Monogenic Forms of Diabetes: Neonatal Diabetes Mellitus and Maturity-onset Diabetes of the Young

The most common forms of diabetes, type 1 and type 2, are polygenic, meaning the risk of developing these forms of diabetes is related to multiple genes. Environmental factors, such as obesity in the case of type 2 diabetes, also play a part in the development of polygenic forms of diabetes. Polygenic forms of diabetes often run in families. Doctors diagnose polygenic forms of diabetes by testing blood glucose in individuals with risk factors or symptoms of diabetes.

Genes provide the instructions for making proteins within the cell. If a gene has a mutation, the protein may not function properly. Genetic mutations that cause diabetes affect proteins that play a role in the ability of the body to produce insulin or in the ability of insulin to lower blood glucose. People have two copies of most genes; one gene is inherited from each parent.

Monogenic Forms of Diabetes

Some rare forms of diabetes result from mutations in a single gene and are called monogenic. Monogenic forms of diabetes account for about 1 to 5 percent of all cases of diabetes in young people. In most cases of monogenic diabetes, the gene mutation is inherited; in the remaining cases the gene mutation develops spontaneously. Most mutations in monogenic diabetes reduce the body's ability to produce insulin, a protein produced in the pancreas that helps the body use glucose for energy. Neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes. MODY is much more common than NDM. NDM first occurs in newborns and young infants; MODY usually first occurs in children or adolescents but may be mild and not detected until adulthood.

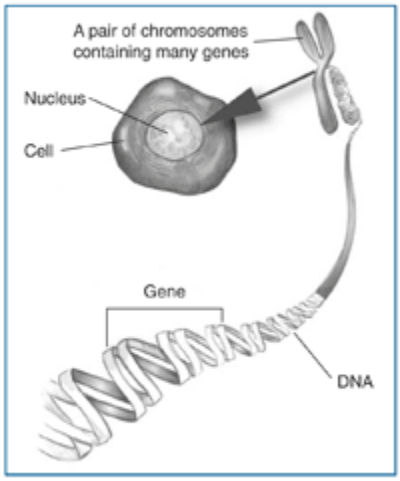
Genetic testing can diagnose most forms of monogenic diabetes. If genetic testing is not performed, people with monogenic diabetes may appear to have one of the polygenic forms of diabetes. When hyperglycemia is first detected in adulthood, type 2 is often diagnosed instead of monogenic diabetes. Some monogenic forms of diabetes can be treated with oral diabetes medications while other forms require insulin injections. A correct diagnosis that allows the proper treatment to be selected should lead

to better glucose control and improved health in the long term. Testing of other family members may also be indicated to determine whether they are at risk for diabetes.

More information about diabetes is provided in the NIDDK health topic, Your Guide to Diabetes: Type 1 and Type 2 and in *National Diabetes Statistics Report, 2014* at www.cdc.govExternal Link Disclaimer.

What is neonatal diabetes mellitus (NDM)?

NDM is a monogenic form of diabetes that occurs in the first 6 months of life. It is a rare condition occurring in only one in 100,000 to 500,000 live births. Infants with NDM do not produce enough insulin, leading to an increase in blood glucose. NDM can be mistaken for the much more common type 1 diabetes, but type 1 diabetes usually occurs later than the first 6 months of life. In about half of those with NDM, the condition is lifelong and is called permanent neonatal diabetes mellitus (PNDM). In the rest of those with NDM, the condition is transient and disappears during infancy but can reappear later in life; this type of NDM is called transient neonatal diabetes mellitus (TNDM). Specific genes that can cause NDM have been identified. More information about each type of NDM is provided in the appendix.

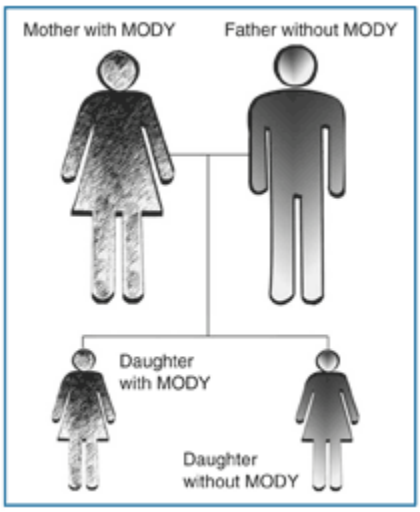


Genes affect a person's risk of developing diabetes.

Symptoms of NDM include thirst, frequent urination, and dehydration. NDM can be diagnosed by finding elevated levels of glucose in blood or urine. In severe cases, the deficiency of insulin may cause the body to produce an excess of acid, resulting in a potentially life-threatening condition called ketoacidosis. Most fetuses with NDM do not grow well in the womb and newborns are much smaller than those of the same gestational age, a condition called intrauterine growth restriction. After birth, some infants fail to gain weight and grow as rapidly as other infants of the same age and sex. Appropriate therapy improves and may normalize growth and development.

What is maturity-onset diabetes of the young (MODY)?

MODY is a monogenic form of diabetes that usually first occurs during adolescence or early adulthood. However, MODY sometimes remains undiagnosed until later in life. A number of different gene mutations have been shown to cause MODY, all of which limit the ability of the pancreas to produce insulin. This process leads to the high blood glucose levels characteristic of diabetes and, in time, may damage body tissues, particularly the eyes, kidneys, nerves, and blood vessels. MODY accounts for about 1 to 5 percent of all cases of diabetes in the United States. Family members of people with MODY are at greatly increased risk for the condition.



Each child of a parent with MODY has a 50 percent chance of inheriting the disease.

People with MODY may have only mild or no symptoms of diabetes and their hyperglycemia may only be discovered during routine blood tests. MODY may be confused with type 1 or type 2 diabetes. People with MODY are generally not overweight and do not have other risk factors for type 2 diabetes, such as high blood pressure or abnormal blood fat levels. While both type 2 diabetes and MODY can run in families, people with MODY typically have a family history of diabetes in multiple successive generations, meaning that MODY is present in a grandparent, a parent, and a child. Unlike people with type 1 diabetes who always require insulin, people with MODY can often be treated with oral diabetes medications. Treatment varies depending on the genetic mutation that has caused the MODY. More information about each type of MODY is provided in the appendix.

What do I need to know about genetic testing and counseling?

Testing for monogenic diabetes involves providing a blood sample from which DNA is isolated. The DNA is analyzed for changes in the genes that cause monogenic diabetes. Abnormal results can determine the gene responsible for diabetes in a particular individual or show whether someone is likely to develop a monogenic form of diabetes in the future. Genetic testing can also be helpful in selecting the most

appropriate treatment for individuals with monogenic diabetes. Prenatal testing can diagnose these conditions in unborn children.

Most forms of monogenic diabetes are caused by dominant mutations, meaning that the condition can be passed on to children when only one parent is affected. In contrast, if the mutation is a recessive mutation, a disease gene must be inherited from both parents for diabetes to occur. For recessive forms of monogenic diabetes, testing can indicate whether parents or siblings without disease are carriers for recessive genetic conditions that could be inherited by their children.

If you suspect that you or a member of your family may have a monogenic form of diabetes, you should seek help from health care professionals-physicians and genetic counselors-who have specialized knowledge and experience in this area. They can determine whether genetic testing is appropriate, select the genetic tests that should be performed, and provide information about the basic principles of genetics, genetic testing options, and confidentiality issues. They also can review the test results with the patient or parent after testing, make recommendations about how to proceed, and discuss testing options for other family members.

Points to Remember

- Mutations in single genes can cause rare forms of diabetes.
- Genetic testing can identify many forms of monogenic diabetes.
- A physician evaluates whether genetic testing is appropriate.
- A correct diagnosis aided by genetic testing can lead to optimal treatment.
- Recent research results show that people with certain forms of monogenic diabetes can be treated with oral diabetes medications instead of insulin injections.

Appendix and Selected References

Appendix: Characteristics of Monogenic Forms of Diabetes

Type of Diabetes	Gene or Syndrome	Affected Protein	How Common	Usual Age of Onset	Type of Inheritance or Mutation	Causes Intrauterine Growth Restriction?	Transient or Permanent?	Treatment
Neonatal Diabetes Mellitus (NDM)			Rare; occurs in about one of every 100,000 to 500,000 live births					
Permanent Neonatal Diabetes Mellitus (PNDM)			50% of all cases of NDM					

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Neonatal Diabetes Mellitus (NDM)			Rare; occurs in about one of every 100,000 to 500,000 live births					
Permanent Neonatal Diabetes Mellitus (PNDM)			50% of all cases of NDM					
PNDM	*KCNJ11*	Kir6.2	Most common type of PNDM	3 to 6 months	Autosomal dominant (10%) Spontaneous	Yes	Permanent (This gene also causes a transient form of NDM; see TNDM section)	Treated with insulin in the past but often can be treated with oral sulfonylureas
PNDM	*ABCC8*	SUR1-sulfonylurea receptor 1	Rare	1 to 3 months	Autosomal dominant (12% of NDM) Spontaneous	No	Permanent (This gene also causes a transient form of NDM; see TNDM section)	Treated with insulin in the past but often can be treated with oral sulfonylureas
PNDM	*GCK*	glucokinase	Rare	1 week	Autosomal recessive	Yes	Permanent	Insulin
PNDM	*IPF1*; also known as *PDX1*	insulin promoter factor 1	Rare	1 week	Autosomal recessive	Yes	Permanent	Treat to replace endocrine and exocrine pancreas functions
PNDM	*PTF1A*	pancreas transcription factor 1 A	Rare	At birth	Autosomal recessive	Yes	Permanent	Treat to replace endocrine and exocrine pancreas functions
PNDM	*FOXP3*, IPEX syndrome	forkhead box P3	Rare	Sometimes present at birth	X-linked	Yes	Permanent	Insulin
PNDM	*EIF2AK3*, Wolcott-Rallison syndrome	eukaryotic translation initiation factor 2-alpha kinase 3	Rare	3 months	Autosomal recessive	Yes	Permanent	Insulin and treatment for associated conditions
Transient Neonatal Diabetes Mellitus (TNDM)			50% of all cases of NDM					
TNDM	*ZAC/HYMAI*	*ZAC*: pleomorphic adenoma gene-like 1	Most common form of NDM	Birth to 3 months	Autosomal dominant Spontaneo	Yes	Transient	Initially, treat with insulin; reduce

Type of Diabetes	Gene or Syndrome	Affected Protein	How Common	Usual Age of Onset	Type of Inheritance or Mutation	Causes Intrauterine Growth Restriction?	Transient or Permanent?	Treatment
Neonatal Diabetes Mellitus (NDM)			Rare; occurs in about one of every 100,000 to 500,000 live births					
Permanent Neonatal Diabetes Mellitus (PNDM)			50% of all cases of NDM					
		or PLAG1 *HYMAI:* hydatiform mole-associated and imprinted transcript			us			dosage as needed; when diabetes recurs, treat with diet modification and physical activity; may also require insulin
TNDM	*ABCC8*	SUR1-sulfonylurea receptor 1	Rare	Birth to 6 months	Autosomal dominant Spontaneous	Varies	Transient (This gene also causes a permanent form of NDM; see PNDM section)	Oral sulfonylureas
TNDM	*KCNJ11*	Kir6.2	Uncommon cause of TNDM but most common cause of PNDM	Birth to 6 months	Autosomal dominant Spontaneous	Yes	Transient (This gene also causes a permanent form of NDM; see PNDM section)	Oral sulfonylureas
TNDM	*HNF1 β* (beta); also known as *HNF1B*	hepatocyte nuclear factor 1B	Rare	Birth to 6 months	Autosomal dominant (60%) Spontaneous	Yes	Transient	Insulin
Maturity-onset Diabetes of the Young (MODY)			1 to 5% of all cases of diabetes in the United States					
MODY 1	*HNF4A*	hepatocyte nuclear factor 4α (alpha)	Rare	Adolescence or early adulthood	Autosomal dominant	No	Permanent	For most, oral sulfonylureas; some patients may need insulin
MODY 2	*GCK*	glucokinase	MODY 2	Mild	Autosomal	Lower than	Permanent	Diet

Type of Diabetes	Gene or Syndrome	Affected Protein	How Common	Usual Age of Onset	Type of Inheritance or Mutation	Causes Intrauterine Growth Restriction?	Transient or Permanent?	Treatment
Neonatal Diabetes Mellitus (NDM)			Rare; occurs in about one of every 100,000 to 500,000 live births					
Permanent Neonatal Diabetes Mellitus (PNDM)			50% of all cases of NDM					
			and MODY 3 account for about two-thirds of all cases of MODY MODY 2 is the second-most common form of MODY	hyperglycemia may be present at birth; otherwise, early childhood	dominant	normal birth-weight can occur		modification and physical activity; medications usually not required; some patients do not require any treatment during childhood
MODY 3	*TCF1*	hepatic nuclear factor 1α (alpha) or HNF1α (alpha) or *HNF1A*	MODY 3 is the most common form of MODY	Adolescence or early adulthood	Autosomal dominant	No	Permanent	Initially, treat with diet modification; can be treated with oral sulfonylureas; some patients may need insulin
MODY 4	*IPF1*; also known as *PDX1*	insulin promoter factor 1	Rare	Early adulthood; can present later	Autosomal dominant	No	Permanent	Oral sulfonylureas; some patients may need insulin
MODY 5	*TCF2*	hepatic nuclear factor 1β (beta) or *HNF1B*	Rare	Adolescence or early adulthood	Autosomal dominant	No	Permanent	Insulin; patients also may need treatment for related conditions such as kidney failure or cysts
MODY 6	*NeuroD1,* or *BETA2*	neurogenic differentiation factor 1	Rare	In the fourth decade of life	Autosomal dominant	No	Permanent	Insulin

*Gene or Syndrome: the name of the gene with the mutation or the syndrome-a grouping of conditions that occur together and indicate a specific disease-caused by the mutated gene

**Type of Inheritance or Mutation:

- **Autosomal dominant.** Normally, every cell has two copies of each gene-one that comes from the mother and one from the father. An autosomal dominant inheritance pattern means that a mutation happens in only one copy of the gene, and a parent with a mutation can pass on a copy of their working gene or a copy of their damaged gene. In autosomal dominant inheritance, a child who has a parent with a mutation has a 50% chance of inheriting that mutation.
- **Autosomal recessive.** Normally, every cell has two copies of each gene-one that comes from the mother and one from the father. An autosomal recessive inheritance pattern means a mutation must be present in both copies of the gene in order for a person to be affected, and each parent must pass on a gene mutation for a child to be affected. If a person only has one copy of the gene mutation, that person is called a carrier. If both parents are carriers of a recessive gene mutation, each child has a 25% chance of being affected.
- **Spontaneous.** A new mutation, or change, in a gene
- **X-linked.** When a trait or a disease occurs in a person who has inherited a mutated gene on the X chromosome, one of the sex chromosomes

***Transient or Permanent: whether the form of diabetes goes away after some time, called transient, or is permanent

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