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GENETIC FACTORS IN COMMON DISEASES

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GENETIC FACTORS IN COMMON DISEASES

- The common diseases do not usually show a simple pattern of inheritance.
- The contributing of genetic factors are often multiple, interacting with each other and environmental factors in a complex manner.
- Its uncommon for either genetic or environmental factors to be entirely responsible for a particular common disease in a single individual.
- In most instances both genetic and environmental factors are contributory, although sometimes one can appear more important than the other

GENETIC SUSCEPTIBILITY TO COMMON DISEASE

- A small proportion of common diseases cases have single gene causes
- The major proportion of the genetic basis of common diseases can be considered to be the result of an inherited predisposition of genetic susceptibility.

GENETIC SUSCEPTIBILITY TO COMMON DISEASE

Common diseases result from a complex interaction of the effects of multi different genes (polygenic inheritance), with environmental factors and influences (multifactorail inheritance).

TYPES AND MECHANISMS OF GENETIC SUSCEPTIBILITY

- Genetic susceptibility of a particular disease can occur through single gene inheritance, e.g. early CHD arising from familial hypercholesterolaemia (FH).
- In an individual with FH gene, the genetic susceptibility is the main determinant of the development of CHD but this can be modified by environmental alteration, e.g. reduction in dietary cholesterol, lack of exercise, and smoking.

TYPES AND MECHANISMS OF GENETIC SUSCEPTIBILITY

- Inheritance of a single gene susceptibility does not necessarily lead to development of the disease.
- For some disease exposure to specific environmental factors will be the main determinant in the development of the disease.

APPROACHES TO DEMONSTRATE GENETIC SUSCEPTIBILITY TO COMMON DISEASES

- Population/migration studies
- Family studies
- Twin studies
- Adoption studies
- Polymorphism association studies
- Biochemical studies
- Animal models

POPULATION/ MIGRATION STUDIES

- Differences in the incidence of a particular disease in different population groups suggest the possibility of genetic factors being important. They could also be explained by differences in environmental factors

FAMILY STUDIES

- Finding a higher frequency of a family history of the disease in relatives than in the general population suggested a genetic susceptibility to the disease.
- Familial aggregation does not prove a genetic susceptibility since families share a common environment.

FAMILY STUDIES

- The frequency of the disease in couples, who share the same environment but will usually have a different genetic background , can be used as a control, particularly for possible environmental factors in adult life.

Family relationships and proportions of genes in common with a proband

Relationship	Proportion of genes in common
Monozygotic twin	1/1
1st degree relative (parent, dizygotic twin, other sib, child)	1/2
2nd degree relative (uncle, aunt, grandparent, nephew, niece, grandchild, half-sib)	1/4
3rd degree relative (first cousin, great-grandparent, great-grandchild)	1/8
4th degree relative (second cousin)	1/16

TWIN STUDIES

- If identical twins, monozygotic (MZ) have the same trait this could be thought to prove that the trait is hereditary.
- This is not necessarily so. Since twins tend to share the same environment it is possible they will be exposed to the same environmental factors.

TWIN STUDIES

- comparing differences in the frequency of the disease between non-identical twins, dizygotic (DZ) and MZ twins pairs.
- Both members of a pair of twins are said to be concordant when either both are affected or neither is affected. the term disconcordant is used when only one member of a pair of twins is affected.

TWIN STUDIES

- Both MZ & DZ shared the same environment, but MZ are genetically identical and DZ no more difference than brothers and sisters.
- If the disease is entirely genetically determined then both members of MZ twins will be affected but not of DZ twins will have similar concordance rates.
- If the disease is entirely caused by environmental factors, then DZ and MZ twins will have similar concordance rates.

TWIN STUDIES

- study differences between MZ twin pairs who have been separated from an early age.
- If the disease is entirely genetically determined then, if one identical twin affected, the other will also be affected even if they have been brought up in different environments.

ADOPTION STUDIES

- Compare the frequency of the disease in individuals who remain with their biological parents with those who are adopted out of their biological family.

POLYMORPHISM ASSOCIATION STUDIES

- DNA polymorphisms allows the possibility of determining whether particular polymorphic variants occur more commonly in individuals affected with a particular disease than in the population in general, or what is known as a polymorphism association

BIOCHEMICAL STUDIES

- Analysis of metabolite or enzyme activity levels in biochemical or metabolic pathways can provide evidence of genetic contribution to some of the common diseases.

ANIMAL MODELS

- Recognition of the same disease which occurs in humans in another species allows the possibility of experimental studies which are often not possible in humans.
- Transgenic animal models experimentally induced for mutations in single genes involved in the metabolic processes or disease pathways of common diseases will provide vital insights into the genetic contribution to these disorders.

DIABETES MELLITUS (DM)

CLASSIFICATION OF DM

- Type 1 or insulin-dependent DM (IDDM)
 - autoimmune, beta-cell destruction, ketonuria.
- Type 2 or non-insulin-dependent DM (NIDDM)
 - usually older onset
 - associated with obesity
- MODY (maturity onset diabetes of the young)
- Gestational diabetes
- Secondary diabetes

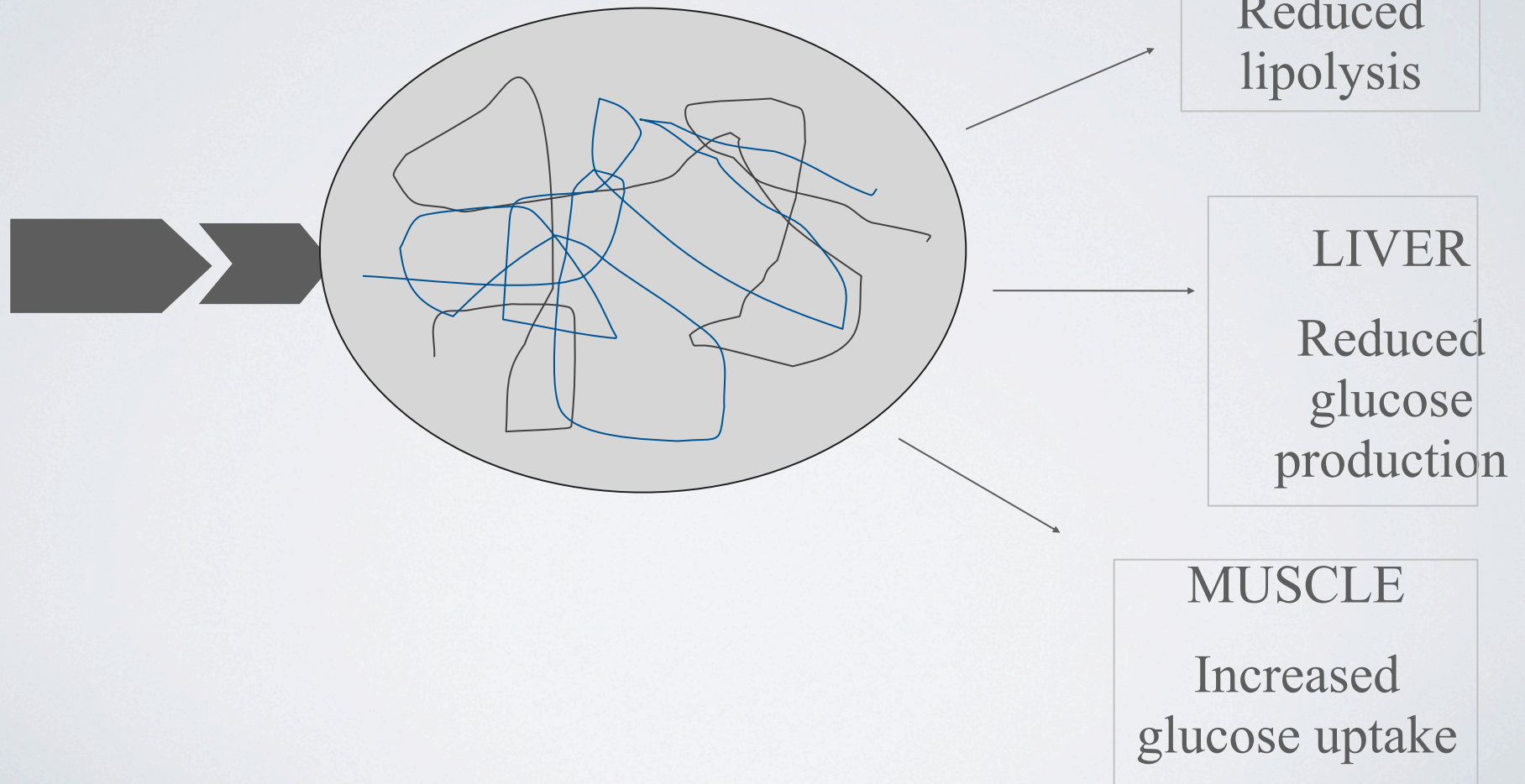
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what is diabetes.....

- The body unable to handle sugar properly.
- Insulin from the pancreas is used in the conversion of glucose to energy.

INSULIN ACTION



Type 1 diabetes

- Autoimmune destruction of pancreatic beta cells.
- Peak incidence at 11-13 years of age.
- Seasonal variation (lowest in Spring Summer).
- Increasing incidence.
- Varying speed of onset.

Genetics of Type 1 Diabetes

- Monozygotic twins - 30-50% concordance
- If father has Type 1: 6% risk
- If mother has Type 1: 1% risk
- If sibling has Type 1: 8% risk
- If non-identical twin has Type 1: 10% risk
- If both parents have Type 1: 30% risk

Genetics of Type 2 diabetes

- If identical twin has Type 2: 100% risk.
- If one parent has Type 2: 15% risk.
- If both parents have Type 2: 75% risk.
- If sibling has Type 2: 10% risk.
- If non-identical twin has Type 2: 10% risk.

Increasing prevalence of Type 2 diabetes

- Insulin resistance associated with:
 - Obesity
 - Inactivity

Prevention of Type 2 Diabetes

- Lifestyle change
 - Target at risk population
 - Diabetes prevention programme
- Change life style
- Health professionals need to set example of proper health diet.

Secondary diabetes mellitus

- Pancreatic destruction
- Haemochromatosis
- Cushings syndrome
- Cystic fibrosis
- Drug therapy
- Recognised genetic syndromes

MODY: Maturity Onset Diabetes in the Young

- Autosomal dominant
- Different phenotypes correspond with different genotypes
 - Hepatic nuclear factor (HNF) 4 alpha
 - Glucokinase (less severe disease)
 - HNF 1 alpha
 - HNF 1 beta

Gestational diabetes

- Genetically heterogeneous
- Increasing insulin resistance in pregnancy
- 50% develop Type 2 diabetes later in life
- Develops 2nd / 3rd trimester
- More common if overweight and inactive
- Neonatal problems:
 - macrosomia / respiratory distress / hypoglycaemia

HYPERTENSION

Hypertension

Twin and family studies indicate that both genes and environmental factors are involved in the determination of blood pressure but the nature of these and their mechanism of interaction are currently obscure.

Hypertension

- Genes may also be important with regard to choice of antihypertensive therapy. For e.g, high blood pressure is associated with a better response to beta blocker in blacks than whites.
- If one parent is hypertensive, the risk to offspring is 30%.
- If both parents are hypertensive, the risk to offspring is 40%.

CORONARY HEART DISEASE

Coronary Heart Disease

- CHD remains the most frequent cause of morbidity and mortality in Western industrialised countries, accounting for more deaths than all forms of cancer combined.
- The role of genes in the causation of atherosclerosis is supported by family studies and concordance rates of 65% for CHD in MD twins.

Coronary Heart Disease

- Patients with genetic hyperlipidemia present with cholesterol levels that are markedly elevated and, in some instance, may have been elevated since childhood.
 - The importance of the recognition of a genetic hyperlipidemia is that it influences therapy and management.

Coronary Heart Disease

- In general, genetic hyperlipidemia do not respond adequately to environmental modulation by diet; drug therapy is often needed to bring down the cholesterol levels.
- genetic hyperlipidemia should be suspected when there is a positive family history, as defined by the presence of angina, heart attack, or stroke in a first-degree relative before 50 years old.

Coronary Heart Disease

- Genes are particularly implicated in premature atherosclerosis when a first degree relative has a history of either angina or heart attack before 50 years of age.
- In this group, the family history is the most important indicator that the individual is at increased risk for CHD.

Coronary Heart Disease

- Important genetic disorders causing premature atherosclerosis:
 - Familial hyperlipidemia (FH): is inherited as an autosomal dominant trait and is penetrant early in life. The molecular basis for this disorder is different mutations in LDL receptor gene.
 - Familial combined hyperlipidemia (FCH): occurs with a frequency of approximately 1-2% in the general population. The diagnosis of FCH can be made in the presence of an elevated LDL cholesterol or triglyceride level in the patient and siblings or other first-degree relatives. The pathogenesis of the disorder is unknown.