Abstract

The information provided within the programs of human genome sequencing facilitate understanding of the etiology of various diseases and of the principles of molecular genetics, while the modern methods at hand permit utilization of genetic information for risk evaluation and also for a most precise establishment of diagnosis and, respectively, for the implementation of suitable treatments for each patient in part. Specialists in oral health will be obliged to acquire notions of human genetics, thus learning to apply the new therapeutical and diagnosis technologies. In this respect, the present study aims at outlining the importance of a continuous professional training of stomatologists, and not only, to keep pace with the permanent evolution and with the technological possibilities in the field of medical genomics and to successfully make use of the actual information and techniques. This challenge requires the implementation of some new medical disciplines, offering to specialists notions of molecular biology, genomics, personalized medicine and individualized treatment.

Keywords: molecular genetics, genomics, oral medicine, individualized treatment.

1. INTRODUCTION

The scientific discoveries recorded in the last century have revolutionized the molecular bases of life. Among them, special mention should be made of the following three discoveries, namely: redefining of the heredity laws by Mendel, in the year 1900 (starting from the proposals made by Gregor Johann Mendel in 1865), unveiling of DNA structure in 1953 and the final realization of the first sequencing and mapping (in a ratio of 95%) of the human genome, in the year 2001 [1]. Along with the elucidation of the DNA structure [2] and subsequent elucidation of DNA replication, genetic code, synthesis of messenger RNA, protein synthesis, genes regulating functions, the discoveries of classical genetics came to be fully understood from the viewpoint of molecular biology principles [3]. Equally, such discoveries were expected to grant progress in a new direction, involving merging of classical genetics with molecular biology and creation of molecular genetics. In the last 50 years, the science called molecular genetics was subjected to some transformations, becoming a science of genomics, characterized by much more specific scopes and means [4].

Genomics actually represents a discipline of genetics applying the recombinant DNA, the method of DNA sequencing, bioinformatics, for sequencing, assembling and analyzing the structure and functions of genomes [5,6].

Nowadays, the term of genome - used for describing the whole heredity information present in human cells [6] – is formed of a nuclear and a mitochondrial genome. To express the distinction between the genome of somatic cells and that of the gamets, terms like haploide and diploide genomes are also emoloyed. Knowledge on the human genome constitutes a precious tool in medical research, absolutely necessary for better understanding the genetic instructions and interactions which define us as humans. From a clinical perspective, by studying gene sequences and the functional dynamics of the genome, as well as the genetic differences among individuals, specialists attempt at understanding the molecular bases of a normal health condition, and also of the morbid state, for establishing new individualized methods in medicine [3]. In this way, the concept of genomic medicine or personalized medicine, referring to making of clinical decisions on the basis of information about some DNA sequence of the patient, has
been created [4]. Accordingly, modern medicine comes to adopt genomic instruments, which permit a much more precise prediction of the disease and a personalized treatment.

2. GENOMICS AND ITS APPLICATIONS IN MEDICINE

Traditionally, medicine focuses on the clinical manifestations and symptomatology of patients, on also considering their medical history; however, unfortunately, such a method is not always efficient, as – according to the reputed physician William Osler (1849–1919) - each individual has a different genetic architecture. More precisely, with the exception of traumas, all diseases and affections have a major genetic component (namely, one or several genes or gene–gene or gene–environment type interactions) [7].

The genomic studies developed in latest years and the results recorded in far-reaching projects, such as: Initial sequencing and analysis of the human genome [1], Finishing the euchromatic sequence of the human genome [8], International HapMap [9]. A second generation human haplotype map of over 3.1 million SNPs [10] opened a new era in medicine: the era of genomics and of personalized medicine or, with a recent term – prediction or precision medicine [11,12]. Personalized medicine is characterized by detection of any susceptibility to certain diseases, of the response to drugs, respectively by utilization of biomarkers that may support prediction and monitored therapeutic intervention [13]. In this way, identification of human genetic variations and their utilization as genetic markers or biomarkers [14] permit understanding of the implications of genetics in inducing and also in the evolution of diseases at a much higher level [15]. Genetic markers provide new instruments for the practical application of personalized medicine, the objective of which is an optimum patient care.

A precise diagnosis and a correct, individualized treatment become possible by the utilization of genomic instruments, such as sequence variations, transcription, proteins, metabolites, respectively genome sequencing. Nowadays, for most complex affections, genomic medicine and stomatology make use of the following instruments: gene therapy, pharmacogenomics (the effect of some drug upon genetic expression) [16], SNP-based diagnosis (polymorphisms of a single nucleotide), diagnosis based on gene prognostication [4], populational screening [17], risk evaluation on the basis of DNA, genetic testing, application of molecular markers (for cancer diagnosis), respectively the genomics-supported therapy and selective dosing of drugs as a function of patient’s metabolism [18].

The fundamental components of personalized medicine are: evaluation of risks (involving the susceptibility of a person to developing some disease); the medical history of the family; utilization and integration of the instruments of genomics and of its derivatives (proteomics, transcriptomics and metabolites); supports for clinical decision (software programs created for assisting clinicians in their decision-making processes) [19]. Consequently, personalized medicine is based on personal data referring to one’s health condition, which reflects one’s metagenomic, proteomic or metabolomic profile [13].

Consequently, anticipated as early as the last century by William Osler in a series of observations and theories, personalized medicine and its instruments came really into being, however the immense volume of information accumulated during genome analysis and sequencing appeared as a new challenge for both physicians and scientists, involving a full understanding and integration of the obtained genomic data for the determination of the cause-effect type relations, respectively of the progress of the disease state even prior to the installation of symptoms. In other words, all these discoveries should be integrated in the health systems and in the working circuit of clinics and hospitals, for attaining a more efficient detection, prevention, diagnosis, individualized treatment and monitoring of diseases, as well as for the application of specific therapies [19,20]. Such an approach requires, nevertheless, multidisciplinary health systems capable of functioning together [21]. The practical application of these modifications is expected in all branches of medicine, stomatology and oral
medicine included [20], if considering that several already-recorded results support this action [22-24].

3. GENOMICS AND STOMATOLOGY

The relevance of oral medicine and the advance of personalized medicine, along with its transposition from a mere theoretical concept to clinical application, may be evidenced by means of pharmacogenomics. Pharmacogenomics became relevant starting with the elucidation of the central part played by enzymes of the p450 (CYP) cytochrome family to drug metabolism [25], which proved the existence of certain inter-individual variations in relation with the response to drugs. A convincing pharmacogenetic example, with special impact in oral medicine, is obviously related to the lack of efficiency, in some patients, of the drugs metabolized by the enzyme coded by gene CYP2D6. As a function of its race, ethnic condition, etc., more than 20% of the population may be affected by the polymorphisms of gene CYP2D6 [26], the individuals affected with some specific polymorphisms at the locus of this gene possibly suffering from pain or adverse reactions to the treatment with codeine (prescribed for dental pains or extraction procedures).

Administration of drugs with adverse effect may have several unfavourable consequences. For example, xerostomia [27] (dry mouth) is a clinical manifestation associated with the administration of one or more unfavorable drugs [28]. Such a type of disease, occurring in one of five persons, may result in an increased susceptibility to periodontal affections, caries, candidoses, disphagia or even systemic diseases (syndrome Sjogren) [29]. Another example involves the patients with Raynaud syndrome, associated, in more than of 95% of cases, with the autoimmune disease called skleroderma, which attacks the teeth and gingiva, possibly causing tooth loss, as well as xerostomia [30]. For stomatologists, detection of the patients affected with skleroderma or syndrome Raynaud is essential, as these persons cannot be given local anaesthesia of novokaine type (usually administered together with epinefrine - a vasoconstrictor) [31]. In patients with Raynaud syndrome, administration of novokaine may provoke extremely dangerous disorders and crises. Hemophilia is another genetically-transmitted disease with oral manifestations, which may be detected by stomatologists through inspection of the buccal cavity and of the pharinx [32], a.s.o.

Genetically, the anomalies characteristic to the oral region may be divided into multifactorial, respectively monogenic and polygenic anomalies. Dental anomalies may occur as either frequent or isolated cases, with clinical variations from one case to another [33]. Investigated at molecular level, numerous polygenic anomalies emerge from monogenically determined units [34], several examples of monogenically determined syndromes with detected genic mutations being at hand in this respect. Among them, mention should be made of: the Aarksog syndrome – facial-genital displasia (mutations at the level of gene FDG1) [35], the Prader-Willy syndrome (deletion of some genes off chromosome 15 and mutations at the level of gene SNORD116) [36], the Marfan syndrome (mutation at the level of gene FBN1 from chromosome 15) [37], the Apert syndrome – craniosynostosis (mutations at the level of gene FGFR2 from chromosome 10) [38], syndrome Crouzon (craniofacial hereditary disostosis) [39], syndrome Treacher Collins (mandibulary hypoplasia) [40], syndrome Raynaud (paroxistic ischemia), etc. Such displasies of the skeleton are transmitted either dominantly autosomally – one single copy of the mutant (maternal or paternal) gene being sufficient for the manifestation of the disease - or recessively autosomally.

For example, the occurrence of syndrome Crouzon is caused by the mutation of gene FGFR2 from chromosome 10 (as in the case of syndrome Apert) [38], the long arm, locus 26 (10p26) which codifies the growth factor of fibroblasts (FGFR2) [41]. Consequently, the bones of the cranium are prematurely sutured, so that one of the effects, also of interest from a stomatological perspective, is the asymmetry between the maxillary and the mandible.

Syndrome Treacher Collins is provoked by the mutations occurring at the level of genes TCOF1, POLR1C, respectively POLR1D – all
playing important parts in the early development of facial bones and tissues [42]. These proteins are also involved in the production of ribosomal RNA, known as essential for a normal functioning and survival of cells, whereas the mutations observed at the level of these proteins reduce the amount of RNA. This deficit, produced at ribosomal level, induces a deficitary cell growth during embryogenesis, affecting the bones of the face, more exactly of the cheeks and mandible, as a result of the under-development of the zygomatic arch.

Part of such dental anomalies, correlated with various other syndromes, has been investigated both abroad [43-46] and in Romania [33].

Also considered a dominantly autosomally transmitted mutation is dentinogenesis imperfecta, a malady affecting 1 person of 6,000. Out of the three types described in literature [47], type I dentinogenesis imperfecta [48] is associated with osteogenesis imperfecta, being manifested clinically as a loss of dental tissue, brownish dentin, fragile enamel, etc. [49]. The teeth have hypoplastic roots and fungus shape, permitting no endodontic treatment. Another example refers to enamel anomalies – amelogenesis imperfecta [50], as several types with different heredity (enamel matrix formed, yet insufficiently mineralized) exist, while the enamel is soft and fragile, and the teeth are yellow-brownish. Hypoplasia results in an insufficient production of enamel, which is very thin, yellow-brownish in colour in the case of homozygote men, while the heterozygote women are affected in a different manner.

Hypodontics (especially important from a clinical perspective), represents an ideal genetic model, due to the frequency it records (affecting ca 5% of the population) and to its relatively simple identification. Hypodontics is determined by a series of very powerful genes, part of them being already identified (PAX 9, MSX 1) [34].

Stomatologists are expected not only to identify and cure the dental and oral diseases, but also to be capable of recognizing the systemic indices of genetic affections and of the general health condition of their patients [51]. As they cannot establish diagnosis through examination of the buccal cavity, they are the most capable ones of observing various anomalies, correlated with developmental malformations, as well as certain genetic disorders, so that they can orient the sick ones towards specialized clinics. Saliva may be employed as a diagnosis instrument, while the salivary biomarkers [52] are already commonly utilized for risk evaluation, prevention of diseases, identification of systemic or oral problems (caries, cancer or periodontal affections) [53], whereas the specialized laboratories may detect the presence of virusi, drugs or hormons from the saliva.

The challenge for stomatologists involves management and utilization of the information provided by the investigations devoted to the human genome [54], whereas a possible challenge of the future would involve identification of some defect in a specific gene, for the establishment of an optimum treatment [55]. It goes without saying that the medical and stomatological industry will profit from the concepts of human and microbial, proteomic and metabolomic genomics, along with pharmacogenomics, as essential elements of the medicine of tomorrow [56-58].

A successful implementation of personalized oral medicine requires a steady scientific basis, sound application principles and a cultural – economic environment capable to accept innovation and to support the cost-efficiency relation [59]. Therefore, in spite of all difficulties, personalized oral medicine should be implemented especially by means of pre and post-university education programs.

4. GENOMICS STUDIED IN SCHOOLS

According to the American Association of Medical Colleges, the existing knowledge in the field of molecular biology and genetic affections, the one related to oral health included, will suffer important modifications, so that the future stomatologists will have to face and keep pace with this challenge [60]. Such a situation assumes a thorough study of some basic notions of molecular biology and genetics, referring to the transmission of characters, structure of the human genome, principles of populational genetics, genetic terminology, as well as the application of all these data in the evaluation and care of the health condition of patients [51]. Training of the stomatologists of tomorrow involves implementation and application of
educational strategies devoted to the treatment and cure of patients suffering from genetic affections. The existing studies [61,62] have evidenced that a vital aspect in this respect is the development – in the future practitioners – of the ability of making correct decisions in relation with the diagnosis and planning of the treatment, in accordance with the latest genomic technologies.

References


