically 50% of offspring are likely to have the same condition. Other family members are also likely to have the mutation and should also be considered for DNA sequencing. Rare subjects have been reported to develop type 1a diabetes with markers of autoimmunity, such as glutamic acid decarboxylase 65kD (GAD65) and/or islet cell autoantibodies (ICA) being positive, despite being negative for these markers at initial diagnosis (8). Mutations in HNF1α have been described as an uncommon cause of "type 2 diabetes," if in a mild form and discovered after age 35–40 years (8).

MODY2. MODY2 is due to decreased beta cell sensing of glucose due to loss of function mutations in glucokinase encoded by the *GCK* gene on chromosome 7p15-p13 (Figure 7.3). The prevalence of *GCK* mutations causing MODY2 in the overall population is suggested to be 0.04%–0.1%; thus, up to 1:1,000 women of childbearing age are likely to have a *GCK* mutation when they present with gestational diabetes (9). This form of MODY presents as mild fasting and postprandial hyperglycemia and is usually asymptomatic.

FIGURE 7.3. Mutations in the Glucokinase Gene Reduce Glucose Phosphorylating Capacity and Result in Diabetes



VARIABLE	WILD TYPE	M210K MUTATION	T228M MUTATION
Turnover rate (sec^{-1})	52.4±5.7	16.7±1.6	0.004±0.0004
Glucose $S_{0.5}$ (mmol/liter)	7.7±0.1	38.7±1.9	5.5±1.5
Hill coefficient	1.66±0.00	1.63±0.04	0.71±0.07
ATP_{Km} (mmol/liter)	0.35±0.01	1.38±0.11	0.62±0.16

The enzyme glucokinase (GCK) phosphorylates glucose to glucose-6-phosphate, permitting its metabolism to generate ATP, thereby inducing insulin secretion as described in Figure 7.2. The glucose-stimulated insulin release (GSIR) threshold requires a glucose phosphorylating capacity of ~30%, normally reached at a glucose concentration of ~90 mg/dL. With heterozygous inactivating mutations in *GCK*, such as those associated with MODY2, the *GSIR* is right-shifted, so that the GSIR is reached at glucose concentrations of ~110–130 mg/dL, permitting adequate insulin secretion at somewhat higher glucose concentrations. This results in a "mild" diabetes phenotype, discovered by chance or during screening for gestational diabetes or other indications. Homozygous inactivating mutations in GCK cannot reach the GSIR threshold and result in neonatal diabetes mellitus. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* ATP, adenosine triphosphate; MODY, maturity-onset diabetes of youth; NDM, neonatal diabetes mellitus.

SOURCE: M. A. Sperling, personal communication

Hyperglycemia may be discovered as an incidental finding in a child or adult during a routine blood chemistry check performed for an unrelated illness; islet cell antibodies are negative and glucose tolerance testing, if performed, shows mild hyperglycemia, rarely exceeding 200 mg/dL with delayed return to modestly elevated basal glucose concentrations in the range of 90–130 mg/dL (5.00–7.22 mmol/L). Insulin levels, if measured, are appropriate but occur at higher than normal glucose concentrations. A1c values are generally in the 6.3%–7.5% (45–58 mmol/mol) range. In the absence of a family history, such patients may be considered to have type 1 diabetes in the early stages and be inappropriately treated with insulin, if they are children, or considered to have type 2 diabetes and be treated with oral hypoglycemic agents or insulin sensitizers, if adults. More commonly, MODY2 due to *GCK* mutations presents as gestational diabetes in women without the stigmata of obesity or other features of insulin resistance. A family history of other affected members (e.g., parents, siblings) should raise suspicion for the presence of this condition. In particular, the parents of an affected child should be investigated, as they may be unaware of their mild hyperglycemia.

Because of the mild hyperglycemia, most patients with MODY2 do not require treatment with pharmacologic agents; diet and exercise are generally recommended (but nonspecific for glycemic control), and microvascular complications are extremely unlikely to occur (9). However, during pregnancy, treatment with insulin may be recommended because a normal, unaffected baby *in utero* will respond to the maternal hyperglycemia with excessive insulin secretion and be at risk for macrosomia with attendant risk at delivery and hypoglycemia after birth, as occurs in an infant of a diabetic mother.

On the other hand, babies who inherit the maternal defect (50% risk) may have a lower birth weight due to relative deficiency of fetal insulin secretion. If both parents are heterozygous for *GCK* mutations, the

infant has a 50% risk of inheriting *each* parent's mutation, but a 25% risk of inheriting *both* mutations and therefore having permanent NDM. Rare cases have been described of patients with MODY2 who have gone on to develop autoimmune (antibody positive) type 1a diabetes in addition to their genetic defect of insulin secretion; hence, periodic evaluation of patients with MODY2 is recommended. In some series, MODY2 is the most common form of MODY identified, and it particularly is the most common form in those diagnosed at age <15–20 years (1,2,3,4,9).

MODY1. MODY1 occurs due to mutations in the HNF4α gene located on chromosome 20q12-q13.1. It was the first transcription factor mutation discovered for MODY; normally, the gene is expressed in liver, kidney, intestine, and islets. HNF4α is a known key regulator of hepatic gene expression, and MODY1, like MODY3, is characterized by progressive insulinopenia with increasing age. Likewise, the clinical features of MODY1 are similar to those of patients with MODY3. Clinical onset of symptoms and recognition of hyperglycemia most commonly occurs in the mid-twenties but may occur later in some families. Most affected individuals are sensitive to the sulfonylurea drugs, which restore insulin secretion and lower glucose, but about one-third of subjects may develop progressive insulinopenia and require a combination of oral hypoglycemic agents or insulin for treatment. A distinguishing and perhaps defining characteristic of MODY1 is that affected subjects weigh about 800 g more at birth than their unaffected siblings, suggesting hyperinsulinemia effects *in utero* (10). Moreover, hyperinsulinemia at birth with symptomatic neonatal hypoglycemia that resolves spontaneously has been reported in some patients (10). These findings suggest that HNF4α mutations at first cause excessive secretion of insulin, directly or indirectly, and only later result in hypoinsulinemia and diabetes. The reasons for this paradox are not known. Patients with HNF4α have been reported to have lower levels of lipoprotein A2 and high-density lipoprotein (HDL) cholesterol, features commonly seen in type 2 diabetes and so may be misclassified, especially if clinical onset of diabetes occurs later in life. Reports of markedly lower concentrations of high sensitivity C-reactive protein (hsCRP) in patients with MODY3 (4) have not been reported in MODY1 (1,2,3,4,11); moreover, the findings of low hsCRP in MODY3 were not confirmed in a more recent report (6). Hence, hsCRP cannot be considered as a screening test to identify patients suspected of having MODY1 before embarking on molecular diagnosis (1,2,3,4,11).

MODY5. MODY5 individuals have a mutation in the HNF1β gene (12,13). HNF1β regulates HNF4α and, hence, may provide a link between MODY5 and MODY1. Originally discovered in Japanese families with MODY, the phenotype is characterized by cystic renal disease and other associated anomalies, including vaginal/uterine malformations, other genital abnormalities, abnormal liver function, hyperuricemia, and the early appearance of proteinuria that is not due to diabetic renal disease. The renal cystic manifestations may predominate with unawareness or absence of diabetes; patients may be referred from a renal clinic for evaluation of incidentally discovered hyperglycemia. Alternatively, MODY5 may be considered because a patient with insulin-requiring diabetes has siblings or parents with renal anomalies and early renal failure. Patients with MODY5 display insulin resistance and hyperinsulinemia with associated dyslipidemia. Unlike patients with MODY3 and MODY1, they do not respond to sulfonylurea drugs and usually require insulin for management. Subclinical pancreatic exocrine deficiency is present in most patients, so both exocrine and endocrine pancreatic functions are affected, and pancreatic size is smaller. Patients who are homozygous for mutations in HNF1β have severe NDM associated with other congenital anomalies (1,2,3,4,12,13).

MODY4, 6–10, X. MODY4 is due to mutation in the gene for the transcription factor PDX1 (pancreatic and duodenal homeobox), also known as IPF1 (insulin promoter factor), on chromosome 13q12.2. This transcription factor is important for specifying the development of the pancreas and duodenum, as well as the transcription of insulin, somatostatin, and other islet hormones. Diabetes results from a combination of reduced gene dosage, together with a dominant-negative inhibition of transcription of *INS* and other factors regulated by the mutant IPF1/PDX1 (14). MODY6 is due to mutation in the transcription factor NEUROD1 that activates transcription of *INS* (15). Presentation is similar to that of patients with MODY3. MODY7 is attributed to mutations in Kruppel-like factor 11 (KLF11), a transcription factor involved in regulating PDX1. MODY8 is attributed to mutations in the carboxyl-ester lipase gene (*CEL*), encoding an enzyme and associated with both endocrine and exocrine pancreatic dysfunction, leading to diabetes with evidence of malabsorption (16). The transcription factor PAX4 (paired homeobox 4) involved in beta cell development was found to be mutated in two Thai families with a MODY syndrome, designated MODY9, a finding not replicated to date in a selected European population of patients with MODY after excluding the common forms (3,17). Mutations in the insulin gene itself may cause a form of MODY designated as MODY10, although mutations in the insulin gene more commonly cause a form of NDM described below (18). MODY X is a term applied to cases where the clinical phenotype is consistent with MODY but a genetic cause has not been identified, i.e., X is the unknown.

All of these rare forms of MODY generally present with a history and phenotype similar to MODY3; diagnostic clues may be provided by the presence of features, such as malabsorption (*CEL*, MODY8), but otherwise are so rare that they are best considered in the context of a likely MODY syndrome, and if negative for the more common types, such patients should be referred to a specialized center for possible molecular diagnosis (1,2,3,4,18). Most subjects thought to be in these groups have benign sequence polymorphisms that are not likely to be disease-causing.

Differentiating the Common Forms of MODY From Type 1 and Type 2 Diabetes

The typical patient with MODY differs from type 1 diabetes in being negative for islet antibodies, differs from type 2 diabetes in typically being lean, is more likely to have a family history of other affected family members in an autosomal dominant pattern, and may have a prolonged "honeymoon" phase or low insulin requirements reflecting retention of endogenous insulin secretion confirmed by a C-peptide level ≥0.8 ng/mL. None of these characteristics is absolute; the increasing prevalence of obesity is blurring distinctions of phenotype between type 1 and type 2 diabetes, and Hispanic and African patients with MODY1–3 are being identified in the United States. For practical purposes, a diagnosis of MODY1–3 should be sought in those considered to have MODY, and MODY5 should be considered in those with renal manifestations unlikely to be secondary to the diabetes (1,2,3,4,18,19). Gene mutation analysis is available from Clinical Laboratory Improvement Amendments (CLIA)-certified commercial laboratories, as well as research centers in the United States and Europe.

OTHER SINGLE GENE DEFECTS ASSOCIATED WITH DIABETES DUE TO DEFECTIVE INSULIN SYNTHESIS/SECRETION

Table 7.1 lists the most common single gene defects associated with defective insulin synthesis or secretion that may result in clinical diabetes. Those defects include the insulin gene (*INS*) itself, which dependent on the severity of the mutation, result in variable degrees of hyperglycemia, ranging from permanent or transient NDM presenting in the first 6–9 months of life to MODY and (rarely) later onset of apparent type 1 diabetes (type 1b diabetes) or type 2 diabetes. No unique features distinguish these forms of clinical diabetes. Variable patterns are, however, imparted by the autosomal dominant versus autosomal recessive forms, as subsequently detailed in the description of NDM.

Wolfram Syndrome: Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness (DIDMOAD)

Wolfram syndrome is an autosomal recessive disorder, characterized by several associated abnormalities that tend to develop in a particular sequence over time. This rare disorder has an estimated population prevalence of 1:770,000 births and a carrier frequency of 1 in 354 people (20,21). Optic atrophy closely follows or precedes the onset of diabetes. In one series, the median age of onset of diabetes was 6 years, followed by progressive optic atrophy at 11 years with near total loss of vision over the following decade. Central diabetes insipidus is the next most common manifestation, followed by sensorineural deafness in the second decade. By the third decade, patients may have incontinence and evidence of neurologic degeneration with cerebellar ataxia and myoclonus by the fourth decade. A wide arc of neurological manifestations includes autonomic neuropathy, loss of sense of taste and smell, hemiparesis, myoclonus, and absent or reduced reflexes. Magnetic resonance imaging demonstrates brain atrophy. Psychiatric illness characterized by dementia and short-term memory loss and suicidal ideation are common later in the evolution of this syndrome. Presumed carriers of this mutation have been reported to be predisposed to psychiatric illness. Affected individuals have insulin deficiency requiring insulin for treatment. The diabetes insipidus responds to desmopressin. Some patients also benefit from hearing aids for their deafness. Gonadal atrophy is also common later in males, although some females have been reported to have successful pregnancies.

Heterozygous carriers of this mutation have an increased frequency of hearing loss and diabetes. A second locus (*WFS2*) on the long arm of chromosome 4 (4q22-24) has only been reported in a consanguineous Jordanian pedigree (21). Here, gastrointestinal bleeding is a major manifestation. The function of the *WFS1* remains unknown. There are some similarities between Wolfram syndrome and mitochondrial diseases, such as Leber's hereditary optic neuropathy (LHON) and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Although diabetes does occur in MELAS, and optic atrophy is a feature of LHON, these syndromes are clearly due to mitochondrial genome mutations (see the section on Maternally Inherited Diabetes and Deafness). Some heteroplasmic deletions in mitochondrial DNA have been found in patients with features similar to Wolfram syndrome, but examination of mitochondrial DNA in patients with classic Wolfram shows no evidence for specific mutations or general mutations or deletions (21).

Thiamine-Responsive Megaloblastic Anemia

Thiamine-responsive megaloblastic anemia (TRMA) and diabetes are due to a defect in the thiamine transporter SLC19A2. TRMA, also known as Rogers syndrome, combines megaloblastic anemia, diabetes, and sensorineural deafness, which respond by variable degrees to thiamine replacement. The *SLC19A2* gene encodes a transmembrane protein that acts as the thiamine transporter and has homology to reduced folate carrier proteins. Cardiac anomalies and abnormalities of the optic nerves and retina may occur occasionally in the TRMA syndrome. Markers of autoimmunity are absent in this autosomal recessive form of diabetes. Pharmacologic doses of thiamine may reverse anemia and diabetes early in the course of the disease; however, sometime during and after puberty, thiamine supplements may become ineffective, so all patients require insulin therapy with regular blood transfusions in adulthood (22).

Pigmented Hypertrichosis and Insulin-Dependent Diabetes

Yet another rare syndrome characterized by pigmented hypertrichosis and insulin-dependent diabetes (PHID) with other multiple associated anomalies is due to the *SLC29A3* gene, which encodes a transporter for nucleosides, nucleobases, and nucleoside analogue drugs. Loss-of-function mutations in this gene cause PHID, as well as the related syndrome

without diabetes termed the H syndrome. PHID patients may have severe exocrine pancreatic deficiency, as well as pigmented hypertrichotic skin patches with chronic inflammation (23).

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. LHON and MELAS may be part of the same familial spectrum and are due to the same gene mutation. Some patients with MIDD have been reported to have classic islet cell antibodies, which may represent coincident autoimmune mechanisms or represent secondary response to pancreatic beta cell destruction related to the mitochondrial gene mutation and its potential effects on inducing apoptosis within the islets.

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. Genetic counseling is important in clarifying the maternal inheritance of this entity to affected family members (24).

TABLE 7.2. Classification of Neonatal Diabetes Mellitus

TRANSIENT (TNDM) 45%	PERMANENT (PNDM) 45%	SYNDROME—RARE 10%
TNDM1 70% of TNDM Involves 6q24. Disturbance of imprinted genes *PLAGL (ZAC)* and *HYMAI* caused by: ▪ Paternal uniparental disomy (sporadic) ▪ Paternal chromosome 6 duplication (dominant transmission) ▪ Relaxation of imprinting maternal hypomethylation—sporadic or mutation in the transcription factor ZFP57 **TNDM2** 15% of TNDM *ABCC8* (SUR1) mutations 10% of TNDM *KCNJ11* (Kir6.2) mutations 5% of TNDM Mutations in *INS*, *HNF1β*, *SLC2A2*	50% *KCNJ11* ±DEND syndrome 30% *INS* mutation 15% *ABCC8* ±DEND syndrome 3% *GCK**, homozygous 2% Others *IPF1/PDX1**, homozygous *HNF1β**	*EIF2AK3*—spondyloepiphyseal dysplasia, renal anomalies *FOXP3*—IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) *GLIS3*—hypothyroid, hepatic fibrosis, glaucoma, cystic kidneys, developmental delay *PTF1A*—pancreatic and cerebellar agenesis *RFX6*—digestive system defects, known as Mitchell-Riley syndrome *NEUROG3*—with congenital malabsorptive diarrhea and enteroendocrine cell dysgenesis *GATA6 and GATA4*—with varying degrees of pancreatic agenesis, pancreatic exocrine dysfunction and cardiac malformations

DEND, developmental delay, epilepsy, neonatal diabetes; GCK, glucokinase; HNF, hepatocyte 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.

* Heterozygous mutations in *GCK*, *IPF1/PDX1*, and *HNF1β* cause MODY2, MODY4, and MODY5, respectively.

SOURCE: M. A. Sperling, personal communication

NEONATAL DIABETES MELLITUS

NDM is defined as diabetes that is diagnosed within the first 6 months of life, though some mutations may cause diabetes that manifests up to age 9 months or later. Because of the benefit that occurs by transfer from insulin to sulfonylurea treatment in those with K_{ATP} channel mutations, it has been suggested that K_{ATP} mutations as a cause should be sought in those presenting with diabetes up to 9 months of age. However, autoimmune diabetes (type 1a diabetes) before 6 months of life is unlikely to occur, so investigating the possible genetic basis of NDM should be undertaken in all babies with diabetes diagnosed when less than 6 months of age and later if they are not found to have islet antibodies. A classification of NDM is shown in Table 7.2.

Epidemiology

The incidence of NDM is estimated to be approximately 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 (6,25). Infants with NDM have low insulin concentrations and generally are small at birth, reflecting the important role of insulin as a fetal growth factor. About one-half of all infants with NDM have permanent diabetes from the outset (PNDM). The other half of infants affected by diabetes in the first weeks to months of life demonstrate the phenomenon of remission in clinical manifestations of diabetes with near normal glucose homeostasis in the absence of any treatment, but relapse at variable times subsequently (Table 7.2) (25,26,27,28,29,30,31). This condition is termed transient neonatal diabetes (TNDM), and of these cases, two-thirds to three-quarters will be due to abnormalities in imprinted genes or methylation defects in the chromosome 6q24 region (Table 7.2) (28). The remaining transient forms of NDM have defects in components of the K_{ATP} channel, including

Kir6.2 encoded by *KCNJ11* or the SUR1 regulatory subunit encoded by *ABCC8*; occasionally, *INS* mutations cause transient NDM. More commonly, mutations in these K_{ATP} subunits, along with mutations in *INS* itself, are responsible for PNDM. Those with *KCNJ11* or *ABCC8* mutations can be treated with sulfonylurea, thereby restoring endogenous insulin secretion, which improves metabolic control and prevents hypoglycemia and wide glycemic excursions (28,29,30,31,32). A second category of PNDM is due to various gene mutations associated with an array of congenital malformations (Table 7.2) (3,4,30,31,32,33,34). Because it is not known at the time of clinical presentation in the newborn whether the diabetes will remit or remain permanent, the four essential mutations that must be checked are the 6q24 imprinting defects, *KCNJ11*, *ABCC8*, and *INS*.

Transient Neonatal Diabetes Due to Imprinting Defects on Chromosome 6q24

Children born with TNDM are generally quite small, weighing approximately 2,000 g at birth. The diabetes is generally diagnosed in the first week or so of life, but it may be delayed until age 2–3 months. Initially, insulin is required for treatment, but requirements seem to diminish as evidenced by hypoglycemia after injections, and remission occurs at a median of about 3 months of life. Some patients with this form of TNDM have macroglossia and occasionally an umbilical hernia, which is reminiscent of the Wiedemann-Beckwith syndrome, another condition characterized by methylation defects observed in the chromosome 11 region rather than chromosome 6q24. During remission, insulin responses to various stimuli appear normal, and the infants have near normal glucose metabolism. Relapse, if it occurs, generally does so in the mid-pubertal years. 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 that is found in familial cases. In others, abnormal methylation of the maternal copy of chromosome 6 renders the genes inactive and permits the unopposed action of the paternal genes on this region. The actual genes involved are *ZAC* (zinc finger gene regulating apoptosis and the cell cycle), also referred to as *PLAGL1* (pleiomorphic adenoma gene-like 1), and a second gene termed *HYMAI* (hydatidiform mole associated and imprinted gene). Those who relapse can sometimes be treated with oral hypoglycemic agents and may not necessarily require insulin (28,31).

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. Females who transmit the duplication do not have affected children, but the sons may pass the risk to their subsequent children. The 6q24 type of TNDM is known as TNDM1, whereas the subtypes due to K_{ATP} mutations are known as TNDM2 (28,32). In the TNDM2 category, comprising some 30% of TNDM, ~15% are due to mutations in *ABCC8*, ~10% are due to *KCNJ11* mutations, and about 5% are caused by mutations in *INS*, *HNF1β*, and the glucose transporter *SLC2A2* (Table 7.2).

Permanent Neonatal Diabetes

The most common mutations responsible for PNDM are those in Kir6.2 (*KCNJ11*) and *INS*, followed by SUR1 (*ABCC8*). Most patients have isolated diabetes only, but those with severe Kir6.2 mutations and some with a SUR1 mutation also may have a syndrome characterized by developmental delay, epilepsy, and NDM (DEND), or intermediate forms of this entity characterized by diabetes and some developmental delay but without epilepsy. Patients are usually diagnosed within the first month, but diagnosis may be delayed beyond age 6 months. Those with SUR1 mutations causing NDM have a similar presentation but are less likely to have DEND. As shown in Figure 7.2, these mutations cause a gain of function, activating the potassium channel so that it stays open and, hence, preventing insulin secretion.

Despite the near absence of insulin and C-peptide when tested and previous dependence on exogenous insulin for treatment, the majority of patients with *KCNJ11* and *ABCC8* mutations respond to high doses of sulfonylurea therapy using glibenclamide (glyburide), which can restore normal insulin secretion in some 85% of subjects, along with restoration of the incretin response to oral feeding (35). This holds true also for those with the SUR1 mutations (36). There is debate whether the use of glibenclamide, particularly if started early, also improves the neurological manifestations, since there is evidence that the glibenclamide also binds to SUR subunits found in nerve, muscle, and brain (17,37,38,39). Clinical experience supports the notion that there is improvement in neurologic sequelae (38,39). Glibenclamide therapy at high doses should be gradually introduced; if possible, treatment should not be begun empirically without a genetic diagnosis, and should be supervised in a hospital setting while transitioning the patient off insulin.

Most children with K_{ATP} mutations represent *de novo* mutations without a family history, though family history is present in some 10%–15%. In these instances of a positive family history, sequencing in the affected family members should be performed because sulfonylureas may still be effective in those with mutations in the *KCNJ11* gene. Because the K_{ATP} channel mutations usually are dominant, each affected individual may pass on the gene to 50% of their offspring. Some parents labeled as having "type 2 diabetes" actually have *INS* mutations that are recessive and can cause NDM in 25% of their offspring (40). Parents of children with what appears to be a *de novo* mutation must be counseled with the possibility of a second child being affected, as a result of germ line mosaicism in which the mutation is present in the gonads (sperm), but not in the peripheral blood.

Mutations in *INS* that are responsible for dominantly inherited NDM generally are associated with misfolding of the insulin molecule, which progressively impairs

insulin secretion (33,40). Generally, there are no associated abnormalities in neurological function with *INS* mutations (40). (See the section on Genetic Defects of the Insulin Gene.)

Other Causes of Neonatal Diabetes Mellitus

Table 7.2 lists the causes of NDM. Excluding the methylation defects associated with chromosome 6q24, K_{ATP} channel defects, and *INS* defects, the remaining causes are rare but provide insight into the regulation of pancreas formation and insulin secretion (3,4,18). It must be emphasized that milder defects in the *KCNJ11* gene are associated with "typical type 2 diabetes" and that *KCNJ11* mutations/polymorphisms are the third most frequent genetic risk factor for type 2 diabetes after *TCF7L2* and *PPARG* (19). As discussed in connection with the monogenic forms of diabetes, homozygous mutation in *GCK* encoding the glucokinase enzyme and homozygous mutation in *PDX1* cause severe neonatal diabetes (see Table 7.2). Some mutations in the GLUT2 transporter encoded by the *SLC2A2* gene (41) and the HNF1β gene (42) cause autosomal dominant NDM (see Table 7.2). Of the others listed in Table 7.2, *EIF2AK3* (eukaryotic initiation factor 2 alpha kinase 3) is likely the most common and is an autosomal recessive disorder characterized by multiple congenital malformations, including spondyloepiphyseal dysplasia, renal failure, recurrent hepatitis, and mental retardation, also known as the Wolcott-Rallison syndrome (43,44). However, NDM may be the initial presentation without other abnormalities.

The mutations responsible for NDM in the *FOXP3* gene result in a syndrome termed IPEX, which stands for immune dysregulation, with polyendocrinopathy and enteropathy on the X chromosome, and is characterized by intractable diarrhea, skin rashes, immune dysregulation, and elevated IgE. This is an X-linked condition (45). Mutations in *GLIS3* cause an autosomal recessive syndrome characterized by congenital hypothyroidism, liver fibrosis, cystic kidney disease, and glaucoma in addition to NDM (46). Mutations in *PTF1A* (pancreas transcription factor 1A) cause an autosomal recessive form of pancreatic agenesis with exocrine and endocrine pancreatic dysfunction, as well as cerebellar agenesis (47). *RFX6* (regulatory factor X, 6) is a gene that regulates pancreatic development together with development of other organs derived from the endoderm; hence, mutations in this gene result in NDM, hypoplastic or annular pancreas, and duodenal and jejunal atresia. The constellation of defects caused by mutations in *RFX6* is also known as the Mitchell-Riley syndrome and carries a poor prognosis with death in the first year of life (48,49). Mutation in *NEUROG3 (Neurogenin3)* is associated with NDM plus congenital malabsorptive diarrhea and enteroendocrine cell dysgenesis (50). *GATA6* and *GATA4* haploinsufficiency are reported to be associated with pancreatic agenesis and congenital heart defects. These gene mutations are more common causes of pancreatic agenesis than homozygous *PDX1* mutations (51).

GENETIC DEFECTS OF THE INSULIN GENE

INS is located on chromosome 11p15.5, and defects in *INS* itself are responsible for a spectrum of disordered glucose homeostasis ranging from NDM, either permanent from the outset or initially transient, as well as later onset apparent type 2 diabetes. The permanent NDM phenotypes can be due to dominantly inherited mutations in critical regions of the preproinsulin molecule, predicted to cause misfolding of the molecule that prevents normal insulin secretion (33). In humans, these dominant mutations represent the second most common cause of PNDM, where clinical manifestations may sometimes be delayed to age 6–12 months or later, in contrast to the more common *KCNJ11* mutations that usually manifest within the first 6 months of life (3,4,18,33,34).

Recessive mutations in *INS* causing NDM also are reported (40). Compared to dominant mutations, these recessive defects cause a more severe form of insulin deficiency and are manifest by lower birth weight (-3.2 SD score vs. -2.0 SD score) and earlier diagnosis (median of diagnosis at age 1 week vs. 10 weeks). Notably, some patients with the recessively inherited insulin mutations have TNDM, while others with homozygous mutations may not manifest clinical diabetes until the teen years or later. Some heterozygous carriers of the recessive mutations have diabetes diagnosed in middle life, suggesting less severe interference with insulin synthesis and resulting in the phenotype of type 2 diabetes (40).

GENETIC DEFECTS OF INSULIN PROCESSING

The prohormone convertases, PC1/3 and PC2, are enzymes that cleave peptide hormones and neuropeptides from precursor molecules in neuroendocrine cells, such as the brain, pituitary and adrenal, as well as the islets in the pancreas. The enzymes, PCSK (proprotein convertase subtilisin/kexin type)-1/3 and -2, act in concert to process proinsulin and proglucagon to yield the respective hormones in islets, as well as cleaving the prohormones for adrenocortical trophic hormone (ACTH) and gonadotropic-releasing hormone (GnRH). As a result, mutations in these genes result in secondary hypocortisolism, hypogonadotropic hypogonadism, and diminished insulin, but elevated proinsulin. The abnormal cleavage of pro-opiomelanocortin (POMC) is likely the cause of obesity, due to faulty signaling to the melanocortin receptor family, including the melanocortin-4 receptor involved in appetite regulation. The abnormal processing and lack of ACTH lead to the secondary adrenal insufficiency with diminished cortisol synthesis and secretion. The hypogonadotropic hypogonadism is likely the result of impaired processing of GnRH (52,53). The effect of abnormal cleavage of the proinsulin molecule leads to a familial form of dominantly inherited hyperproinsulinemia (54,55). Since proinsulin has about 5% of the biological activity of insulin, large amounts of this molecule may compensate for the lack of normal insulin and lead to minimal or no disturbances in glucose homeostasis under normal circumstances, but symptoms of glycemic dysfunction

manifest at times of physiological stress, such as pregnancy, resulting in gestational diabetes. A mutation in PC2 results in a dominant form of hyperproinsulinemia with more severe effects on diminishing insulin biological activity that can lead to a type 2 diabetes phenotype. These insulinopathies had been described in the 1980s without knowing the actual genetic basis (54,55). The PCSK-2 mutations cause greater deficiency in insulin action resulting in mild diabetes, but without obesity; whereas the PCSK-1/3 mutation is associated with obesity and low cortisol, generally not found in the PCSK-2 mutations. The incidence of these mutations is not known; they appear to be very rare.

GENETIC DEFECTS IN INSULIN ACTION: INSULIN RECEPTOR AND POSTRECEPTOR DEFECTS

The insulin receptor gene is located on chromosome 19p13.2 and codes for a heterotetramer consisting of two extracellular α subunits that bind insulin and two membrane-spanning β subunits with an intracellular tyrosine kinase domain that initiates a signaling cascade. Both subunits are encoded by the single gene, and mutations in this gene may cause distinct syndromes depending on the severity of disrupted insulin signaling. As many as 0.1%–1% of the population is suspected of having some mutations that interfere with insulin action, but most can be overcome by increasing insulin secretion (56). Among mutations that impair insulin action and cause diabetes are three syndromes: Donohue syndrome (Leprechaunism), Rabson-Mendenhall syndrome, and insulin resistance syndrome type A. All are rare, and no data on the precise incidences of these syndromes are available.

Donohue Syndrome

Donohue syndrome is the most severe and rare form of insulin resistance and is due to near total absence of insulin receptor function. Affected individuals are characterized by severe intrauterine growth retardation, dysmorphic features, hyperinsulinemia, and abnormal glucose homeostasis. The abnormal glucose homeostasis is characterized by *hyperglycemia during and after feeding,* due to virtual absence of insulin action, which is essential to enable peripheral glucose uptake and utilization, as well as *hypoglycemia during fasting* due to the absence of insulin action, which is necessary to enable storage of glucose as glycogen. The dysmorphic features consist of prominent eyes, low-set and posteriorly rotated ears, thick lips, thick skin with absence of subcutaneous fat, distended abdomen, and the appearance of enlarged genitalia in the male and cystic ovaries in the female. Birth weight is on the order of ≤2,000 g. Insulin concentrations in the blood are around 1,000 microIU/mL (6,000 pmol/mL), and C-peptide concentrations are markedly elevated. Exogenous insulin is ineffective; insulin-like growth factor-1 may have some benefits, but data are sparse and the indication is considered off-label for investigational use only. Death usually occurs within 1–2 years after birth (57).

Rabson-Mendenhall Syndrome

Patients with Rabson-Mendenhall syndrome have some residual insulin action and, therefore, somewhat different dysmorphic features, primarily involving abnormalities of teeth and nails, which are dysplastic and differ from those with Donohue syndrome. Pineal hyperplasia has been reported as well in Rabson-Mendenhall syndrome. Because the mutation is not as severe, these patients are not at risk of dying early and, later in life, manifest the classic signs of insulin resistance, including acanthosis nigricans and hirsutism. They also manifest postprandial hyperglycemia and fasting hypoglycemia for reasons discussed for the Donohue syndrome. Those with severe forms of Rabson-Mendenhall syndrome may develop diabetic ketoacidosis because of a decline in later life in the ability to maintain high insulin concentrations required to overcome the insulin resistance. Although there is no absolute genotype-phenotype correlation, in general, insulin receptor mutations that retain some residual insulin binding correlate with prolonged survival (57).

Insulin Resistance Syndrome Type A

The insulin resistance syndrome type A is a relatively mild and more common form of insulin receptor mutation defined by the presence of hyperandrogenism, acanthosis nigricans, and marked insulin resistance with glucose intolerance and hyperinsulinemia. This syndrome was named type A because it occurs in younger females with virilization and accelerated growth, in whom it was believed that the receptor defect was primary, to contrast it from type B, a syndrome found in older females who have circulating antibodies to the insulin receptor. Given the focus on the metabolic syndrome, in which polycystic ovary syndrome (PCOS) is a major feature and there are also variable degrees of insulin resistance, hyperinsulinemia, and carbohydrate intolerance, it may be that the insulin resistance syndrome type A is not a distinct entity (58).

ABNORMAL FUNCTION OF CILIA

Alstrom syndrome is a rare disease with incidence of <1:100,000 births in European populations due to a mutation in the *ALMS1* gene, located on chromosome 2p13. This gene codes for a protein that is believed to be involved in the organization of microtubules and transport of various materials, as well as the normal function of cilia. The protein plays a role in processes such as hearing, vision, the regulation of body weight, and normal function of the heart, lungs, kidneys, liver, and pancreatic insulin synthesis and secretion. Clinically, the diagnosis depends on the presence of the onset of retinal dystrophy with photodysphoria and either obesity or cardiomyopathy in an infant. During childhood, adolescence, and adulthood, additional phenotypes evolve, including insulin resistant diabetes, which manifests at around the time of puberty and is associated with acanthosis nigricans. The clinical manifestations of cardiomyopathy may not become apparent until adolescence. Nonalcoholic fatty liver disease develops during puberty. Chronic renal failure appears in about 25% of patients during the second decade of life. The differential diagnosis should include Bardet-Biedl syndrome, which has similar clinical features and, like Alstrom syndrome, is generally classified with the ciliopathies (18,59).

CONCLUDING REMARKS FOR MONOGENIC DIABETES

Monogenic forms of diabetes are uncommon, ranging in prevalence from ~2%–3% of new cases of diabetes for MODY to 1:100,000 births for NDM and rarer still for the syndromic forms of diabetes. Defining their genetic bases has shed light on the complexity of pancreas formation and function and the regulation of insulin secretion. In turn, knowing the genes regulating these processes has enabled a clearer understanding of the nature of MODY and NDM, enabled rational treatments based on the pharmacogenetics of the K_{ATP} channel, and demonstrated that the same genes are involved in the more common forms of what clinically appears to be type 1 and type 2 diabetes. Correct diagnosis requires molecular confirmation, which enables correct treatment, avoids unnecessary use of insulin or other inappropriate agents, and permits genetic counseling. As the ability to sequence genes at reduced costs becomes an established part of medical management (60,61), these discoveries are likely to have wide impact on practice.

RESOURCES

The following websites provide access to expert advice and assistance with possible mutation analysis in patients suspected of having monogenic forms of diabetes:

- *www.diabetesgenes.org*, an information resource on genetic types of diabetes located in the United Kingdom at the University of Exeter
- *www.kovlerdiabetescenter.org/portfolio/monogenic-diabetes-registry-genetics-of-diabetes-studies*, a monogenic diabetes registry located in the United States at the University of Chicago
- *www.genetests.org,* a compendium of sites and locations of mutational analysis performed for research or via CLIA-certified laboratories

GENETIC LIPODYSTROPHIES

A classification of the genetic lipodystrophies is presented in Table 7.3. Detailed discussion of the most common types of genetic lipodystrophies that predispose patients to diabetes follows the listing and notations in Table 7.3.

EPIDEMIOLOGY

Overall, based on literature reports of fewer than 2,000 patients, the estimated prevalence of genetic lipodystrophies may be less than 1 in a million. The autosomal recessive congenital generalized lipodystrophy (CGL) has been reported in about 300–500 patients, with clustering of patients reported from Lebanon and Brazil where there is increased prevalence of consanguinity. The autosomal dominant familial partial lipodystrophy (FPL) has been reported in ~500–1,000 patients. Affected females are recognized easily and, thus, are reported more often than males.

Dutour *et al.* (62) studied 100 consecutive patients from Marseille, France, with the metabolic syndrome presenting with obesity, diabetes, or thyroid disorders and identified only one male and one female patient with missense mutations in the lamin A/C (*LMNA*) gene. Of these, only the female patient was described to have slight lipoatrophy. Thus, the prevalence of FPL could be ~1% among those presenting with the metabolic syndrome to a tertiary care hospital. Urbanek *et al.* (63) determined variants in *LMNA* in 43 women presenting with PCOS and identified two missense novel variants. None of the variants previously found in patients with FPL were observed. Further analysis of these variants in a case-control study of 624 women with PCOS and 544 controls failed to show any statistically significant association with PCOS. Thus, the authors concluded that genetic variation in *LMNA* was not a major contributor to the etiology of PCOS.

Thus, precise estimates for population prevalence of these monogenic syndromes are not available. However, it is expected that as investigators collect data from next generation, whole genome, or exome sequencing in healthy controls and patients with diabetes, hypertriglyceridemia, and PCOS, better estimates of the prevalences of these disorders will emerge. The population prevalence of autosomal recessive syndromes may be estimated based on the frequency of heterozygous variants in candidate genes. Such studies are underway; however, most subjects participating in these consortia are of European origin. Enrollment of many subjects from all over the world will be required to determine the worldwide prevalence of these monogenic syndromes.

AUTOSOMAL RECESSIVE LIPODYSTROPHIES

Congenital Generalized Lipodystrophy

In 1954, Berardinelli from Rio de Janeiro, Brazil, reported two boys (2 and 6 years old) with an undiagnosed endocrine-metabolic syndrome presenting with marked hepatosplenomegaly, acromegaloid gigantism, fatty liver, and hyperlipidemia (64). In 1959, Seip reported a detailed description of the phenotype of three additional patients and highlighted the onset of generalized lipodystrophy from birth, and thus, they were recognized as having CGL (65). The diagnosis of CGL is usually made at birth or soon thereafter. However, some patients may have a normal appearance at birth and subsequently lose body fat.

Overall, approximately 300–500 cases of this syndrome have been reported thus far (66,67,68). Clusters of cases have been reported from Brazil and Lebanon from regions where there is an increased prevalence of consanguinity (69,70). Based on the assumption that only one-quarter of the actual number of cases may be reported in the literature, the estimated prevalence of CGL is about 1 in 10 million (68).

Patients with CGL have the appearance of extreme muscularity at birth due to near complete absence of adipose tissue in the body. They are known to grow at

an accelerated rate during early childhood, and the bone age may be greater than the chronological age at this time (71,72). They have a markedly increased appetite and slight enlargement of the hands, feet, and mandible, termed acromegaloid features. Nearly all patients have an umbilical prominence (71,73). Acanthosis nigricans is noted later during childhood or adolescence (71) and can be very severe, involving extensive areas of the body. Besides the typical neck, axillae, and groin regions, acanthosis nigricans can also affect the trunk, hands, knees, elbows, and ankles. Liver enlargement due to hepatic steatosis is usually noticed during infancy. A few patients develop cirrhosis and its complications later on in life (74,75), and many patients develop splenic enlargement. In females, mild hirsutism, clitoromegaly, and irregular menstrual periods are common, and some present with primary or secondary amenorrhea and polycystic ovaries. Some patients have hypertrophic cardiomyopathy and mild mental retardation (76,77).

TABLE 7.3. 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 (FPL)	*FPLD5* (CIDEC)	615238	Single patient reported.	Histopathology of subcutaneous fat showed multilocular, small lipid droplets in adipocytes.
II. Autosomal dominant lipodystrophies				
Familial partial lipodystrophy (FPL)	FPLD1, Kobberling variety (unknown)	NA	Loss of subcutaneous fat from the extremities.	Molecular basis is unknown.
	FPLD2, Dunnigan variety (*LMNA*)	151660	Loss of subcutaneous fat from the extremities and trunk (sparing the face and neck) at puberty.	*LMNA* encodes nuclear lamina proteins, lamins A and C. Defective lamins A and C may disrupt nuclear function, resulting in death of adipocytes.
	FPLD3 *(PPARG)*	604367	Loss of subcutaneous fat from the distal extremities.	PPARγ is essential for adipogenesis. Dominant negative PPARγ mutations may inhibit adipocyte differentiation.
	FPLD4 (*PLIN1*)	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.
	(*AKT2*)	NA	Single family reported with loss of subcutaneous fat from the extremities.	AKT2 is involved in adipocyte differentiation and downstream insulin receptor signaling.
Atypical progeroid syndrome	(*LMNA*)	NA	Variable loss of subcutaneous fat.	Different heterozygous mutations in *LMNA* cause partial or generalized lipodystrophy.
SHORT syndrome	(*PIK3R1*)	269880	Short stature, *H*yperextensibility or inguinal hernia, *O*cular depression, *R*ieger anomaly, and *T*eething delay	*PIK3R1* encodes the p85α 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; CIDEC, cell death-inducing DNA fragmentation factor a-like effector c; FPLD, familial partial lipodystrophy; LMNA, lamin A/C; NA, not applicable; PLIN1, perilipin 1; 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.

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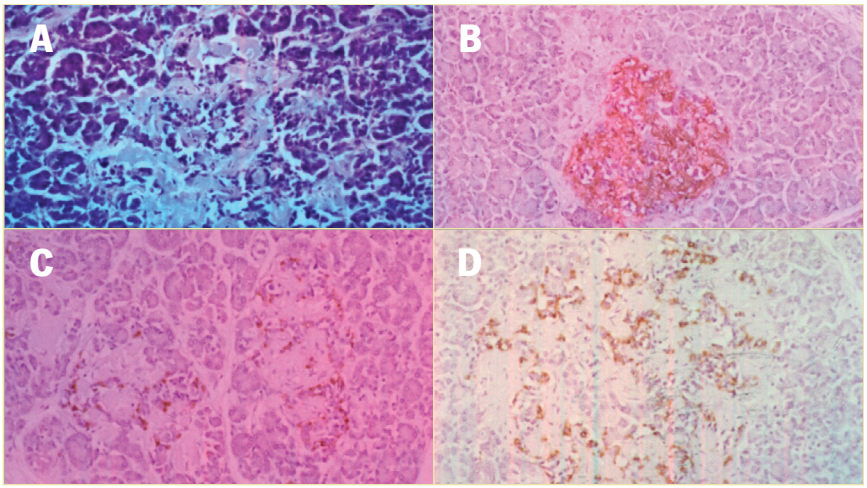
CGL is characterized by high levels of fasting and postprandial insulin, noted very early in life (71). This extreme hyperinsulinemia suggests severe insulin resistance in childhood. Patients also have extreme hypertriglyceridemia, which can predispose them to recurrent episodes of acute pancreatitis (73). The levels of HDL cholesterol also tend to be low. The onset of diabetes usually occurs during the pubertal years; however, diabetes has been reported as early as 6 weeks of life. In some patients, diabetes occurs during the neonatal period and is subsequently followed by a euglycemic period; they again develop diabetes after puberty. Garg *et al.* (78) reported marked amyloidosis of pancreatic islets and beta cell atrophy on autopsy of a young adult female with CGL (Figure 7.4). Thus, it appears that prolonged and extreme insulin resistance from birth causes amyloidosis and beta cell death due to similar mechanisms involved in patients with type 2 diabetes. Diabetes is challenging to manage in CGL patients and may require extremely high doses of insulin to control hyperglycemia (79). Patients are reportedly resistant to ketosis due to endogenous hyperinsulinemia. Since patients with CGL have extreme paucity of body fat, they have markedly low levels of serum adipocytokines, such as leptin and adiponectin (80,81). Extreme hypoleptinemia may contribute to excessive appetite and metabolic complications in patients with CGL.

FIGURE 7.4. Severe Islet Amyloidosis in Congenital Generalized Lipodystrophy



(A) Hematoxylin and eosin stain showing marked hyaline deposits in the islet of Langerhans. The hyaline deposits stained red on Congo red staining and showed apple-green birefringence on polarization diagnostic of amyloid. (B) Immunostaining with anti-amylin antibody showing intense staining for amylin in an islet with amyloidosis. (C) Immunostaining with anti-insulin antibody showing marked reduction of beta cells in an islet with amyloidosis. (D) Immunostaining with anti-glucagon antibody showing presence of alpha cells in an islet with amyloidosis. The patient had congenital generalized lipodystrophy (CGL) type 1, and histopathology was studied on autopsy.

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At this time, four distinct genetic varieties of CGL are known. However, type 1 and type 2 are the most common subtypes of CGL. The first locus for CGL was discovered on chromosome 9q34 using a genome-wide linkage analysis approach by Garg *et al.* (82). The authors also reported genetic heterogeneity and a possibility of another locus. Subsequently, the second locus was found on chromosome 11q13 (70). By positional cloning of the 9q34 region, Agarwal *et al.* (83) identified mutations in the 1-acylglycerol-3-phosphate-O-acyltransferase 2 (*AGPAT2*) gene in patients with CGL type 1. Mutations in a new gene called Berardinelli-Seip Congenital Lipodystrophy 2 (*BSCL2*) on chromosome 11q13 were reported by Magre *et al.* (70). Two new genes have been reported to be linked to CGL. A homozygous nonsense mutation in caveolin-1 (*CAV1*) has been reported in a single patient with CGL type 3 (84). CGL type 4 has been linked to mutations in polymerase I and transcript release factor (*PTRF*) (85).

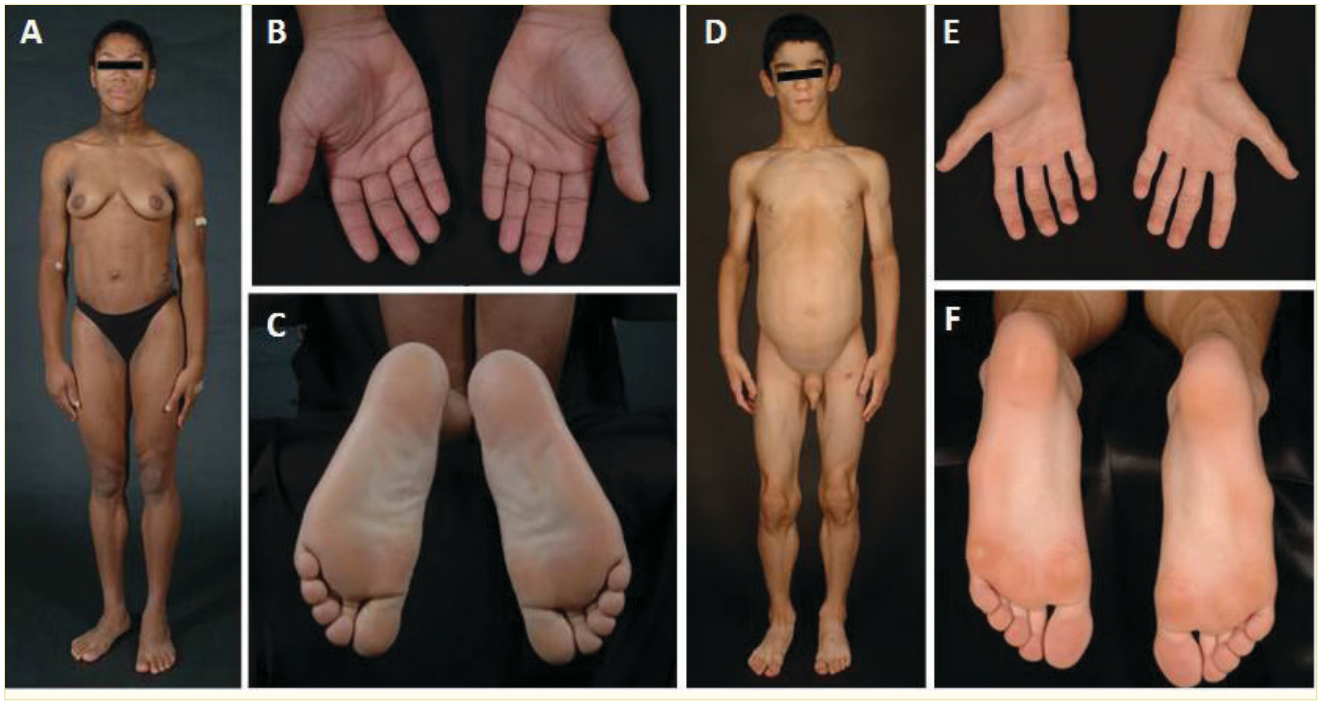
CGL Type 1: *AGPAT2* Mutations. Besides the clinical features mentioned above, patients with CGL type 1 have an increased prevalence of focal lytic lesions in the appendicular skeleton. Metabolically active adipose tissue located in most subcutaneous areas, intra-abdominal and intrathoracic regions, and bone marrow is totally deficient, but mechanical adipose tissue, which is located in the palms, soles, under the scalp, orbital, and periarticular regions, is spared (Figure 7.5A–C) (73,86,87).

There are 11 distinct isoforms of AGPATs, the key enzymes belonging to the acyltransferase family, which play a critical role in the biosynthesis of triglycerides and phospholipids in cells (Figure 7.6) (83,88). The AGPATs acylate lysophosphatidic acid (1-acylglycerol-3-phosphate) to phosphatidic acid (1, 2 diacylglycerol-3-phosphate). The AGPAT2 isoform is highly expressed in the adipose tissue. It is also expressed in the liver and skeletal muscle, but at lower levels. Thus, AGPAT2 deficiency may cause lipodystrophy by lack of triglyceride biosynthesis in the adipocytes or by lack of phospholipid synthesis, which may affect adipocyte function. Most patients harbor null mutations with no enzymatic activity demonstrable *in vitro*. However, some compound heterozygotes have a null and a missense mutation (with some residual enzymatic activity), and a few have homozygous missense mutations. However, the type of mutation does not determine the severity of lipodystrophy, as all the patients have near complete loss of adipose tissue. Nearly all patients of African origin harbor the founder mutation, c.589-2A>G (p.Val197Glufs*32), on one or both alleles (77).

CGL Type 2: *BSCL2* Mutations. Patients with CGL type 2 display an increased prevalence of cardiomyopathy and mild mental retardation (76,77). Both metabolically active and mechanical adipose tissue are lacking in CGL type 2 patients (Figure 7.5D–F) (86,87). Serum leptin levels are lower in patients with CGL type 2 than type 1, but serum adiponectin levels are higher (81); the reason for this observation is not clear.

BSCL2 encodes a 398 amino acid transmembrane protein called seipin (70). Research suggests a role for seipin in lipid droplet formation and in adipocyte

FIGURE 7.5. Clinical Features of Patients With Congenital Generalized Lipodystrophy Types 1 and 2



(A) Anterior view of a 19-year-old female of African American origin with congenital generalized lipodystrophy type 1, showing generalized lack of fat, extreme muscularity, and acromegaloid features. She developed diabetes at age 14 years. Acanthosis nigricans was present in the neck, axillae, and groin. She had a homozygous splice site mutation (c.589-2A>G; p.Val197Glufs*32) in *AGPAT2*. (B) Palms of the patient shown in panel A showing normal subcutaneous fat. (C) Soles of the patient shown in panel A showing normal subcutaneous fat. (D) Anterior view of an 8-year-old boy from Spain with congenital generalized lipodystrophy type 2, showing generalized lack of fat and extreme muscularity. Only mild acanthosis nigricans was present in the neck and axillae. He had compound heterozygous mutations in *BSCL2*: c.193delCinsGGA (p.Pro65Glyfs*28) and c.325_326insA (p.Thr109Asnfs*5). (E) The palms of the patient shown in panel D showing loss of subcutaneous fat. (F) Soles of the patient shown in panel D showing loss of subcutaneous fat.

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differentiation (89,90). Studies with the seipin homolog in yeast suggest that it may play a role in fusion of lipid droplets (Figure 7.6). Nearly all *BSCL2* mutations reported in patients with CGL type 2 are null.

CGL Type 3: Caveolin-1 Mutation. CGL type 3 has only been reported in a Brazilian girl who had short stature and presumed vitamin D resistance (84). This patient also had hepatosplenomegaly with hepatic steatosis and onset of diabetes at age 13 years. Additionally, she had acanthosis nigricans and severe hypertriglyceridemia. She had primary amenorrhea at age 20 years and functional megaesophagus. The patient had well-preserved mechanical and bone marrow fat.

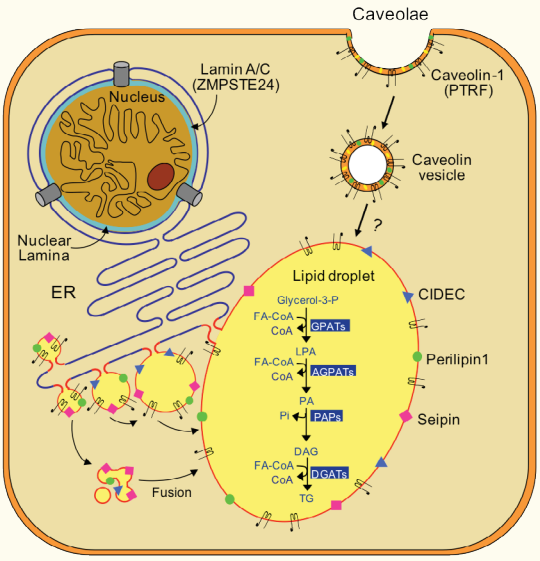
Caveolin-1 is expressed in abundance in caveolae, specialized microdomains on cell membranes of adipocytes (91). Caveolae bring phospholipids and other lipid material from outside to inside the cell, and they may contribute this material to lipid droplets. Thus, caveolin-1 mutation may cause lipodystrophy due to defective lipid droplet formation (Figure 7.6).

CGL Type 4: *PTRF* Mutations. CGL type 4 due to *PTRF* mutations has been reported in approximately 20 patients (85,92,93). These patients have a peculiar phenotype besides having CGL. They manifest developmental delay, as well as congenital myopathy with percussion-induced myoedema, pyloric stenosis, and atlantoaxial instability (94,95). Patients with CGL type 4 also have increased levels of creatine kinase in the serum, suggestive of myopathy. These patients are prone to developing serious arrhythmias, such as catecholaminergic polymorphic ventricular tachycardia, prolonged QT interval, and sudden death (92,93). Patients have well-preserved mechanical and bone marrow fat. PTRF, also known as cavin, plays a critical role in the biogenesis of caveolae. PTRF regulates the expression of caveolin-1 and -3 and may also contribute to lipid droplet formation (Figure 7.6) (85).

Molecular Diagnosis. Patients with CGL should be easily diagnosed at birth or soon thereafter by pediatricians. The two main types of CGL can be distinguished based upon their clinical features. CGL type 4 has a distinct phenotype of myopathy. Molecular diagnosis at research laboratories is available for confirmation. Molecular diagnosis may be helpful for understanding the risk of having another child with CGL and can also be used for prenatal screening. Besides patients with known genotypes, a few patients with CGL do not have mutations in any of the four known loci, and thus, there may be novel genes to be discovered for CGL.

Differential Diagnosis. CGL should be differentiated from acquired generalized lipodystrophy, Donohue syndrome, atypical Werner syndrome, generalized lipodystrophy due to *LMNA* mutations, and neonatal progeroid syndrome.

FIGURE 7.6. Lipid Droplet Formation in Adipocytes



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 translocate fatty acids to LDs. PTRF controls expression of caveolin-1 and -3. The classic 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 DAG 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.

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Mandibuloacral Dysplasia Associated Lipodystrophy

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive disorder reported in about 40 patients so far. It is characterized by hypoplasia of the mandible and clavicles, as well as acro-osteolysis (resorption of the terminal phalanges) (96,97). Other clinical features include delayed closure of cranial sutures, joint contractures, mottled cutaneous pigmentation, and short stature. Patients also show "progeroid features," such as bird-like faces, high-pitched voice, skin atrophy, pigmentation, alopecia, and nail dysplasia. Patients with MAD either have partial loss of subcutaneous fat from the extremities (type A) due to mutations in *LMNA* (97) or more generalized loss of subcutaneous fat involving the face, trunk, and extremities (type B) due to mutations in zinc metalloproteinase (*ZMPSTE24*), which is involved in posttranslational processing of prelamin A to mature lamin A (98). Hyperinsulinemia, insulin resistance, impaired glucose tolerance, diabetes, and hyperlipidemia have been reported but are usually mild to moderate in severity (96).

Familial Partial Lipodystrophy Due to CIDEC Mutation (FPLD5)

A 19-year-old Ecuadorian girl with autosomal recessive FPL has been reported to harbor a homozygous missense mutation in cell death-inducing DNA fragmentation factor a-like effector c (*CIDEC*) (99). She developed diabetic ketoacidosis at age 14 years and also had hypertriglyceridemia and hypertension. On biopsy of subcutaneous fat, multilocular, small lipid droplets were reported in adipocytes consistent with the findings in a mouse model of FPL (99,100).

AUTOSOMAL DOMINANT LIPODYSTROPHIES

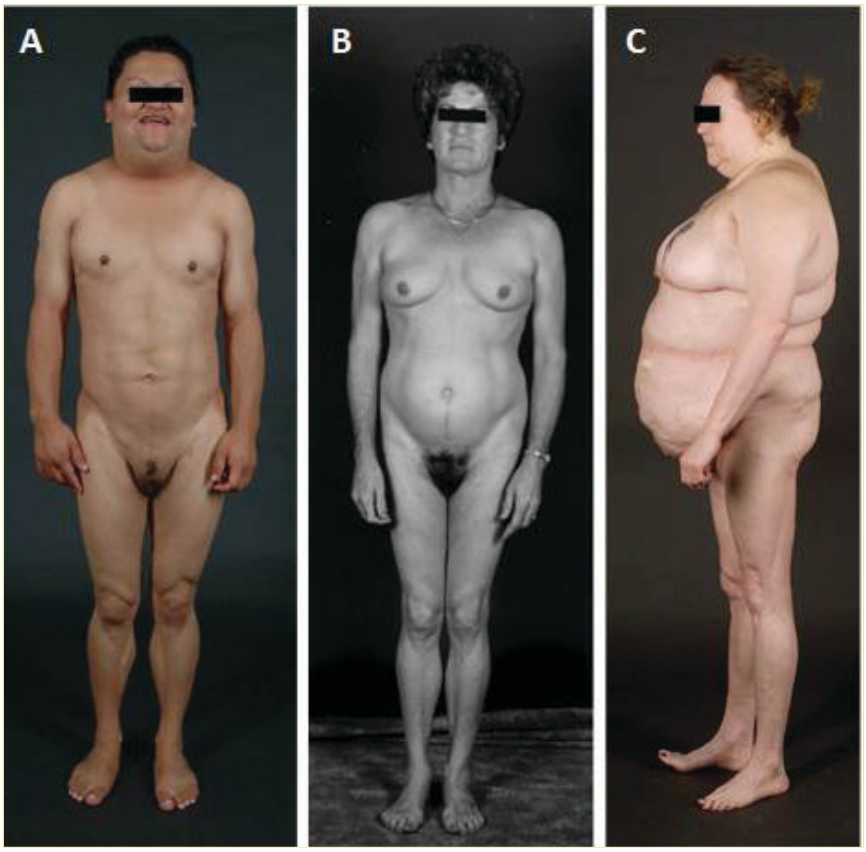
Familial Partial Lipodystrophies

The characteristic clinical feature of patients with FPL is the loss of body fat from the upper and lower extremities, as well as in some patients, from the truncal region (101,102). Most patients follow an autosomal dominant inheritance pattern. The phenotype can be easily recognized in affected women; however, recognition of men affected with FPL is difficult because even some normal healthy men also appear very muscular and have markedly low subcutaneous fat. Therefore, most of the ascertainment of affected patients and pedigrees has been through female probands. The diagnosis should be suspected in patients who show signs of insulin resistance early in life manifested by acanthosis nigricans or PCOS and early onset of diabetes and severe hypertriglyceridemia. Patients who have these manifestations but do not have generalized obesity should be suspected to have FPL, and physicians should examine for fat loss from the extremities, particularly from the gluteal region. Many patients gain fat in nonlipodystrophic regions, such as the face, under the chin, posteriorly in the neck resulting in a dorsocervical hump, and in the intra-abdominal region. Some women also gain fat in the perineal region, especially in the labia majora and pubic region. Several distinct subtypes of FPL have been reported, and the molecular genetic bases of four distinct subtypes are known.

Type 1: Kobberling Variety (*FPLD1*). After the original description by Dunnigan *et al.* (101), Kobberling *et al.* (102) from Germany reported a distinct phenotype of FPL. The Kobberling variety is less common and has been reported in only two small pedigrees and four sporadic cases (102,103,104). The age of onset of lipodystrophy and the mode of inheritance are not clear. On the basis of clinical findings, the loss of adipose tissue in the Kobberling variety is restricted to extremities only. Patients have normal amounts of fat in the face area and may have normal, or even excess, subcutaneous fat in the truncal area. The genetic basis for this particular variety is unknown.

Type 2: Dunnigan Variety Associated With *LMNA* Mutations (FPLD2). FPL type 2, the Dunnigan variety (FPLD), was initially described in an abstract form by Ozer *et al.* (105), who reported a 52-year-old woman and several members of her family with "fat neck syndrome" but loss of subcutaneous fat from the limbs. All affected patients had hypertriglyceridemia, and some had impaired glucose tolerance and diabetes. Subsequently, Dunnigan *et al.* (101) provided a detailed phenotypic description of two families with an autosomal dominant variety of FPL. Initial reports of this syndrome were restricted to the description of affected females only, possibly because recognition of affected males was difficult. It was also thought that the syndrome may have an X-linked dominant inheritance pattern with lethality in hemizygous males (103). Ascertainment of additional pedigrees subsequently showed that it clearly followed an autosomal dominant inheritance pattern (106). Since the original description, approximately 500–1,000 patients may have been reported with FPLD. Most are of European origin, but other ethnicities have been reported to have FPLD, such as Asian Indians and African American patients.

FIGURE 7.7. Clinical Features of Patients With Familial Partial Lipodystrophy



(A) A 28-year-old Hispanic woman with familial partial lipodystrophy, Dunnigan variety (FPL, type 2) due to heterozygous missense mutation in the *LMNA* gene. She had loss of fat from the extremities and trunk beginning at puberty and had excess fat accumulation in the face, neck, and perineal region. She had acanthosis nigricans in the axillae and groins. (B) A 64-year-old white woman with familial partial lipodystrophy (FPL, type 3) due to heterozygous missense mutation in *PPARG*. She had loss of fat from the face, extremities and trunk and had excess fat accumulation in the truncal region. (C) A 48-year-old white woman with familial partial lipodystrophy (FPL, unknown variety). She had loss of fat from the extremities but had excess fat accumulation in the face, neck, and truncal region.

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The onset of FPLD occurs in late childhood or at puberty. Therefore, children at birth have normal body fat distribution. Even as young children, their appearance is completely normal, but during late childhood or with onset of puberty, patients start losing subcutaneous fat in the upper and lower extremities, including the gluteal region. At the same time, they start gaining subcutaneous fat in nonlipodystrophic regions, such as the face, neck, and in the intra-abdominal region (Figure 7.7A) (107). Acanthosis nigricans also appears at the time of puberty and approximately one-third of women affected with FPLD have irregular periods, oligoamenorrhea, and hirsutism suggestive of PCOS (108). Characterization of the phenotype by whole body magnetic resonance imaging has revealed marked loss of subcutaneous fat from the extremities but preservation of intermuscular fat present in between the muscle fascia (109). Excess accumulation of fat is seen in the intra-abdominal and intrathoracic regions as well. Some patients develop a round face, dorsocervical hump, double chin, and enlargement of supraclavicular fat pads, and these patients are mistaken as having Cushing's syndrome. Although the data are limited, it appears that affected women are more severely affected by metabolic derangements than affected males (108,110). The prevalence of diabetes in affected women is approximately 50% compared to 20% in the affected men (108). Women also show extreme hypertriglyceridemia and low levels of HDL cholesterol and increased prevalence of coronary heart disease.

Diabetes usually develops after the second decade of life, and the risk factors for development of diabetes include multiparity and excess fat deposition in the nonlipodystrophic regions, such as the chin. Autopsy study in a patient revealed severe amyloidosis of pancreatic islets, which may be related to the onset of hyperglycemia and diabetes in patients with FPLD (111). Some patients with FPLD also develop cardiomyopathies, which manifest both as cardiac conduction system disturbances resulting in atrial fibrillation requiring pacemaker implantation and premature congestive heart failure requiring cardiac transplantation (112,113).

Using a genome-wide linkage analysis approach, Peters *et al.* (106) reported the FPLD locus on chromosome 1q21-22 in five large informative pedigrees. Subsequently, Cao and Hegele (114) screened for candidate genes in the

chromosome 1q21 region and reported a single missense mutation, p.Arg482Gln in *LMNA* in a Canadian pedigree. Since then, several missense mutations in *LMNA* have been reported in patients with FPLD, most of them affecting the C-terminal amino acids (115,116,117).

Mutations in *LMNA* interestingly have also been reported in various other disorders, such as idiopathic cardiomyopathy, muscular dystrophies, Hutchison-Gilford Progeria syndrome, Charcot-Marie-Tooth neuropathy, MAD, and atypical progeroid syndrome (117). Some patients with FPLD harboring *LMNA* mutations show features of overlap syndrome and have some mild muscular dystrophy, as well as cardiac conduction system disturbances (112,113). Thus, *LMNA* mutations may also cause a multisystem dystrophy syndrome that can affect various tissues, including adipose, cardiac, skeletal muscle, nerve, cutaneous, and skeletal tissue (112).

How specific mutations in *LMNA* cause adipocyte loss from mainly extremities remains unknown. Disruption of interactions of lamins A and C with chromatin or other nuclear lamina proteins during the cell division may lead to premature cell death or apoptosis of adipocytes. The accumulation of excess fat in nonlipodystropic regions may be a secondary phenomenon.

Most missense mutations in FPLD accumulate in or affect exon 8 of *LMNA,* which encodes the globular C-terminal (tail) portion of the protein. Particularly, the arginine residue at position 482 seems to be a hot spot, and about 75% of patients with FPLD have a substitution of this residue to tryptophan, glutamine, or leucine (117). Some patients who have mutations in exon 11, which can only affect lamin A and not lamin C, seem to have a milder, atypical FPLD (118). More importantly, patients who have mutations in exon 1 or nearby exons affecting the amino terminal residues have associated cardiomyopathy (112,113). Some of these patients also show evidence of mild muscular dystrophy with slightly increased serum creatine kinase levels. In some families, these mutations lead to severe congestive heart failure in the third decade, resulting in a need for cardiac transplantation.

By clinical examination, it is difficult to diagnose affected men, as well as prepubertal children, with FPLD. Therefore, molecular diagnosis may be helpful in characterizing these patients. Furthermore, genotyping for mutations which are also associated with cardiomyopathies may be particularly important for predicting prognosis.

Type 3: FPL Associated With *PPARG* Mutations (*FPLD3*). Using a candidate gene approach, Agarwal and Garg (119) identified a heterozygous missense mutation, p.Arg397Cys, in *PPARG*, a gene that encodes peroxisome proliferator-activated receptor gamma (PPARγ), in a 64-year-old woman who presented with diabetes, hypertriglyceridemia, hypertension, and hirsutism. She also had lipodystrophy of the face and extremities that was noticed much later in life (Figure 7.7B). Since then, approximately 30 patients with FPL due to *PPARG* mutations have been reported (120). These patients manifest insulin resistance with diabetes, hypertension, and hypertriglyceridemia. The age of onset of this variety of lipodystrophy is not precisely known but may range from the second decade or later. Also, the pattern of progression of fat loss is not very clear. Patients have more fat loss from the distal extremities than from the proximal extremities. Patients have variable loss of fat from the face, and some patients have normal or increased fat on the face. Given the role of PPARγ as a transcription factor in adipogenesis and adipocyte differentiation, mutations in *PPARG* may result in lipodystrophy due to defective differentiation of adipocytes. *PPARG* is highly expressed in adipose tissue; however, why patients with *PPARG* mutations develop lipodystrophy of the extremities and not other adipose tissue depots is not clear.

Type 4: FPL Associated With *PLIN1* Mutation (*FPLD4*). Gandotra *et al.* (121) reported two heterozygous frameshift mutations in *PLIN1* (which encodes perilipin 1) in five patients from three families with FPL of European origin. All of them had fatty liver, hypertriglyceridemia, and hyperinsulinemia. Three patients had diabetes, and four had reduced levels of HDL cholesterol. Lipodystrophy was most striking in the lower limbs and femorogluteal depots. Acanthosis nigricans was present in all probands, and two patients also had a cushingoid appearance. The investigators reported the histopathology of subcutaneous adipose tissue from four patients with *PLIN1* mutations, revealing reduced size of adipocytes and increased macrophage infiltration and adipose tissue fibrosis. Upon overexpression of *PLIN1* in 3T3-L1 preadipocytes, the investigators noted that mutant perilipin 1 resulted in smaller lipid droplets compared to the wild type perilipin 1 (121). Perilipin 1 is the most abundant protein coating lipid droplets in adipocytes (122). It is essential for formation and maturation of lipid droplets and storage of triglycerides, as well as release of fatty acids from these lipid droplets. Mutant forms of perilipin 1 fail to bind to AB-hydrolase-containing 5, which results in constitutive coactivation of adipose triglyceride lipase and increased basal lipolysis (123).

Type AKT2: FPL Associated With *AKT2* Mutations. George *et al.* (124) reported a heterozygous missense mutation, p.Arg274His, in *AKT2* in four subjects from a family who presented with insulin resistance and diabetes. The proband, a 35-year-old Caucasian female, developed diabetes at age 30 years, whereas her affected mother and grandmother developed diabetes during their late thirties. A maternal uncle, a middle-aged person, had no diabetes but had hyperinsulinemia. Three of the four affected subjects had hypertension. The proband also had loss of subcutaneous fat from the extremities (Stephen O'Rahilly, personal communication). However, the precise pattern of subcutaneous fat loss is not clear. AKT2 is a phosphoinositide-dependent serine/threonine kinase and is also known as protein kinase B. AKT2 is predominantly expressed in insulin sensitive tissues. Overexpression of the mutant form, p.Arg274His, in 3T3-L1 mouse preadipocytes resulted in markedly reduced lipid

accumulation. Previously, a mouse model of AKT2 deficiency showed features of lipodystrophy, insulin resistance, and diabetes with increasing age (125). Thus, taken together, lipodystrophy in patients with *AKT2* mutations may be related to reduced adipocyte differentiation and may be likely due to dysfunctional insulin signaling at the postreceptor level.

Other Types of FPL. The four known FPL genes are not able to explain the genetic basis of all FPL patients, and additional loci are likely to be discovered (Figure 7.7C) (119,126). In depth characterization of the clinical phenotype related to the pattern of fat loss in FPL patients with mutations in different genes may be helpful in identification of different phenotypes without resorting to molecular diagnosis.

Differential Diagnosis. FPL should be differentiated from conditions such as Cushing's syndrome, truncal obesity, multiple symmetric lipomatosis, and acquired generalized lipodystrophy, as well as highly active antiretroviral therapy-induced lipodystrophy in HIV-infected patients.

Atypical Progeroid Syndrome Due to LMNA Mutations

About 30 patients have been reported to have partial or generalized lipodystrophy, insulin resistant diabetes, and progeroid features with missense mutations in *LMNA* (127). Additional clinical features include mottling, pigmentations and sclerosis of skin, liver steatosis, cardiomyopathy, short stature, cardiac valvular abnormalities, and deafness. Particularly striking is the lack of breast tissue in many females. Some women also develop premature ovarian failure. These patients are also predisposed to developing premature diabetes.

Short Stature, Hyperextensibility of Joints and/or Inguinal Hernia, Ocular Depression, Reiger Anomaly, and Teething Delay (SHORT) Syndrome

A total of 30 patients have been reported with SHORT syndrome. The pedigrees reveal both autosomal recessive (128,129) and dominant (130,131,132) modes of transmission (128,129,130). Reiger anomaly consists of eye abnormalities, such as iris hypoplasia, Schwalbe ring, iridocorneal synechiae, micro- or megalocornea, and dental anomalies, such as hypodontia, microdontia, enamel hypoplasia, and atypical teeth. Other clinical features include intrauterine growth retardation, failure to thrive, delayed speech development, small head circumference, bilateral clinodactyly, and sensorineural hearing loss. Different patterns of fat loss have been reported. In many patients, lipodystrophy affects the face, upper extremities, and sometimes the trunk, with relative sparing of the lower extremities. Others had lipodystrophy affecting only the face, gluteal region, and elbows (131,132). Diabetes occurs as early as the second and third decade of life and is usually associated with insulin resistance. Patients with SHORT syndrome harbor *de novo* heterozygous mutations in the phosphatidylinositol 3-kinase regulatory subunit 1 (*PIK3R1*) gene (133,134,135). The molecular genetic basis of the autosomal recessive variety of SHORT syndrome remains to be determined.

MANAGEMENT OF DIABETES IN PATIENTS WITH LIPODYSTROPHY

Diabetes control in patients with lipodystrophies can be challenging. A multipronged strategy should be used, including diet, physical activity, and drug therapy. Reduction of energy intake and increased physical activity are important in patients with FPL to avoid excess fat deposition in non-lipodystrophic regions. Many patients with FPL have increased risk of coronary heart disease, and they should limit intake of saturated and trans-unsaturated fats and dietary cholesterol. Patients presenting with acute pancreatitis and extreme chylomicronemia should be advised to consume an extremely low fat diet. However, whether such diet will be beneficial in the long term to reduce hepatic steatosis and serum triglycerides and improve glycemic control remains unclear.

Controlling excessive hunger in children with generalized lipodystrophy is extremely difficult. Metreleptin may be able to suppress appetite especially in patients with generalized lipodystrophy (79,136). However, enough energy should be provided for proper growth and development. 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 (79,136,137,138). Metreleptin replacement, however, is only modestly efficacious in patients with FPL (79,136,139). Metreleptin therapy has been approved by the U.S. Food and Drug Administration for improving metabolic complications in patients with generalized lipodystrophies.

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). Other patients can achieve good glycemic control with oral hypoglycemic drugs, such as metformin and sulfonylureas. Metformin can improve insulin sensitivity, reduce appetite, and induce ovulation in patients with PCOS. Thiazolidinediones can also be used; however, they can induce unwanted growth of adipose tissue in non-lipodystrophic regions in patients with FPL (140,141). Although, patients with *PPARG* mutations and FPL should respond better to thiazolidinediones, there are not much data to support that assumption. Three FPL patients have been reported to have had marked improvement in diabetes control and dyslipidemia following roux-en-y gastric bypass surgery (142,143,144).

CONCLUDING REMARKS FOR LIPODYSTROPHIES

Genetic lipodystrophies are rare monogenic syndromes with an estimated prevalence of less than 1 in one million. In the last two decades, elucidation of the molecular basis of many of these syndromes has revealed the important role of adipose tissue development, differentiation, and death pathways in adipocyte biology (87,107). Studies of lipodystrophy patients and the mouse models of these syndromes will further reveal the mechanisms by which lack of triglyceride storage capacity

in the adipose tissue induces metabolic complications, especially diabetes. These developments are expected to lead to discoveries of targeted therapies for these syndromes. Diagnosis of genetic lipodystrophies is based on clinical criteria. In many patients, genetic testing can confirm the diagnosis and allow for genetic counseling. Metreleptin replacement therapy has been approved in the United States to treat metabolic complications in patients with generalized lipodystrophy, who are usually severely hypoleptinemic. In the future, next generation sequencing is expected to unravel the molecular basis of extremely rare subtypes of genetic lipodystrophies.

RESOURCES

The following websites provide access to expert advice and assistance with possible mutation analysis in patients suspected of having genetic lipodystrophies:

- *www.utsouthwestern.edu/education/medical-school/departments/internal-medicine/divisions/nutrition/lipodystrophy/index.html,* an information resource on genetic lipodystrophies at the UT Southwestern Medical Center, Dallas, TX
- *www.genetests.org,* a compendium of sites and locations of mutational analysis performed for research or via CLIA-certified laboratories

LIST OF ABBREVIATIONS

A1c . . . . . glycosylated hemoglobin
ACTH . . . . adrenocorticotropic hormone
ADP . . . . . adenosine diphosphate
AGPAT . . . 1-acylglycerol-3-phosphate-O-acyltransferase
AKT . . . . . a phosphoinositide-dependent serine/threonine kinase, also known as protein kinase B
ATP . . . . . adenosine triphosphate
BSCL . . . . Berardinelli-Seip congenital lipodystrophy
Ca_v. . . . . voltage-gated calcium channel
CEL . . . . . carboxyl-ester lipase
CGL . . . . . congenital generalized lipodystrophy
CLIA. . . . . Clinical Laboratory Improvement Amendments
DEND. . . . developmental delay, epilepsy, and neonatal diabetes mellitus
FPL . . . . . familial partial lipodystrophy
FPLD . . . . familial partial lipodystrophy, Dunnigan variety
G6P glucose-6-phosphate
GCK . . . . . glucokinase
GLUT . . . . glucose transporter
GnRH. . . . gonadotropic-releasing hormone
HDL . . . . . high-density lipoprotein
HIV. . . . . human immunodeficiency virus
HNF . . . . . hepatocyte nuclear factor
hsCRP . . . high sensitivity C-reactive protein
IPF . . . . . insulin promoter factor
K_{ATP}. . . . . ATP-regulated potassium channel
Kir . . . . . inward rectifying potassium channel
LHON. . . . Leber's hereditary optic neuropathy
LMNA. . . . lamin A/C
MAD. . . . . mandibuloacral dysplasia syndrome
MELAS. . . mitochrondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
MIDD . . . . maternally inherited diabetes and deafness
MODY . . . maturity-onset diabetes of youth
NDM . . . . neonatal diabetes mellitus
PC . . . . . prohormone convertases
PCOS. . . . polycystic ovary syndrome
PCSK. . . . proprotein convertase subtilisin/kexin type
PDX . . . . . pancreatic and duodenal homeobox
PHID . . . . pigmented hypertrichosis and insulin-dependent diabetes
PLIN. . . . . perilipin
PNDM . . . permanent neonatal diabetes mellitus
PPAR . . . . peroxisome proliferator-activated receptor
PTRF . . . . polymerase I and transcript release factor
SHORT. . . Short Stature, *H*yperextensibility of Joints and/or Inguinal *H*ernia, *O*cular Depression, *R*eiger Anomaly and *T*eething Delay Syndrome
SUR . . . . . sulfonylurea receptor
TNDM. . . . transient neonatal diabetes mellitus
TRMA . . . . thiamine-responsive megaloblastic anemia
WFS . . . . . wolframin

CONVERSIONS

Conversions for A1c, glucose, and insulin values are provided in *Diabetes in America Appendix 1 Conversions.*

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DUALITY OF INTEREST

Drs. Sperling and Garg reported no conflicts of interest. Dr. Garg possesses rights to the following intellectual property: 1) DePaoli AM, Taylor S, Oral EA, Garg A. (2007) Use of leptin for treating human lipoatrophy and method of determining predisposition to said treatment. U.S. Patent 7,183,254; and 2) DePaoli AM, Oral EA, Taylor S, Garg A. (2010) Use of leptin for treating human lipoatrophy and method of determining predisposition to said treatment. European Patent No. 10165256.8-2107/2219031.

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