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**International Task Force for Prevention  
Of Coronary Heart Disease**

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*Coronary heart disease and stroke:  
Risk factors and global risk*

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**Genetic risk for coronary heart disease**

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Slide 1:

**Pathways in which mutations or polymorphisms have been shown to modify the risk of coronary artery disease**

## Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

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- lipoprotein metabolism
- homeostasis of blood pressure
- glucose metabolism
- hemostasis
- inflammation response genes
- oxidation mediators
- adhesion mediators
- gene regulatory factors

in case of frequent MI events in the family detailed analysis of genetic factors may be helpful

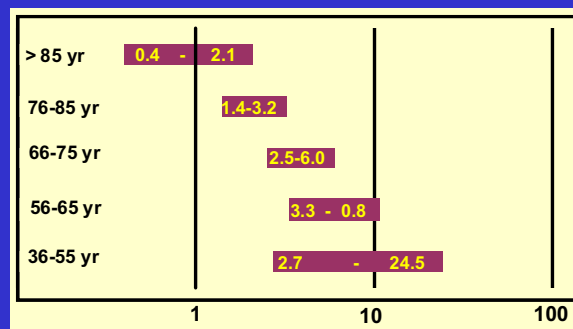
**Pathways in which mutations or polymorphisms have been shown to modify the risk of coronary artery disease**

As is shown on this slide, polymorphisms or mutations in genes involving numerous biological and metabolic pathways have been shown to modify the risk for coronary artery disease. Analysis of genetic factors is therefore particularly useful in families in whom there is a clustering of premature myocardial infarction.

Slide 2:

## Relative hazard for death due to coronary heart disease

### Relative Hazard for Death by Coronary Heart Disease - by age of twin sib at CHD death -



#### monozygotic male twins

after adjustment for smoking, blood pressure, diabetes, BMI, decade of birth, zygosity, education, marriage status

Marenberg et al. NEJM 330, 1041-6, 1994

### Relative hazard for death due to coronary heart disease

This slide shows the results from the Swedish twin registry. If one of the twins died of coronary heart disease between the age of 36 and 55 years, then the other twin's hazard of dying from coronary heart disease was 10 times greater than the hazard when one's twin did not die of CHD. However, if one of the twins died of coronary heart disease above the age of 85 years, the risk of the other twin dying of coronary heart disease was not increased. This data strikingly underlines two points: 1. The strong genetic component in premature death from coronary heart disease, and 2. The absence of such a genetic component in death from coronary heart disease occurring at an advanced age.

Slide 3:

## Mutations and polymorphisms in genes affecting lipoprotein metabolism

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- homeostasis of blood pressure
- glucose metabolism
- hemostasis
- inflammation response genes
- oxidation mediators
- adhesion mediators
- gene regulatory factors

major risk determinants

- Familial Hypercholesterolemia (FH)
- Familial Defective Apo B-100 (FDB)
- Type III Hyperlipoproteinemia (TIIHL)
- Sitosterolemia
- Homocystinuria
- Familial HDL deficiencies (APOA1, TD)
- Familial Combined Hyperlipidemia (FCHL)

other genes of interest include

lipoprotein lipase, hepatic lipase, lysosomal acid lipase, acid sphingomyelinase, LCAT, CTX, NPC1, apolipoproteins (a) AII, AIV, CII, and CIII

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

### Mutations and polymorphisms in genes affecting lipoprotein metabolism

This slide summarizes current data on the mutations and polymorphisms in genes affecting lipoprotein metabolism with impact on risk of coronary artery disease. There are several major risk determinants such as Familial Hypercholesterolemia, and Familial Defective Apo B-100. Whereas these have a large impact in the individuals in which they occur, their impact in the population at large is small. By contrast, a number of polymorphisms in other genes of small effect have been described (such as lipoprotein lipase). Whereas these polymorphisms have a small effect in the individual, the high frequency with which they occur means that their impact at a population level may be substantial.

Slide 4:

## Polymorphisms in genes affecting blood pressure

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- **homeostasis of blood pressure**
- glucose metabolism
- hemostasis
- inflammation response genes
- oxidation mediators
- adhesion mediators
- gene regulatory factors

major risk determinants

- insulin-resistant diabetes mellitus with acanthosis nigricans and hypertension (PPAR- $\gamma$  mutation)
- essential hypertension (3q21-25)

other genes of interest include

angiotensin I, angiotensin converting enzyme, angiotensin II receptor, 11 $\beta$ -ketoreductase, CYP11B1, B2, NF1, unknown genes at mapped loci

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

#### Polymorphisms in genes affecting blood pressure

This slide shows some of the genes in which polymorphisms have been described which affect blood pressure. The genetic background to essential hypertension is not known although a predisposition locus has been described on the short arm of chromosome 3.

A large number of polymorphisms with impact on blood pressure has been described. These are likely to affect risk of coronary heart disease, although in many cases the magnitude of this risk is not known.

Slide 5:

## Mutations and polymorphisms in genes affecting glucose metabolism

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- homeostasis of blood pressure
- **glucose metabolism**
- hemostasis
- inflammation response genes
- oxidation mediators
- adhesion mediators
- gene regulatory factors

major risk determinants

- several monogenic disorders known to cause diabetes mellitus (e.g. mutations in insulin receptor, insulin promotor factor 1, hepatic nuclear factors 1 and 4a, glucokinase)

other genes of interest include

glucose transporters, insulin, HLA DQ and DR

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

### Mutations and polymorphisms in genes affecting glucose metabolism

In recent years mutations have been described in a number of genes of major affect which influence glucose metabolism. One example is the mutation in the glucokinase gene which leads to maturity onset diabetes of the young. These mutations are rare, however, and their impact in the overall population is small. Much research is therefore being devoted to identifying the genes which contribute to type II diabetes mellitus which has a population prevalence of at least 5%.

Slide 6:

## Mutations and polymorphisms in genes affecting hemostasis

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- homeostasis of blood pressure
- glucose metabolism
- **hemostasis**
- inflammation response genes
- oxidation mediators
- adhesion mediators
- gene regulatory factors

major risk determinants

- major risk is associated with disorders of the clotting system in conjunction with an open foramen ovale

genes of interest include

clotting factors II, V, VII, PAI1, fibrinogen

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

#### Mutations and polymorphisms in genes affecting hemostasis

Mutations and polymorphisms which affect the clotting system have been described in many genes, including plasminogen activator inhibitor 1, factor V, and factor VII. The impact of these polymorphisms on coronary artery disease risk is known only for some genes such as plasminogen activator inhibitor 1. However, it is likely that polymorphisms in the other genes also affect CAD risk. In addition, there is likely to be close interaction between the clotting system and other risk factors. For example, it has been shown that the combination of a raised Lp(a)-level and the factor V Leiden mutation greatly increases the risk of stroke in children.

Slide 7:

## Mutations and polymorphisms in genes affecting the inflammatory response

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- homeostasis of blood pressure
- glucose metabolism
- hemostasis
- **inflammation response genes**
- oxidation mediators
- adhesion mediators
- gene regulatory factors

major risk determinants

currently no specific determinants known; some loose links have been reported to IL6 and NF $\kappa$ B

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

#### Mutations and polymorphisms in genes affecting the inflammatory response

The atherosclerotic plaque is a site of inflammation and it is therefore highly likely that genes affecting the inflammatory response promote or retard its development. However, at the present time, little specific information is available on the impact of polymorphisms in these genes on coronary artery disease risk.

Slide 8:

## Mutations and polymorphisms in genes affecting mediators of oxidation

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- homeostasis of blood pressure
- glucose metabolism
- hemostasis
- inflammation response genes
- **oxidation mediators**
- adhesion mediators
- gene regulatory factors

major risk determinants

- homocystinuria

other genes of interest include

CBS, MTHFR, PON, NOS

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

### Mutations and polymorphisms in genes affecting mediators of oxidation

The oxidation hypothesis of atherogenesis, that is that the oxidation of low density lipoprotein is a crucial step in atherogenesis, is still controversial. However, the bulk of experimental data indicates that either oxidation or chemical or enzymatic modification of LDL, or a combination of these, is important for macrophage foam cell formation. Several pathways have been identified which affect the redox potential within the arterial wall. Notably, these include genes affecting homocysteine metabolism, such as cystathione, betasynthase (CBS), methylenetetrahydrofolate reductase (MTHFR), or genes affecting oxidation per se such as paraoxonase (PON) or nitric oxide synthase (NOS).

Slide 9:

## Mutations and polymorphisms in genes affecting cellular adhesion

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- homeostasis of blood pressure
- glucose metabolism
- hemostasis
- inflammation response genes
- oxidation mediators
- **adhesion mediators**
- gene regulatory factors

genes of interest include

collagen IIIa, GP IIIa, e-selectin, VCAM, ICAM

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

#### Mutations and polymorphisms in genes affecting cellular adhesion

The very first step in atherogenesis is the adhesion of circulating blood cells to the arterial endothelium. This mechanism is now well understood and proceeds in two steps, the first of which is a loose binding to molecules of the selectin family, and the second of which is a tighter binding to intracellular adhesion molecules, such as vascular cellular adhesion molecule (VCAM). It is therefore not surprising that polymorphisms in genes affecting cellular adhesion are receiving interest as possible risk determinants for coronary artery disease.

Slide 10:

## Mutations and polymorphisms in transcription factors

### Genetic Variation and CHD Risk

- pathways in which mutations or polymorphisms have been shown to modify CAD risk -

- lipoprotein metabolism
- homeostasis of blood pressure
- glucose metabolism
- hemostasis
- inflammation response genes
- oxidation mediators
- adhesion mediators
- **gene regulatory factors**

major risk determinants

- PPAR- $\gamma$  [mutation]

other genes of interest include

PPAR- $\gamma$  [SNPs], SREBP, IRE, HNF1-5

adapted from Funke & Assmann: Curr. Opin. Lipidol. 10, 285-91, 1999

### Mutations and polymorphisms in transcription factors

A major focus of cellular biology at the present time is the regulation of gene transcription by transcription factors. In recent years, transcription factors impacting on pathways which affect intermediate phenotypes in CHD risk have been identified. These include the peroxisomal proliferator activated receptor  $\gamma$  (PPAR- $\gamma$ ), the sterol response element binding protein (SREBP), the insulin response element (IRE), and the hepatocyte nuclear factors 1-5 (HNF 1-5).