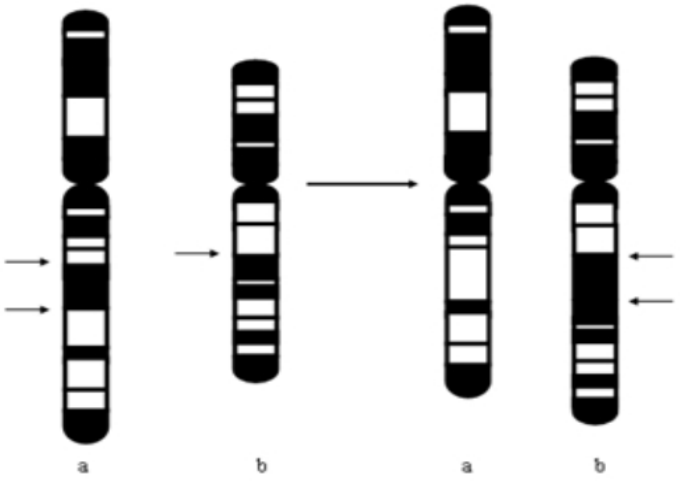
## GENETICS DISORDERS CONTINUED

### Insertion translocation (Transpozition)

While one chromosome is broken off from two different points, another chromosome is broken off at one point. After these breaks off, one piece of double broken chromosomes goes into the other chromosome and it is united with it. The children of these people, it could be observed duplications or deletions of the piece inserted the other chromosome because of segregation anomalies.

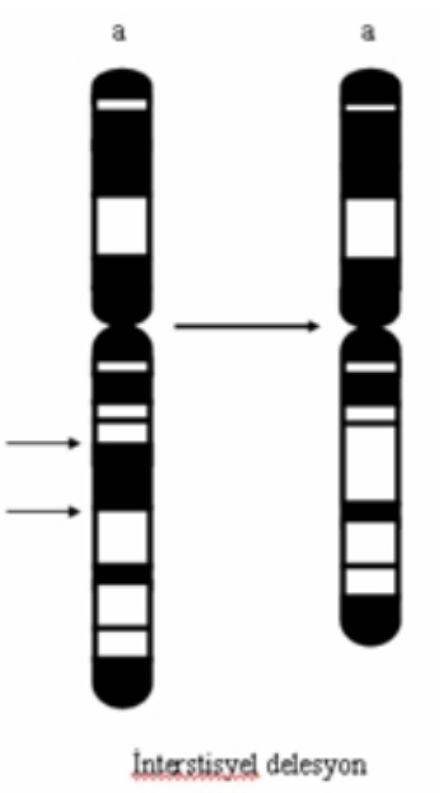
***Insertion translocation mechanism***



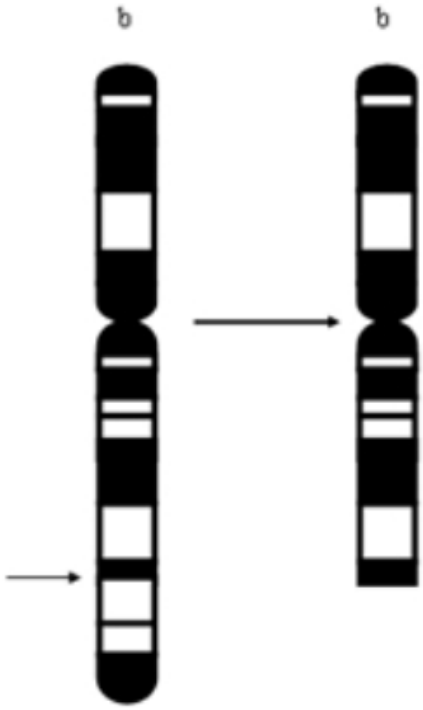

### DELETIONS (DECREASE)

A chromosome segment disappears after it is broken off and this causes an unbalance. This breaking can be two different ways at one of which is terminal piece disappears (terminal deletion) and at the other one is that after double breaks, extracted piece disappears and chromosome is again united. Extracted piece disappears because it is not centromeric generally. But if it is centoromeric, by holding spindal fibers it goes to the polars and does not disappear during cell division. This situation has no repetition risk.

***Deletion mechanism***




İnterstisyel delesyon

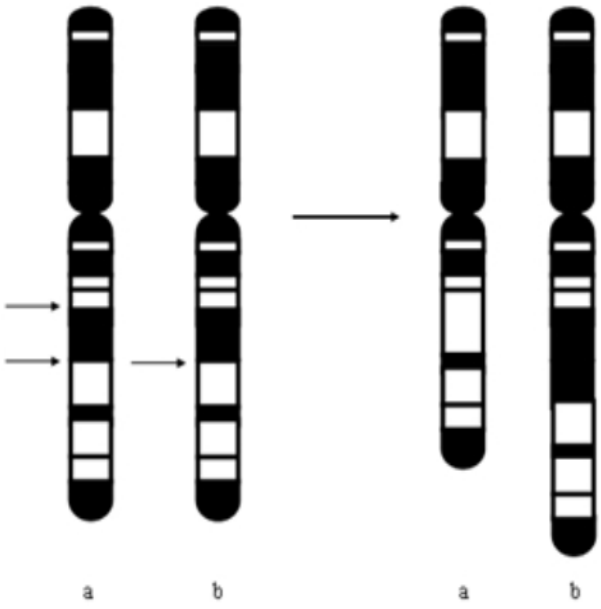



Terminal delesyon

**DUPLICATION (INCREASE)**

At one of two homologous chromosomes, there occurs double breaks, while another chromosome is broken off once. After these events the piece that is broken off from double broken chromosome goes into the other chromosome and it is inserted on it. Duplication is mainly observed at meiosis. And there are double copies of a piece of a chromosome.

***Duplications mechanism***




**INVERSION**

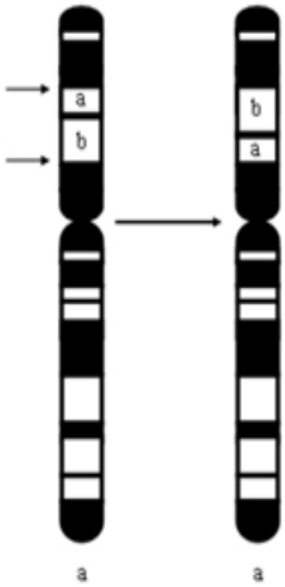
There are two breaks off from two different points of a chromosome. This extracted piece is united at same place after being reversed in itself. This inversion in general does not cause a phenotype at disease carriers because there is a balanced arrangement. There are two types of inversion:

- **Paracentric inversion**
- **Pericentric inversion**

**Paracentric inversion**

There is a break off, not including centomere, at either long or short arms. After the breaking, the piece is united again in the form of reverse. Because of the fact that there is no chance on height, it can be defined by the band structure method. But gene line changes and it does not affect phenotype. Furthermore in the gamete dispersion of people who have inversions, recombinant chromosomes that generally occur at unbalanced gametes are in the form of acentric or dicentric. Even if this type of inversion is reported very rarely, they do not let give birth alive. Hence the risk of having a child alive is very low for a disease carrier.

***Paracentric inversions mechanism***




**Pericentric inversion**

There are two breakings, including centomere, at both long and short arms. After the breaking, the piece is merged again in the form of reverse. Both the height of the chromosome and the gene line are changed. An individual having this type of inversion produces gametes having duplication or deficiency of chromosome segments. These segments are pieces stayed inversion distal. The risk of having a child with unbalanced karyotype is 1%-15%. And pericentric inversion has its specific risks. At people having large paracentric inversion, the pieces left at distal are less than those at small pericentric inversion. And also it is observed that there are decrease or increase on pieces left at distal. Therefore having recombinant children for these people is more possible. Inversion 9 is the best known inversion seen human chromosomes. Because of the fact that on studies it is transcribed that this inversion does not cause anomaly births, it is accepted as polymorphism.

***Pericentric inversions mechanism***


**Single gene defects**

These are also known as Mendelian inheritance disorders, from the first genetic work of Gregor Mendel. In these disorders, a single gene is responsible for a defect or abnormality. Single gene disorders usually have greater risks of inheritance. Single gene disorders can be:

- **Dominant.** An abnormality occurs when only one of the genes from one parent is abnormal. If the parent has the disorder, the baby has a 50 percent chance of inheriting it. Examples include the following:
  - **Achondroplasia.** Imperfect bone development causing dwarfism.
  - **Marfan syndrome.** A connective tissue disorder causing long limbs and heart defects.
- **Recessive.** An abnormality only occurs when both parents have abnormal genes. If both parents are carriers, a baby has a 25 percent chance of having the disorder. Examples include the following:
  - **Cystic fibrosis.** A disorder of the glands causing excess mucus in the lungs and problems with pancreas function and food absorption.
  - **Sickle cell disease.** A condition causing abnormal red blood cells.
  - **Tay-Sachs disease.** An inherited autosomal recessive condition that causes a progressive degeneration of the central nervous system, which is fatal (usually by age 5).

- **X-linked.** The disorder is determined by genes on the X chromosome. Males are mainly affected and have the disorder. Daughters of men with the disorder are carriers of the trait and have a one in two chance of passing it to their children. Sons of women who are carriers each have a one in two chance of having the disorder. Examples include the following:
  - **Duchenne muscular dystrophy.** A disease of muscle wasting.
  - **Hemophilia.** A bleeding disorder caused by low levels, or absence of, a blood protein that is essential for clotting.

**Multifactorial problems**

Some birth defects do not follow a single gene or chromosomal abnormality pattern. They may be due to several problems, or a combined effect of genes and the environment. It is difficult to predict inheritance of abnormalities caused by multiple factors. Examples include heart defects, cleft lip or cleft palate, and neural tube defects (defects in the spine or brain).

**Molecular Basis of Diabetes**

**Definition:**

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects of insulin secretion, insulin action, or both

**Diabetes classification:**

There are two main types of diabetes: type-1 and type-2. Type-1 diabetes is due to the autoimmune-mediated destruction of pancreatic beta cells, resulting in insulin deficiency. Patients with type-1-diabetes require exogenous insulin for survival. Its frequency amounts to nearly 10% of all diabetes cases. There is marked geographical variation in its prevalence, Scandinavian countries showing the highest rate of this illness. Type-2 diabetes accounts for approximately 90% of diabetes cases, and is characterized by impaired insulin action and/or abnormal insulin secretion. The worldwide diabetes epidemic relates particularly to type-2 diabetes. Besides type-1 and type-2 diabetes, there are other specific types of diabetes as described on Table 1. To understand the metabolic and molecular mechanisms responsible for type-2 diabetes, it is necessary to understand the regulation of fuel metabolism in the human body.

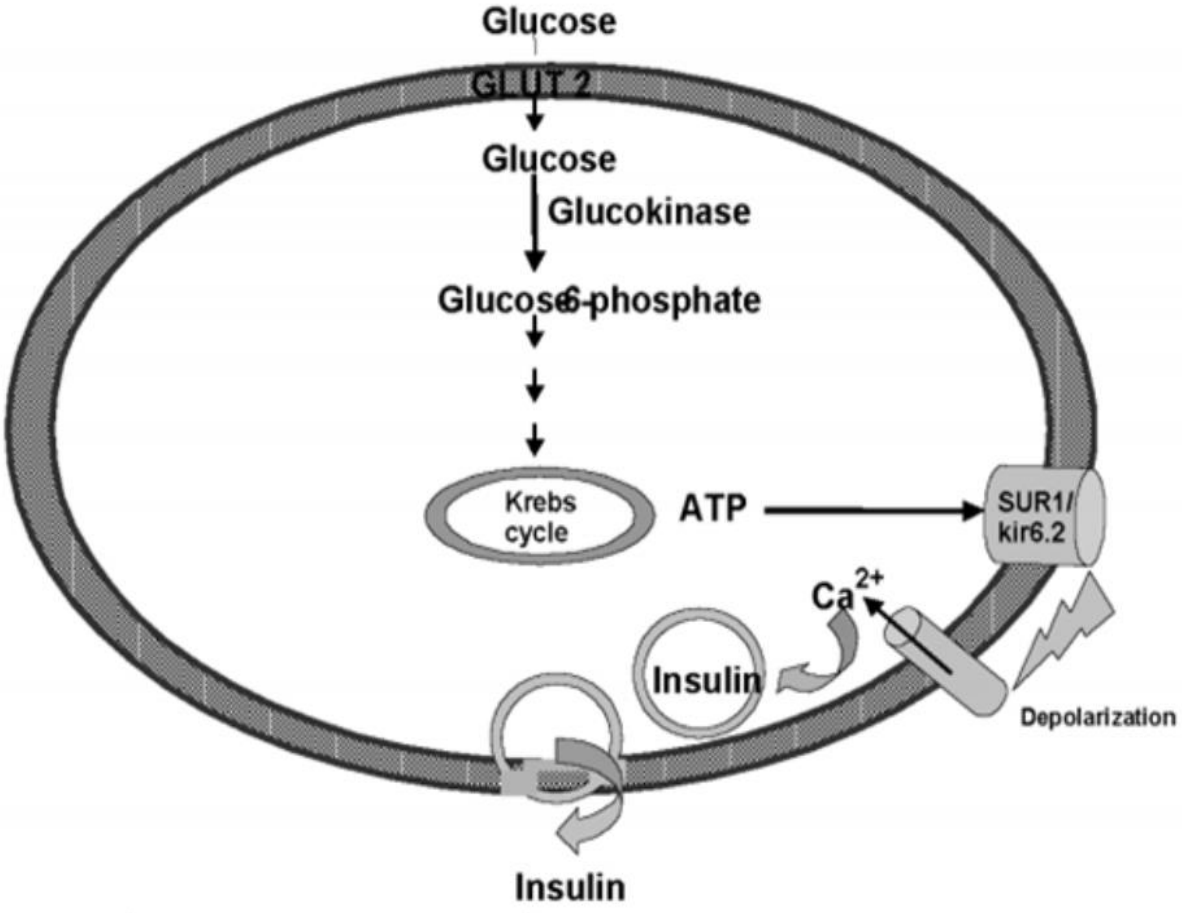
**Basic principles of metabolism:**

In the fed state, fuels in excess are stored as glycogen and triglycerides. During the fasting state these reservoirs are broken down to provide fuels. Energy reservoirs are built up and broken

down in response of hormonal messages. In the fed state, coordination of insulin secretion by the pancreatic beta cells along with the responsiveness to insulin of major glucose metabolic tissues such as muscle, liver and fat, control plasma glucose. Insulin promotes glucose uptake, glycogen synthesis in the liver and muscle, lipid formation to be stored in the adipose tissue, and protein synthesis in most cells. The rate limit step in whole body glucose uptake is the transport of glucose into skeletal muscle cells, this accounts for more that 75% of glucose uptake. Alongside the insulin stimulatory effect on fuel reservoir synthesis, in the fed state, the hormone has restrained functions on glucose output and lipolysis. In the fasting state, decreased plasma insulin concentration and increased counterinsulin hormones, such as glucagons, glucocorticoids, and catecholamines, contribute to glucose output via glycogen breakdown and gluconeogenesis, and via lipolysis as well as decreased synthesis and increased protein degradation. Beside the classical regulating hormones, a considerable piece of evidence indicates that adipose tissue hormones, adipokines, as well as free fatty acids, influence metabolism and fuel expenditure. Below, we describe the basic knowledge of the molecular mechanisms involved in insulin secretion and of responsiveness to insulin in normal conditions. We also describe the role of adipose tissue in fuel metabolism.

**Molecular mechanisms of insulin secretion**

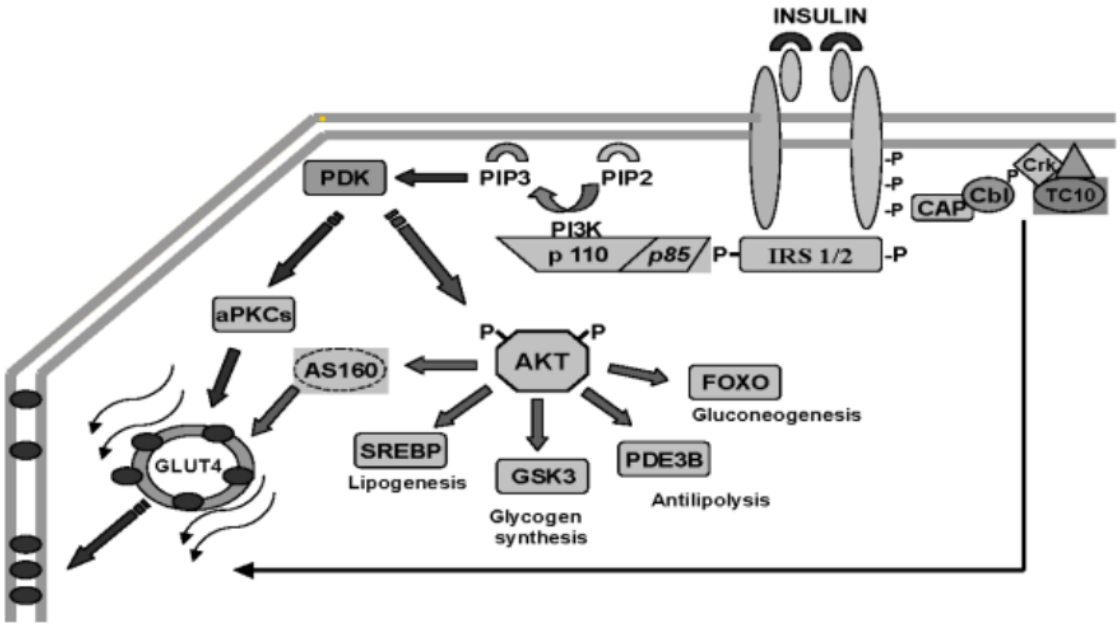
Insulin secretion in response to glucose is a complex, multistep process that requires transport and oxidation of glucose, electrophysiological changes and fusion of insulin-containing secretory granules with the beta-cell plasma membrane. Glucose enters the cell by facilitated diffusion mediated by a group of structurally related glucose transport proteins (GLUT), characterized by 12 hydrophobic helical domains. To date, at least 12 GLUTs have been described [8]. In the pancreatic beta cell, glucose is transported by the glucose transporter 2 isoform (GLUT2). Glucose is phosphorylated to form glucose-6-phosphate by glucokinase. This enzyme plays a critical role in glucose-induced insulin secretion and is considered the glucosensor of the pancreatic beta cell. Due to its kinetic characteristics, glucokinase is a determining factor for glucose phosphorylation and hence for its metabolism through glycolysis and oxidation.




Insulin secretion in response to glucose: Glucose enters the cell by facilitated diffusion mediated the glucose transporter 2 isoform (GLUT2) and it is phosphorylated to form glucose-6-phosphate by glucokinase. The generation of ATP by glucose oxidation leads to closure of the ATP-sensitive K+ channel, a hetero-octamer comprised of four subunits of the sulphonylurea 1 receptor (SUR1) and four subunits of the inwardly rectifying K+ channel Kir6.2. The closing of the ATP-sensitive K+ channel leads to depolarization of the plasma membrane and influx of extracellular calcium. This leads to fusion of insulin-containing secretory granules with the plasma membrane and the release of insulin into the circulation.

**Molecular mechanisms of insulin signaling**

Insulin starts its action by binding to the insulin receptor; this leads to a cascade of events that involves protein and membrane phospholipid phosphorylation, scaffold and docking proteins, and cytoeskeleton activity.




**Molecular mechanisms of insulin signaling.** The insulin interaction with its receptor promotes insulin receptor autophosphorylation, and catalyses the phosphorylation of cellular proteins such as members of the IRS family and Cbl. Upon tyrosine phosphorylation, these proteins interact with signalling molecules, resulting in a diverse series of signalling pathways, including activation of PI3K and the activation of TC10. These pathways act in a concerted fashion to coordinate the regulation of glucose transporter 4 (GLUT4) vesicle trafficking, protein synthesis, enzyme activation and inactivation, and gene expression, which results in the regulation of glucose, lipid and protein metabolism.

**Metabolism in type-2 diabetes**

**Insulin secretion:**

Type-2 diabetes arises when pancreatic beta cells fail to secrete sufficient insulin to andle with the insulin resistance demand, because of acquired betacell secretory dysfunction and/or decreased beta-cell mass. Recent studies have presented evidence that the beta-cell mass plays a pivotal role in determining whether an individual will progress to type-2 diabetes. These defects may be caused by primary beta-cell defects, such as seen in the monogenic diabetes forms of MODY, or by secondary beta-cell defects, caused by glucotoxicity, increased free fatty acids, cytokines, mitochondrial dysfunction and/or metabolic stress.

Type-2 diabetes is characterized by impaired insulin action and/or abnormal insulin secretion. An early abnormality in the disease is insulin resistance; a defective state in which insulin is unable to exert its biological effects at circulation concentrations that are effective in

normal subjects. Insulin resistance has been proposed as the key linking factor for the metabolic syndrome disease cluster of glucose intolerance, hypertension and dyslipidemia. Insulin resistance leads to profound decreases in glucose uptake and glycogen synthesis in peripheral tissues. Impaired hepatic glycogen stores and glycogen synthase activity are also observed in insulin resistance. Insulin resistance yields to defective suppression of hepatic glucose output, under the fasting as well as the fed state. Resistance to the antilipolytic action of insulin also favors triglyceride breakdown in adipose tissue and the generation of free fatty acids, which inhibit insulin-stimulated glucose uptake and metabolism in skeletal muscle, stimulate hepatic gluconeogenesis and interfere with insulin receptor signals. Changes in serum adipokine concentrations are also part of the insulin resistant state. At the pre-onset of type-2 diabetes, resistance to the glucose-lowering action of insulin tends to lead a slight increase of blood glucose concentration, which stimulates insulin secretion and causes hyperinsulinemia. Initially hyperinsulinemia is able to overcome insulin resistance. The diabetic state develops when insulin secretion cannot longer be sustained to compensate insulin resistance, and it is at this stage that fasting and post-prandrial hyperglycemia is apparent.

**Genetic factors:**

After the elucidation of Mendelian disorders with diabetes as a major phenotypic feature it has become clear that type-2 diabetes is heterogeneous and may result from defects in one or more molecular pathways. Genetic defects of the beta cell, usually referred to as maturity-onset diabetes of the young (MODY), can result from mutations in any of at least six different genes. Most of the MODY subtypes are caused by mutations in transcription factors, which are involved in the tissue-specific regulation of gene expression in the liver and in pancreatic beta-cells. Other related genetic factors are due to insulin receptor mutations.