

## **POLYGENIC AND MILTUFATORIAL DISORDES**

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Many factors influence our susceptibility to disease. These include our stress load, our environment and the toxins we absorb from it, the total number of infectious agents we are exposed to as well as our underlying genetic susceptibility to these diseases.

Multifactorial is the term given to the mode of transmission shown by a large number of diseases which show familial clustering but which is not in accord with any recognized pattern of single gene inheritance. These diseases include several common congenital malformations and acquired disorders of childhood and adult life. The underlying genetic mechanism is thought to involve interaction of

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relatively large numbers of genes – hence oligogenic or polygenic – with environmental factors.

The ultimate cause of Alzheimer's (AD) is unknown. Genetic factors are suspected, and dominant mutations in three different genes have been identified that account for a much smaller number of cases of familial, early –onset AD. For the more form of late onset AD, ApoE is the only repeatedly confirmed susceptibility gene.

Coronary artery disease is well-recognized complication of several single-gene disorders involving lipid metabolism. Over 20 genes have been proposed as candidates for polygenic coronary artery disease. These include genes which control lipid metabolism, blood pressure, clotting, and fibrinolysis.

*Key words:* multifactorial disorders, disease, polygenic

## INTRODUCTION

The risk of many common diseases is thought to be influenced by multiple genes as well as environmental factors (BRIEN et al. 2000). These complex diseases include asthma, diabetes, epilepsy, hypertension, manic depression and schizophrenia (LAITINEN et al. 2001, LAITINEN et al. 2004). Certain developmental abnormalities are also included in this category, such as cleft lip/palate, congenital heart defects and neural tube defects (TAIPALE 2003).

Complex diseases have a low heritability compared to single gene disorders. For example, only 2-5 per cent of the close relatives of diabetes also suffer from diabetes, much lower than would be case for a single gene disorder like cystic fibrosis. This indicates that no single genetic factor is responsible for the disease. Many factors influence our susceptibility to disease. These include our stress load, our environment and the toxins we absorb from it, the total number of infectious agents we are exposed to as well as our underlying genetic susceptibility to these diseases. It is thought that the incidence of any complex disease is dependent on a balance of risks. There is a balance between gene variants with positive and negative effects, and between environmental factors with positive and negative effects. Too many negative factors, both genetic and environmental, can tip the balance towards disease (KERE et al. 1996).

In general the disorders that fall into this category can be divided into two groups: those that present at birth or early childhood, such as non-syndromal cardiac defects and Hirschsprung disease, and those that occur in later life, such as diabetes mellitus and schizophrenia.

Despite extensive research, the underlying molecular pathogenesis of most of these disorders remains unclear. Generally the prevailing evidence points to a complex and poorly understood interaction between genes at more than one locus with environmental factors that may be involved before or after birth.

Multifactorial inheritance is suspected on the basis of family, twin, and adoption studies.

#### *Approaches to finding susceptibility genes*

The identification of genes which contribute to multifactorial disorders is an area of intense activity amongst the scientific community, where vast amounts are being invested by the research funding bodies and by the pharmaceutical industry. The goal is to identify genes which play an important role in conveying susceptibility to the common disorders of adult life with a view to developing tests for their preclinical detection and new genetically based approaches for their prevention and treatment. Unfortunately, progress to date has been very limited. Three main strategies have been applied: linkage analysis, association studies, and linkage disequilibrium (TOIVONEN 2000).

#### *Examples of multifactorial disorders*

Present at birth or onset in infancy	Acquired with onset in childhood or adulthood
Cardiac defects, e.g. atrial septal defect, tetralogy of Fallot	Alzheimer disease
Ventricular septal defect	
Cleft lip/ palate	Asthma
Congenital dislocation of the hip	Autism
Hirschsprung disease	Coronary artery disease
Neuronal tubes defects	Depression – unipolar and bipolar
Pyloric stenosis	Diabetes mellitus – types 1 and 2
Talipes	Hypertension
	Inflammatory bowel disease, Crohn disease and ulcerative colitis
	Schizophrenia

#### *Alzheimer's disease*

Alzheimer's disease (AD) is the most frequent type of dementia in the elderly and affects almost half of all patients with dementia. Clinically it manifests as progressive loss of memory, emotional disturbance, and loss of intellectual skills. Alzheimer's disease has been identified as a protein misfolding disease, or proteopathy, due to the accumulation of abnormally folded amyloid beta protein and tau protein in the brains of AD patients (KERR and SMALL 2005). The neuropathological findings consist of neurofibrillary tangles made up of tau protein, which are neurotoxic, and senile plaques consisting of amyloid fibres known as AB which are derived from amyloid precursor protein (APP) (YANKER et al. 1990, OHNISHI and TAKANO 2004).

Rare cases of Alzheimer's are caused by dominant genes that run in families. These cases often have an early age of onset. The first gene to be implicated was APP on chromosome 21. This encodes the amyloid precursor protein. The small number of mutations identified in APP lead to an increase in

production of APP and hence AB, this being the chief constituent of the characteristic senile plaques. This observation is thought to explain the high incidence of Alzheimer disease seen in older adults with Down syndrome (TIRABOSCHI et al. 2004, LOTT and HEAD 2005).

Linkage analysis identified susceptibility loci on chromosomes 14 and 1 where genes known as Presenilin-1 (PS1) and Presenilin-2 (PS2) were isolated. PS1 and PS2 are thought to act by enhancing APP processing, leading to overproduction of AB which in turn leads to the formation of senile plaques and neurofibrillary tangles (WANG et al. 2004, CAI et al. 2006, VETRIVEL et al. 2006).

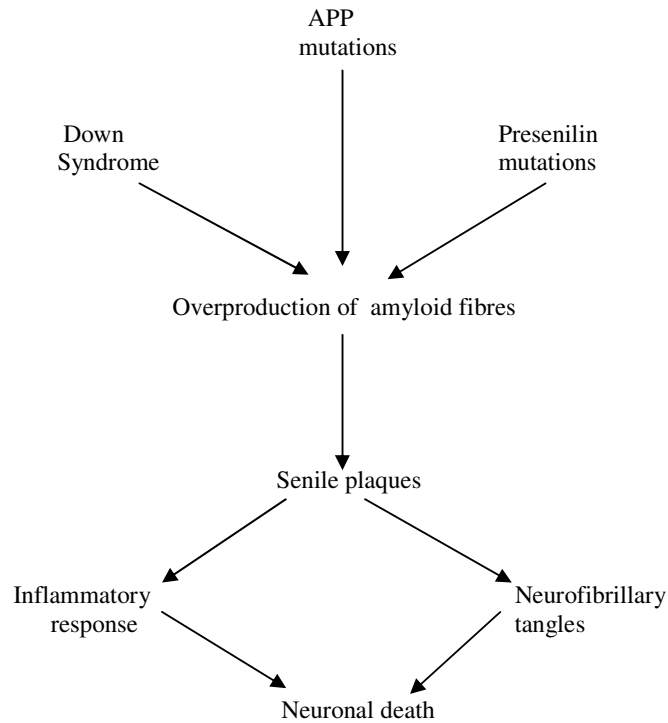


Fig.1. Simplified diagram to explain the pathogenesis of Alzheimer's disease.  
Adapted from McGuffin P, Owen MJ, Gottesman II(2002) *Psychiatric genetics and genomics*.Oxford University Press, Oxford.

Also, linkage analysis in families focused attention on chromosome 19 where a polymorphism at the APOE locus was found to show a strong association with late-onset Alzheimer disease. Apolipoprotein E (ApoE) is synthesized in the liver and brain and is involved in lipid metabolism and tissue repair. There are three common alleles at the APOE locus: E2, E3, and E4. The frequency of the E4 allele

is significantly increased in patients with Alzheimer disease, to the extent that the odds ratio for developing Alzheimer disease is increased 12-fold for E4E4 homozygotes as compared with E3E3 homozygotes. The lifetime risk for developing Alzheimer disease being around 35% for E4E4 men and 50% for E4E4 women (POLVIKOSKI et al. 1995).

Thus, the ultimate cause of Alzheimer's is unknown. Genetic factors are suspected, and dominant mutations in three different genes have been identified that account for a much smaller number of cases of familial, early-onset AD. For the more form of late onset AD, ApoE is the only repeatedly confirmed susceptibility gene (MANEV H. and MANEV R. 2006).

#### *Coronary artery disease*

Failure to compensate for the deleterious effects of various factors may result in development of different pathophysiologies in the cardiovascular system, such as, ischemia, hypertension, atherosclerosis and infarction (PAJOVIĆ et al. 1999, KANAZIR et al. 2004). The general picture of the molecular mechanisms of the induced pathophysiology in the CVS pointed out the importance of stress duration and intensity as etiological factors, and suggested that future studies should be complemented by the careful insights into the individual factors of susceptibility to stress, prophylactic effects of 'healthy' life styles and beneficial action of antioxidant rich nutrition (FINKEL 1998, ALLEN 1998, ALLEN and TRESINI 2000).

Coronary artery disease is well-recognized complication of several single-gene disorders involving lipid metabolism (HOLVOET 1999). Over 20 genes have been proposed as candidates for polygenic coronary artery disease (HUANG et al. 1993, IMBERT et al. 1996, ISHII et al. 1997). These include genes which control lipid metabolism, blood pressure, clotting, and fibrinolysis (KARIN and HUNTER 1995, KONISHI et al. 1997). One particular polymorphism which has been studied at length is that of an insertion (I)/deletion (D) in intron 16 of ACE, the gene which encodes the enzyme which converts angiotensin I into angiotensin II (CARMINE and ERNESTO 2007). Homozygotes for the DD genotype have higher plasma and tissue levels of the enzyme than those with the ID or II genotype. They also show a higher incidence of coronary artery disease, with one study suggesting that in the absence of other risk factors such as smoking, hypertension, diabetes, and obesity, the ACE DD genotype accounts for 35% of cases of myocardial infarction (PARTHASARATHY et al. 2001, FANG et al. 2002).

Finally, it is essential that we take advantage of the strides that have been made in the human genome project to understand our underlying genetic susceptibilities as well as the infectious and environmental components that compromise disease states (BOSMA et al. 1998, PAJOVIĆ 2007, PHEGLEY et al. 2002).

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**POLIGENSKE I MULTIFAKTORSKE BOLESTI**

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## I z v o d

Izučavanja etiopatogeneze mnogih obolenja ukazuju na izuzetnu složenost molekularnih mehanizama, s obzirom da pored genetskih faktora, faktori sredine značajno utiču na njihovu fenotipsku ekspresiju. Poligeno nasleđivanje uz sadejstvo faktora spoljašnje sredine naziva se multifaktorsko nasleđivanje.

Mnoge bolesti se nasleđuju multifaktorski, kao što su dijabetes, epilepsija, shizofrenija, Alzheimer-ova bolest, reumatoidni artritis, arterijska hipertenzija, čir na želucu, kao i urođene anomalije dece: rascep usne i nepca, iščašenje kukova, defekt nervne cevi i dr.

Multifaktorske bolesti i tip njihovog nasleđivanja je veoma teško pratiti, jer ne podležu pravilnostima prenošenja unutar porodice, zbog očiglednog uticaja činilaca sredine na ispoljavanje poligena.

Poligeno nasleđivanje Alzheimer-ove *bolesti* javlja se posle 65 godine. Linkage analiza je u ovim familijama fokusirala pažnju na hromozom 19, gde je uočen polimorfizam lokusa APOE, koji je u strogoj asocijaciji sa kasnom pojavom bolesti.

Preko 20 gena su kandidati za poligena koronarna arterijska obolenja. Geni su uključeni u metabolizam lipida, krvni pritisak, zgrušavanje i fibrinolizu; posebno je izučavan ACE gen, koji kodira enzim za prevođenje angiotenzina I u angiotenzin II.

U razjašnjavanju molekularnih mehanizama nastanka i prenošenja multifaktorskih bolesti, veoma je važno identifikovati faktore spoljne sredine, koji inter-reaguju sa genetskom osetljivošću i značajno je modifikuju.

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