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Commentary

Genetics of Maturity-Onset Diabetes of the Young (MODY)

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DESCRIPTION

Maturity-onset diabetes of the young (MODY) is a complex of monogenic disorders characterized as non-insulin dependent form of diabetes due to autosomal dominantly inherited classically in young adults before the age of 25 years.

Simply it is defined as:

Maturity onset diabetes of the young (MODY) is mutations in an autosomal dominant gene disrupting insulin production leading to several hereditary forms of diabetes mellitus.

Since ages this MODY is the rarest cause of diabetes about 1% of diabetes cases and being misdiagnosed as type I diabetes mellitus or type 2 diabetes mellitus. Later, this Maturity onset diabetes of young was described as an dominantly inherited autosomal type of diabetes that resulted due to heterozygous mutations due to various number of factors like transcription and pancreatic β-cells maturation. Along these factors they are additional reasons like mutations of β-cells that are involved in glucose sensing enzyme.

Some of the Characteristic features that causes MODY are

- Autosomal inheritance,
- Early onset of diabetes,
- No signs related to the autoimmune process or insulin resistance, and

Additionally maturity onset of diabetes young shows clinical characterisations in the patients with

Type 1 diabetes mellitus atypical features:

- Measurable C-peptide in the presence of hyperglycemia
- Absence of pancreatic islet autoantibodies
- Low insulin requirement for treatment
- Lack of ketoacidosis when insulin is omitted from treatment

Type 2 diabetes mellitus atypical features

- Lack of significant obesity
- Onset of diabetes before age 45 years
- Lack of acanthosis nigricans

MODY genes causes disruption of insulin production processes and end up with hyperglycemia, the continuity or severity with time may causes the damage of organs such as eyes, kidneys, nerves, and blood vessels. People with certain types of mutations may show raised blood sugar with mild or no symptoms of DM as a short term complication. These same individuals may not also develop high blood glucose levels as a long-term complications. These symptoms which can be identified only through routine blood test.

Before going deep into genes causing MODY, let us know about types of MODY. These are 13 types of MODY. These types are categorised based on the gene that causing MODY. Mutations in pancreatic β-cell development or insulin secretion can cause MODY.

HNF4A(MODY 1): HNF4A, is a transcription factor that affects glucose metabolism. which is expressed mainly in the liver, pancreas and kidneys.

GCK MODY 2: Glucokinase, acts as the glucose sensor of pancreatic β-cells. which serves as a key regulating enzyme in insulin secretion stimulated by glucose.

HNF1A MODY 3: HNF1Ais expressed in pancreatic β-cells, the liver, intestines, it is a critical transcription factor for INS and GLUT2 (encoding a glucose carrier) in mature β-cells

IPF1 MODY 4: Pancreatic and duodenal homeo-box 1 (encoded by PDX1), also known as insulin promoter factor 1 (IPF1), is a gene transcriptions in the pancreas, including for insulin, glucose transporter-2, and glucokinase.

HNF1B MODY 5: HNF1B is expressed in the early phase of embryonic development in the pancreas, kidneys, liver, and genital tract.

KLF11 MODY 6: KLF11 is expressed in pancreatic islet cells and β-cells. Similar to expression in exocrine cells, KLF11 mRNA expression in β-cells may be up-regulated by trans-forming growth factor-β.

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NEUROD1 MODY 7: NEUROD1 is a regulating gene of the pancreas and INS expression. It regulates INS expression by binding to a complex promoter that is formed after dimerization with protein E4.

CEL MODY 8: The CEL gene is mainly expressed in mammary glands and pancreatic acinar tissue, but it is not expressed in β-cells.

PAX 4 MODY 9: Paired box gene 4 (encoded by PAX4) is a transcription factor that acts in β-cell development.

INS MODY 10: It has been predicted that these mutations decrease the folding of pro-insulin molecules or cause stress and β-cell apoptosis in the endoplasmic reticulum via endoplasmic reticulum protein retention.

BLK MODY 11: BLK encodes a non-receptor tyrosine kinase of proto-oncogenes of the Src family, which act in cellular multiplication and differentiation, and are present in many cells and tissues, mainly in pancreatic β-cells.

These are in further classified into heterozygous MODY includes all the types except MODY 2 and MODY 4, where these comes under homozygous MODY.

The treatment for MODY is generally standard medication but exceptional like MODY2, MODY 1, and MODY3. Sulfonylureas have been shows effectiveness in treating individuals with HNF1A-MODY by activating ATP sensitive potassium channels. Gliclazide improves fasting blood glucose levels compared to metformin. Patients with HNF1B-MODY generally do not respond to sulfonylureas and typically require insulin.

Therefore this, autosomal dominant mutation in genes involved biosynthesis and metabolism in insulin may cause MODY.

Treatment requires different approaches from other types of disease. Therefore healthcare providers are advised to formulate MODY drugs and treatment methods based upon identified pathophysiology and phenotypic presentations of its subtypes.