

# Contemporary role of medical genetics in internal medicine

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## Abstract

Molecular biology and medical genetics, one of the most dynamically developing fields of medicine, nowadays is also a base for development of basic and clinical research in internal medicine. Understanding of crucial genetic pathomechanisms of many common diseases was possible due to the newest and modern molecular methods and tools. Moreover, development of genetics also made possible the discovery and understanding of the pathogenesis of many different diseases. However, not so long ago, we discovered precise pathomechanisms leading from damage of a single gene to a related pathological phenotype. Now, we have just started to explain molecular mechanisms of complex, multifactorial diseases. To achieve these goals, we need permanent development of genetic tests, genomics and proteomics. After fulfilling these conditions, we will get a chance to implement all molecular and genetic hopes, particularly their practical application in the clinic.

**Key words:** medical genetics, genetic testing, internal medicine.

## Introduction

Over 100 years ago, William Castle and Jason Phillips published one of the first papers devoted to genetics and its significance for medicine [1]. Today, the PubMed database contains over 2.3 million scientific studies on molecular biology and genetics. For several years the eventful development of molecular genetics has been observed, particularly considering its use in medicine. In the last twenty years molecular biology and medical genetics have revolutionized all branches of medicine, currently determining the basis of scientific research and development of clinical internal diseases. The turning point of perceiving the genetics of the most common diseases was possible owing to the latest introductions of molecular biology instruments as well. These modern research tools, i.e. DNA microarrays, serial analysis of gene expression (SAGE), single nucleotide polymorphism (SNP) analyses, haplotype analyses (HapMap) have recently provided invaluable possibilities, previously unavailable. The introduction of DNA microarray (i.e. DNA chip) proved to be particularly crucial in examining genetics and pathogenesis of a great number of diseases. The classical approach, i.e., linkage analysis and association analysis based on candidate gene selection, has numerous limitations resulting from the inability to analyse a consid-

erable part of the whole population variability. However, DNA microarrays allow for the simultaneous examination of hundreds of thousands of genetic markers, and thus the practical study of markers representative for the whole or almost the whole genome (genome-wide association study – GWAS) [2, 3]. This modern approach allows for relatively fast and reliable confirmation or exclusion of previously discovered genetic markers, by means of the classical association techniques mentioned above, and also discovery of a great number of new ones. Another milestone in the development of molecular genetics was, at the beginning of this millennium, sequencing almost the whole human genome. Naturally, this achievement could not have been possible without previous technological progress including the discovery of: the exact human DNA structure, restriction enzymes and, above all, polymerase chain reaction (PCR), the development and automation of the DNA sequencing process and also creating genetic and physical maps of the human genome within the Human Genome Project (HGP) [4, 5]. In 2001 an international consortium dealing with human genome sequencing published a working project and in 2004 the final version of the whole human genome sequence. Hundreds of scientists from approximately 20 research centres in France, Germany, the USA, Great Britain, China and Japan presented a human genome consisting of 3.1 billion ( $3.1 \times 10^9$ ) base pairs. The haploid human genome is composed of 3 100 000 000 nucleotides forming, inter alia, approximately 23 000 protein-coding genes and their printing would cover the way from Europe to the American west coast and their diploid form also the way back. In a collective declaration of the governments of six countries taking part in the above-mentioned project it has been stated that in this manner science presents “the molecular instructions of human life.” On the one hand the instructions were very extensive or rather very long, while on the other hand they seemed to be very simple, composed of only four nucleotides. However, it just indicates that genetic information is coded very concisely. Furthermore, as mentioned above, current estimations show that in the whole genome there are approximately 20–30 thousand protein-coding sequences, in other words, genes that are physiologically significant, and this constitutes a mere 1% of human DNA. The rest are repeated sequences, among other things, transposons or mobile sequences, duplications, micro- and minisatellites, tRNA and rRNA genes, as well as plenty of “junk” or vastly modified fragments of repeated sequences which are basically unrecognizable. Does this mean that approximately 99% of human DNA is genetically

insignificant? Naturally, not exactly, as e.g. some transposons code regulatory proteins responsible for certain variabilities in the human immune system, but questions about interpretations of human genome sequence still remain open and will pose a challenge to the scientific world in the near future.

### Disease genotype and phenotype

It has been known for a number of years that genetic factors play an important role in the pathogenesis of various diseases, though for a long time details of this predisposition, i.e., specific loci and its mutations or polymorphism that would increase the risk of disease, have not been known. Based on the studies of families and monozygotic twins and the large population studies of specified SNP and the analysis of haplotypes related to the presence of various diseases, subsequent proofs of an existing palpable genetic basis determining disease development have been obtained [6, 7].

Genetics was traditionally perceived in the light of infrequently occurring monogenic diseases; however, they belong mostly to the sphere of paediatrics and constitute an insignificant percentage of ambulatory paediatric counselling and child mortality. Right now the fact that practically every medical problem may have a genetic basis is becoming more and more clear. From the patient's family history at the very beginning of subject study we obtain information that a number of generally encountered diseases such as hypertension, cardiovascular diseases, diabetes or asthma are genetically based. Obviously, these conditions are multifactorial and include both genetic and environmental factors and their mutual influence. It results in the fact that in people having the highest genetic predisposition to development of a disease, identification and elimination of the risk factors should be most effective in this group of patients. Therefore identification of people with genetic predispositions will considerably facilitate the prevention of a disease through the correction of risk factors. Taking into consideration the above-mentioned information and the fact that cardiovascular diseases are the most common diseases of adult age and also have a strong genetic determinant in their aetiopathogenesis, after taking into account neoplastic diseases as another cause of mortality, then it will become evident that the majority of patients die of diseases, to a greater or lesser extent, conditioned genetically [8].

Traditionally, genetics dealt with the study of monogenic diseases, i.e., diseases generated by a single mutation or a deletion of a gene. The development of genomics, transcriptomics and proteomics induced the increase of interest in the influence of a genetic basis in emerging complex

diseases such as diabetes, hypertension or coronary artery disease (CAD). However, the interpretation of a genetic component influence of diseases not monogenically inherited requires not only knowledge of the particular gene sequences but also, as some scientists claim, above all the cognizance of the exact expression of proteins coded by them and their functions. Therefore it seems that the whole human genome sequencing and the knowledge of approximately 30 000 loci coding of the discovered proteins do not explain the complexity of multifactorial diseases. The way to discovering particular mechanisms leading to manifestation of phenotypes of a disease entity is far from over. Firstly, the majority of mutated alleles influence more than one human organ or system; therefore a disease phenotype will be characterised by various clinical symptoms. Secondly, the same mutated allele will variably form a various phenotype of people according to whether they are hetero-, homo- or hemizygous in relation to it. This variability will relate to the frequency of appearance of a disease symptom, its strength and the time after which it emerges. In other words, the manifestation of a specific phenotype in a disease entity will be dependent on the penetration strength of the related alleles. Thirdly, numerous genetic and environmental factors, inter alia, age, gender, genetic background, mutations, somatic mutations, transpositions and rearrangements, maternal factor, influence of mitochondrial genome, temperature, diet, teratogens, coincidence and medical interventions and therapy demonstrate an influence on intensity or suspension of a particular gene's expression. On the other hand, the existence of similar or identical disease phenotypes may result from completely different mutations. This heterogeneity may relate to various genes but may also be present at an inner-gene level at the time when it results from various mutations within a single locus. It appears that molecular mechanisms determining close relations between a genotype and a phenotype of a patient are still not fully known and only their thorough and complete discovery will enable a general study of the molecular aetiopathogenic base of multifactorial diseases and induce the individualization of patients' diagnostic-therapeutic process.

Genotype may be the reason for specific abnormalities and diseases but also, which is much more common in clinical medicine, participates in their pathogenesis. In the first instance, mutated genes may impair embryogenesis to such an extent that a specific clinical pathology will manifest to a greater or lesser extent. In the second instance, mutations will facilitate or prevent the activity of exogenous causes of a disease, creating a peculiar genetic susceptibility which constitutes a very sig-

nificant or, according to some scientists, the most significant pathogenetic element of a disease entity. It means that the response of an organism to a causative factor, the course and progress of a disease and a full recovery depend on numerous, not yet recognised elements of a patient's genotype.

### Molecular genetics in internal diseases

Numerous genetic factors apart from well-documented monogenic disorders of lipid metabolism incline to atherosclerotic changes, and in this manner lead clinically to the symptoms of coronary artery disease, myocardial and cerebral infarction. Hitherto the strategies of genetic studies of CAD have been grounded in linkage analysis and association studies based on candidate gene selection. Numerous genes of various connection strength with the risk of CAD manifestation have been identified, among others, genes for prothrombin,  $\alpha$ -adducin, endothelial nitric oxide synthases, apolipoprotein E, plasminogen activator inhibitor type 1 and many more [9–11]. Furthermore, two more genes predisposing to CAD have been identified. The first is the *ABCC6* gene connected with the development of pseudoxanthoma elasticum and the second is responsible for the production of Klotho protein. However, one of the most significant discoveries was the observation of a very strong association with locus 9p21.3 (rs1333049). The candidates in this region could be inhibitor genes of cyclin-dependent kinases *CDKN2A* and *CDKN2B* – it is known that these genes are engaged in cell cycle control. What is even more interesting, *CDKN2B* expression is induced by tumour growth factor- $\beta$  (TGF- $\beta$ ) and the TGF- $\beta$  pathway plays a considerable role in the pathogenesis of atherosclerosis. Moreover, it was observed that rs1333049 conditioned susceptibility to the formation of aneurysms [12, 13] and perhaps other disorders [14]. Including this genotype in the algorithm calculating a disease risk for an individual patient in one of the studies resulted in a transfer of patients to a higher class of disease risk. According to the obligatory standards it should result in a change of the hitherto existing treatment of these patients. This interesting observation suggests that the employment of a single genotype (rs10757274) may assist in classification of patients to particular CAD risk groups and consequently may have significant clinical implications for this group of patients [15, 16]. Obviously, not every single atherosclerosis gene of this kind has been discovered but their still growing number and insignificant influence of allelic variants of such a single candidate gene may indicate that susceptibility to coronary artery disease (CAD) is determined by numerous infrequent and ethnically specific allele genes individually having an inconsiderable influence on

the formation of a genotype. It is advisable to search for genes responsible for the presence of atherosclerotic changes among the genes inclining to diabetes and hypertension and also accountable for the control of a vessel's diameter and reactivity and also its capability to create bifurcations. Undoubtedly this group should be extended to genes influencing platelet adhesion, the blood coagulation system and fibrinolysis, as well as genes regulating endothelium and smooth muscle functions. The design and execution of screening of a gene series in order to determine the influence of typical mutations or polymorphisms on the risk of development of atherosclerotic changes is currently becoming the most significant task.

Among cardiac arrhythmias a great number of studies have concerned the genetic basis of the existence of atrial fibrillation. Numerous families with a history of atrial fibrillation in several generations were identified and no morphological or functional reasons in the cardiovascular system were discovered. Hitherto the studies have indicated locus 10q2.3; however, only sequencing of the whole region owing to modern tools of molecular biology has gradually marked potential points decisive for development of a disease [17]. It has been demonstrated recently that the risk of atrial fibrillation is significantly higher in people with specified genotypes in the range of rs2200733 and rs10033464 polymorphisms [18]. These conclusions have been confirmed in the course of independent studies in various populations indicating an approximately 1.5-fold increase of this arrhythmia connected with the presence of allele rs2200733T or rs10033464T [19]. It should be emphasized that rs2200733T and rs10033464T variants are frequently present in white populations (~40% of people) and therefore studies of their role in cardiac arrhythmia may be significant for a vast number of patients.

Many genes and environmental factors have also an unquestionable influence on regulation and the value of blood pressure; however, it was not discovered that this defined disease entity was, except for cases of hypertension secondary to identification of monogenic diseases (Liddle syndrome, Bartter syndrome, Von Hippel-Lindau disease, multiple endocrine neoplasia type 2), inherited in a typical Mendelian or multifactorial manner. Numerous systems, especially the renin-angiotensin system, are engaged in the physiological regulation of blood pressure. Besides previously identified insertion-deletion polymorphisms of the angiotensin-converting enzyme gene and its influence on arterial blood pressure value, the gene for angiotensinogen plays a significant role. Two polymorphic M/T variants in positions 174 and 235 considerably determine both plasma concentration of angiotensino-

gen and the blood pressure value in homozygous people [20]. As can be seen, the inheritance of susceptibility to the development of hypertension is a complex and still studied phenomenon.

The pathogenesis of various endocrine system diseases has a genetic basis as well. Many monogenic diseases influencing functions of the endocrine system have been identified. From a practical point of view more important, though less known, are pathomechanisms conditioning development of multifactorial diseases. In disorders such as autoimmune hypothyroidism and adrenal insufficiency or diabetes type 1, multigenic predisposition determines the development of autoimmune reaction designated directly against an organ. Participating in the aetiopathogenesis of these diseases are both genes influencing the actual autoimmune reaction and genes conditioning the peculiarity of an immune response against a specific organ. In this aspect the best documented is the participation of genes *MHC2*, *CD 40* and *CTLA4* regulating the proper way of autoantigen presentation [21]. Cytotoxic T-lymphocyte antigen 4 coded by the *CTLA4* gene is a membrane protein essential for correct T-lymphocyte functioning in the course of the autoantigen presentation reaction. Its proper variant restrains T-lymphocyte activation under the influence of autoantigen presentation. Mutated alleles coding various abnormal variants of this protein are responsible for incorrect reaction to autoantigen presentation and intolerance, initiating a cascade of immunological responses to own antigens and, as a result, damaging and provoking a disorder of an organ. These modern research tools, i.e. DNA microarrays, serial analysis of gene expression (SAGE), single nucleotide polymorphism (SNP) analyses, haplotype analyses (HapMap) have recently provided invaluable possibilities, previously unavailable. The studies of the genetic basis in diabetes type 2 do not provide such spectacular results. Besides identified and infrequent monogenic cases of diabetes type 2, the rest refer to multifactorial diabetes. Therefore various environmental and genetic factors play a significant role in it. It appears indisputable that genetic conditions concern both pathomechanisms of insulin secretion by pancreatic  $\beta$  cells, peripheral sensitivity to insulin and the presence of disease phenotype. The clinical picture of these disease forms results from the interaction of various environmental factors but also from abnormal or polymorphic genetic variants of various genes. In this aspect a few single nucleotide polymorphisms of the calpain 10 gene, variants of peroxisome proliferator-activated- $\gamma$  (PPAR- $\gamma$ ) receptors, polymorphisms of genes coding the Kir 6.2 subunit of a crucial potassium channel in  $\beta$  cells, and mutations of the insulin receptor gene were examined and also, by the GWAS method in screen-

ings of the whole genome, variants connected with a high risk of disease development [22]. In a few cases the connection of a given genetic variant with the development of diabetes type 2 was confirmed; however, in relation to a number of potential genes participating in pathogenesis of a disease it appears that there is still a long way to establish the genetic basis of the disease.

Thromboembolism is a frequent and serious complication of the haemostatic system. The most frequent and significant molecular defects participating in the process of correct haemostasis are: point mutation in the factor V gene (Leiden type mutation) clinically responsible for resistance to activated protein C, genetic defects leading to a deficiency of protein C, protein S, antithrombin, plasminogen and fibrinolysis disorders [23]. Deficiencies of particular plasma proteins, although crucial for physiological haemostasis, are not very frequent. On the other hand, Leiden type mutation in a population of European patients with venous thromboembolism occurs with the frequency of approximately 35-45%. It is clinically significant in female patients e.g. using oral contraceptives or employing hormone replacement therapy on account of respectively 10-30-fold and 10-20-fold increased risk of venous thromboembolism. It is estimated that 80% of patients undergoing such therapy with a present thromboembolism are homozygous in relation to the above-mentioned factor V mutation [24]. Another subject of interest to scientists studying the genetic basis of haemostasis disorders are polymorphisms of genes in proteins such as prothrombin, fibrinogen, factor VII, plasminogen activator inhibitor and also thrombomodulin, histidine-rich proteins, tissue inhibitor of the coagulation system or heparin cofactor II. From the coagulation factors mentioned above, a well-documented connection with the presence of venous thromboembolism concerns G/A mutation in position 20210 [25]. It is believed that this variant is decisive for a higher total concentration of prothrombin in plasma, as well as higher concentration of prothrombin fragment F1+2. The significance of this mutation for thromboembolism manifestation is particularly significant in patients with additional disease risk factors, inter alia, tobacco smoking, obesity, hypercholesterolaemia and diabetes.

Systemic diseases of connective tissue are another large group of diseases where genetic conditions are significant for pathogenesis. Obviously the basis is multifactorial and multigenic and genes regulating the immunological response, including HLA, seem to have the dominating significance. In the case of systemic lupus erythematosus the risk of the disease in another family member is 100-fold higher than in the general population. One of the significant genetic factors conditioning the devel-

opment of the disease is polymorphism of HLA class III genes coding complement components [26]. Genetic variants may lead to the deficiency of components C2, C4A, C4B and factor B particularly. These disorders influence the impairment of opsonization and the transport of immune complexes. Especially well documented appears to be the influence of component C4 deficiency. It was observed that in nearly 70% of homozygotes, in the sphere of gene polymorphism for this factor systemic lupus erythematosus or "lupus like disease" developed. Moreover, in these patients the early presence of a disease phenotype, fast emergence of antibodies and frequent occurrence of lupus nephritis are observed. Other examined variants for which a connection with the development of systemic lupus erythematosus was confirmed are, among others, polymorphism of the gene for TNF- $\alpha$  and TNF- $\beta$ , polymorphism of the TNF- $\alpha$  promoter gene, polymorphisms of genes for cytokines IL1A and IL-10, as well as polymorphisms of Fc $\gamma$ RIIa and Fc $\gamma$ RIII receptor genes having a crucial role in the process of immune complexes' removal [27]. What is interesting, it has been observed that there are some genetic variants for, inter alia, HLA-B40, HLA-DR4 or IL-10 whose presence is linked to the decreased risk of lupus development. It confirms the exceptionally complex aetiopathogenesis of systemic lupus erythematosus, including the complex multifactorial genetic basis.

#### **Possible therapeutic interventions based on genetic risk**

Alongside the molecular studies detecting a particular genetic disease and examining its pathogenesis, genetic tests will be developed more and more often in clinical practice allowing one to estimate the susceptibility of a patient to the development of a disease. The object of these tests is to determine the risk of developing a disease, and they are divided into presymptomatic tests, in the case of diseases in which a genetic defect is 100% associated with the risk of developing a disease, and predisposition tests, when such genetic changes are not equivalent to disease phenotype manifestation but increase the risk of its occurrence. Currently specific genetic tests and treatment methods accompany more and more numerous genetic diseases. In this way e.g. identifying a hereditary variant of long QT syndrome connected with ventricular arrhythmia enables an early electrocardiographic diagnosis and use of, even preventively, antiarrhythmic therapy, including cardiostimulator and defibrillator implantation. Patients with a genetic burden of hypertrophic cardiomyopathy may be previously examined, treated with  $\beta$ -blockers and, first of all, informed of complete compliance with a preventive protocol, i.e. avoid-

ance of physical exercise and dehydration. The role of gene defects in factor V coagulation and prothrombin were mentioned earlier. Female patients who are heterozygous or particularly homozygous in the context of the mutated factor V should avoid oral contraceptives or hormone replacement therapy and after surgical interventions, immobilization and traumas should receive preventive doses of low molecular weight heparin. The detection of mutations connected with the presence of familial polyposis or hereditary non-polyposis colorectal cancer in the patient's family members requires an early preventive imaging examination and in some cases forces a preventive surgical intervention. Similar procedure rules will refer to genetically conditioned cases of breast, ovary or thyroid cancer, some skin cancers or melanoma. The mutation detection in genes *PKD1* and *PKD2* in patients with hereditary polycystic kidney disease will direct a patient to a nephrologist and enable early hypertension treatment, prevention and treatment of urinary system infections or use of vaptan treatment. The employment of genetic examinations in reference to *AVPR2*, *AQP2* or *AVP* gene mutations will enable, replacing biochemical trials, an unequivocal differentiation of renal diabetes insipidus from pituitary diabetes insipidus. This detection will decide on either administration of fluid, thiazide or amiloride treatment in the first case or use of vasopressin treatment in the second case.

These are only a few of the possibilities of employment of molecular genetics in medicine. Even though genetic diagnostics and medical intervention attempts based on it are in the early stage of practical use, it is expected that its development will enable early and well-directed diagnostic and therapeutic procedures for numerous significant diseases.

## Conclusions

Molecular biology and medical genetics, one of the most dynamically developing fields of medicine, nowadays is also a base for development of basic and clinical research in internal medicine. Understanding of crucial genetic pathomechanisms of many common diseases was possible due to the newest and modern molecular methods and tools. Moreover, the development of genetics also made possible the discovery and understanding of the pathogenesis of many different diseases. However, not so long ago, we discovered precise pathomechanisms leading from damage of a single gene to the related pathological phenotype. Now, we have just started to explain molecular mechanisms of complex, multifactorial diseases. To achieve these goals, we need permanent development of genetic tests, genomics and proteomics. After fulfilling these conditions, we will get a chance to implement

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