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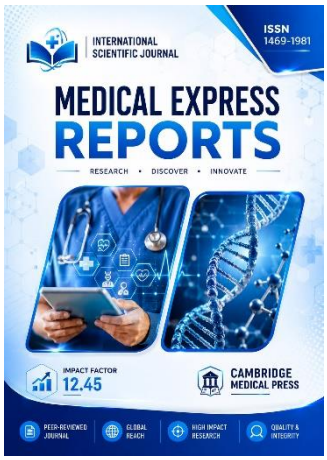

HEREDITARY AND GENE DISEASES: CLASSIFICATION, MOLECULAR MECHANISMS, GLOBAL BURDEN AND MODERN APPROACHES TO DIAGNOSIS, PREVENTION AND THERAPY (A LITERATURE REVIEW)

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ABSTRACT

Hereditary diseases are conditions caused by changes in the genetic material that can be transmitted from parents to offspring. They include gene (monogenic) disorders, chromosomal disorders and multifactorial diseases. The aim of this review was to summarise current knowledge on the classification, molecular mechanisms, global burden, diagnosis, prevention and treatment of hereditary and gene diseases. A narrative review of PubMed, Scopus and Google Scholar sources was carried out, and 26 publications were analysed. Of 6,172 rare diseases catalogued in Orphanet, 71.9% are genetic and 69.9% begin exclusively in childhood; together they affect 3.5–5.9% of the world population. About 312,000 newborns with sickle cell anaemia were born worldwide in 2010, and the global birth prevalence of phenylketonuria is 1:23,930. In children with suspected genetic disease, genome and exome sequencing reached diagnostic yields of 41% and 36%, compared with 10% for chromosomal microarray. Newborn and carrier screening, genetic counselling, dietary and enzyme therapies, gene

replacement and CRISPR-Cas9 gene editing are changing the outlook for many patients. Knowledge of medical genetics is also important for dentists, since many hereditary syndromes have oral and dental manifestations.

INTRODUCTION

Every human cell carries about three billion base pairs of DNA, and the sequencing of the human genome showed that only a small part of this sequence codes for proteins [1]. A change in a single nucleotide of an essential gene, the loss or gain of a whole chromosome, or the combined effect of many small variants together with environmental factors can lead to disease. Such conditions, which are caused by changes in the genetic material and may be transmitted from parents to children, are called hereditary diseases [2, 3].

Individually, most hereditary diseases are rare, but together they represent a large medical and social problem. The Orphanet database contains information on 6,172 rare diseases, of which 71.9% are genetic and 69.9% begin exclusively in childhood; rare diseases as a whole affect 3.5–5.9% of the world population, or 263–446 million people at any point in time [4]. According to the World Health Organization, an estimated 240,000 newborns die every year within 28 days of birth because of congenital disorders, and these disorders cause a further 170,000 deaths of children aged 1 month to 5 years [5]. Genetic causes account for an important part of this burden.

The scientific study of heredity began with the experiments of Gregor Mendel on garden peas, published in 1866, which established that hereditary factors are transmitted as discrete units. At the beginning of the twentieth century, Archibald Garrod applied these laws to human medicine and described alkaptonuria and other conditions as “inborn errors of metabolism”, proposing for the first time that a hereditary disease may be caused by the absence of a specific enzyme. The discovery of the structure of DNA in 1953, the identification of the correct number of human chromosomes in 1956 and the description of trisomy 21 in Down syndrome in 1959 laid the foundations of modern medical and clinical genetics [2, 3].

The last two decades have changed medical genetics more than the previous century. Next-generation sequencing has made it possible to read the whole exome or genome of a patient in a few days, international databases collect information on hundreds of thousands of genomes, and new treatment methods — from enzyme replacement to gene therapy and genome editing — have moved from laboratories to clinical practice [6, 7]. For medical and dental students, an understanding of the basic principles of hereditary diseases is necessary not only for genetics examinations but also for future clinical work: recognising a hereditary syndrome, referring a family for counselling and explaining the risk of recurrence are tasks that every doctor may face.

AIM

To summarise current scientific data on the classification, molecular mechanisms, global burden, diagnosis, prevention and treatment of hereditary and gene diseases, with attention to their importance for medical and dental practice.

MATERIALS AND METHODS

A narrative literature review was carried out. Sources were searched in PubMed/MEDLINE, Scopus and Google Scholar using the keywords “hereditary disease”, “genetic disorder”, “monogenic disease”, “chromosomal abnormality”, “rare diseases”, “newborn screening”, “exome sequencing”, “genome sequencing”, “gene therapy” and “CRISPR-Cas9”. Priority was given to systematic reviews and meta-analyses, large epidemiological studies, international recommendations, reports of the World Health Organization, landmark clinical trials and standard textbooks of medical genetics. In total, 26 sources published between 2001 and 2023 were analysed. Quantitative data were taken directly from the original publications and presented in tables and figures.

RESULTS AND DISCUSSION

1. Basic concepts and classification

The terms “hereditary”, “genetic” and “congenital” are related but not identical. A congenital disorder is present at birth, but it may have a non-genetic cause such as an infection or a teratogen; conversely, many hereditary diseases, for example Huntington disease, appear only in adulthood [2, 5]. Hereditary diseases are traditionally divided into three main groups (Figure 1). Gene, or monogenic, diseases are caused by pathogenic variants in a single gene and are inherited according to Mendel’s laws. Chromosomal diseases result from changes in the number or structure of chromosomes. Multifactorial diseases are caused by the combined action of many genes and environmental factors. Mitochondrial disorders, caused by variants in the mitochondrial genome, are often considered a separate group because they are transmitted only through the mother [3].

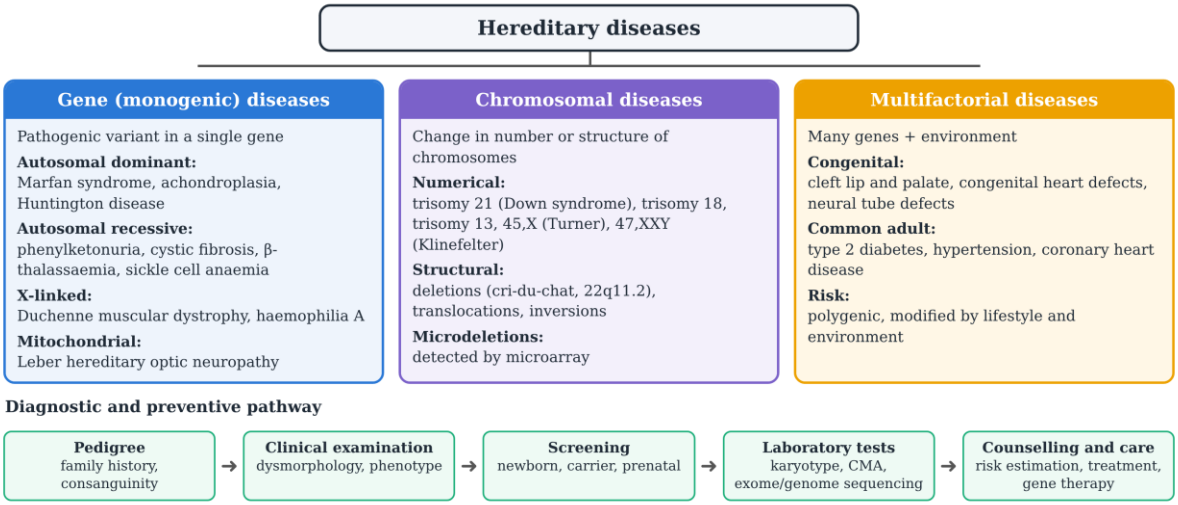

Figure 1. Classification of hereditary diseases and the main steps of diagnosis and prevention.

The catalogue Online Mendelian Inheritance in Man (OMIM) has collected information on human genes and genetic phenotypes for several decades and is one of the main reference resources for clinicians and researchers; it links each disorder with its gene, mode of inheritance and clinical description [8]. Population databases such as gnomAD, which contains data from more than 141,000 people, make it possible to estimate how often a given variant occurs in healthy individuals and which genes are intolerant of loss-of-function variation [6]. These resources are essential for correct interpretation of genetic test results.

2. Global burden of hereditary diseases

The distribution of rare diseases by cause and age of onset is shown in Figure 2. The large share of genetic diseases among rare disorders and their predominant onset in childhood explain why paediatric services are most affected [4]. At the same time, most of the population burden is concentrated in a relatively small number of more frequent conditions.

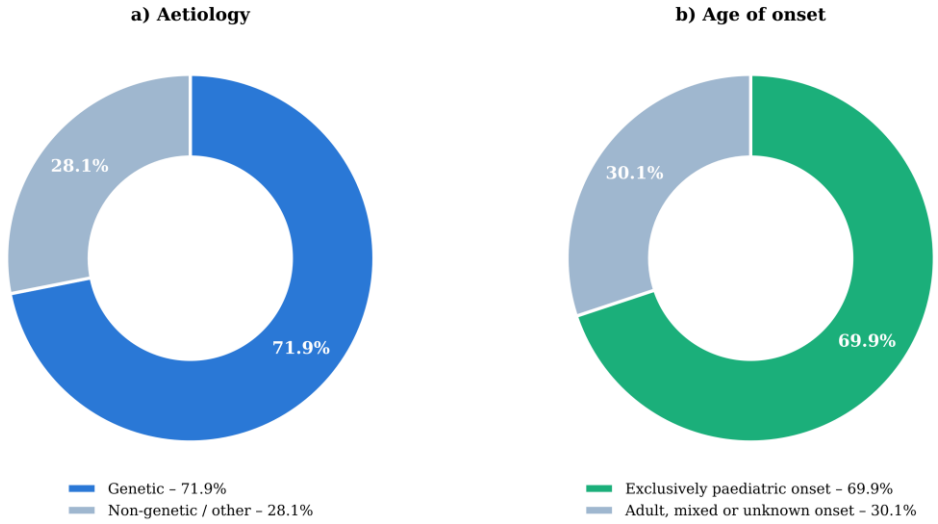

Figure 2. Distribution of the 6,172 rare diseases catalogued in Orphanet by aetiology (a) and age of onset (b) (based on [4]).

The frequency of individual gene diseases varies greatly between populations. Phenylketonuria (PKU), the most common inborn error of amino acid metabolism, affects about 0.45 million people worldwide, with a global birth prevalence of 1:23,930; the figure ranges from 1:4,500 in Italy to 1:125,000 in Japan [9]. Cystic fibrosis is most frequent in people of European descent: its incidence ranges from about 1:1,353 in Ireland to 1:25,000 in Finland and averages 1:4,500 in Western Europe [10, 11]. Duchenne muscular dystrophy, an X-linked disorder, has an estimated worldwide incidence of about 1:3,500 male births; long-term newborn screening in Wales found 1:5,136 [12].

Haemoglobin disorders are the most common monogenic diseases in the world. In 2010 an estimated 5,476,000 newborns were carriers of sickle haemoglobin and 312,000 were born with the homozygous form of the disease [13]. Nigeria (about 91,000 affected newborns) and the Democratic Republic of the Congo (about 39,700) carried the largest burden, and the number of

affected births is expected to grow by 2050 [14]. The high frequency of haemoglobin variants in tropical regions is explained by the protective effect of the carrier state against malaria, and carriers of haemoglobin disorders are found in a large part of the world population [15]. These geographical differences are illustrated in Figure 3 and summarised in Table 1.

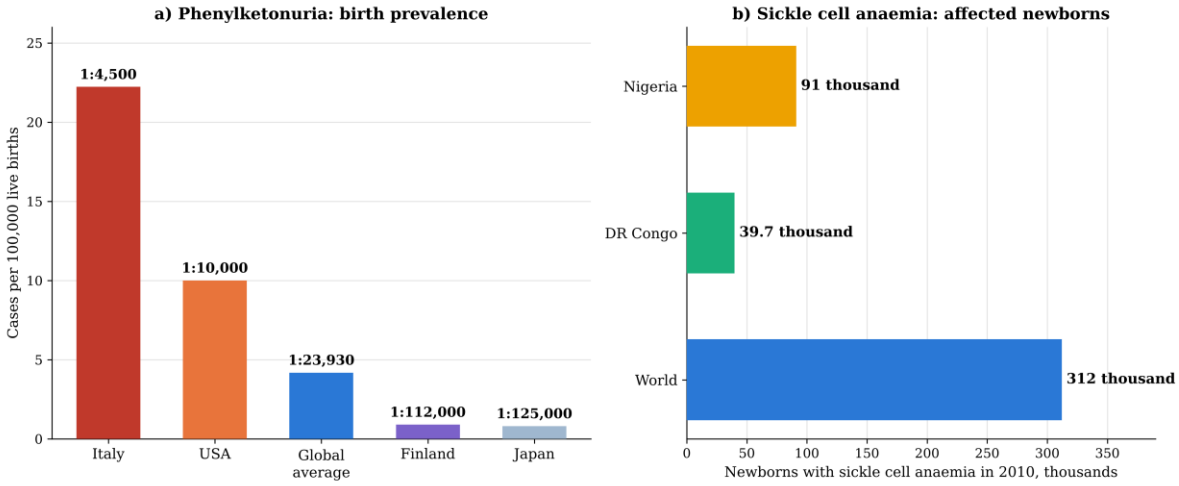

Figure 3. Geographical differences in the burden of gene diseases: birth prevalence of phenylketonuria (a) and number of newborns with sickle cell anaemia in 2010 (b) (based on [9, 13, 14]).

Table 1

Main characteristics of selected gene diseases

Disease	Gene (location)	Inheritance	Frequency	Main approaches to treatment
Phenylketonuria [9]	PAH (12q23)	Autosomal recessive	1:23,930 live births worldwide (1:4,500–1:125,000)	Newborn screening, low-phenylalanine diet
Cystic fibrosis [10, 11]	CFTR (7q31)	Autosomal recessive	≈1:4,500 in Western Europe (1:1,353–1:25,000)	Specialised care, CFTR modulators
Sickle cell anaemia [13]	HBB (11p15)	Autosomal recessive	≈312,000 affected newborns per year	Screening, hydroxyurea, transplantation, gene editing [16]
Duchenne muscular dystrophy [12]	DMD (Xp21)	X-linked recessive	≈1:3,500 male births	Multidisciplinary care; gene-based therapies under study

Disease	Gene (location)	Inheritance	Frequency	Main approaches to treatment
Spinal muscular atrophy type 1 [17]	SMN1 (5q13)	Autosomal recessive	—	Gene replacement therapy
Huntington disease [2]	HTT (4p16)	Autosomal dominant	—	Symptomatic; predictive testing and counselling

Consanguineous marriages increase the probability that both parents carry the same recessive variant inherited from a common ancestor. Such marriages are traditional in many communities of the Middle East, North Africa, Central and South Asia, and they are associated with a higher frequency of autosomal recessive diseases in the offspring [18]. The World Health Organization also lists consanguinity among the factors that increase the prevalence of rare congenital disorders [5]. This aspect is important for genetic counselling in regions where marriages between relatives remain common.

3. Molecular mechanisms of gene diseases

Pathogenic variants can affect the gene in different ways. Missense variants replace one amino acid with another; the classic example is the substitution of glutamic acid by valine in the sixth position of the β-globin chain in sickle cell disease. Nonsense variants create a premature stop codon, and the resulting messenger RNA is usually destroyed by nonsense-mediated decay. Small insertions and deletions shift the reading frame, splice-site variants disturb the removal of introns, and large deletions or duplications remove or add entire exons, as in most cases of Duchenne muscular dystrophy [2, 3]. A special group is formed by unstable trinucleotide repeat expansions, which increase from generation to generation and cause anticipation — earlier onset and more severe disease in subsequent generations, as in Huntington disease and myotonic dystrophy.

From the functional point of view, variants are divided into loss-of-function and gain-of-function variants. Loss of function usually leads to recessive disorders, because one normal copy of the gene is sufficient to maintain the function of the enzyme, as in PKU or cystic fibrosis. Dominant disorders arise when half of the normal amount of protein is insufficient (haploinsufficiency), when the abnormal protein interferes with the normal one (dominant-negative effect), or when the variant gives the protein a new harmful property [2]. Additional mechanisms include genomic imprinting, in which the expression of a gene depends on its parental origin, mosaicism and mitochondrial heteroplasmy, in which normal and mutant mitochondrial DNA coexist in different proportions [3].

Interpretation of a variant found in a patient requires a standardised approach. The joint recommendations of the American College of Medical Genetics and Genomics and the

Association for Molecular Pathology classify variants into five categories — pathogenic, likely pathogenic, uncertain significance, likely benign and benign — on the basis of population frequency, computational predictions, functional data, segregation in the family and other criteria [19]. The category "variant of uncertain significance" is particularly important for clinicians: such a variant should not be used for clinical decisions until additional evidence becomes available.

4. Patterns of inheritance

The mode of inheritance determines the risk for relatives and is the basis of genetic counselling (Figure 4). In autosomal dominant inheritance, an affected heterozygous parent transmits the disease to each child with a probability of 50%, regardless of the child's sex; the disease is usually seen in several generations. In autosomal recessive inheritance, both parents are usually healthy carriers, and each pregnancy carries a 25% risk of an affected child, a 50% chance of a carrier and a 25% chance of a child with two normal copies. In X-linked recessive inheritance, a carrier mother transmits the variant to half of her sons, who are affected, and to half of her daughters, who become carriers; an affected father cannot transmit the disease to his sons [2].

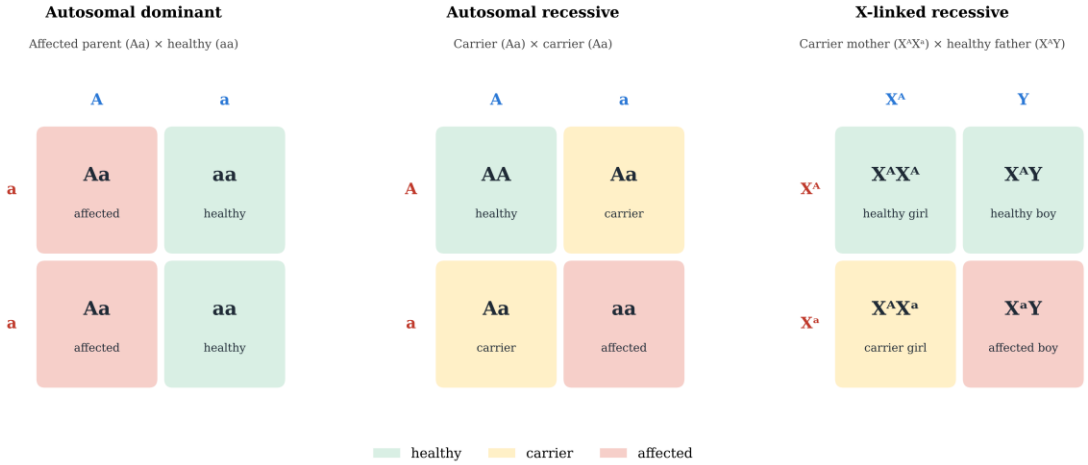

Figure 4. Probability of inheritance for the main Mendelian patterns: autosomal dominant, autosomal recessive and X-linked recessive.

In practice, these classical patterns may be modified by incomplete penetrance, variable expressivity, new (de novo) mutations, germline mosaicism and the action of modifier genes. Therefore, the first step of every genetic consultation is a carefully drawn pedigree of at least three generations. The use of standardised pedigree symbols, recommended by the National Society of Genetic Counselors, allows information to be exchanged reliably between specialists [20].

5. Selected gene diseases

Phenylketonuria is caused by variants in the PAH gene, which encodes phenylalanine hydroxylase. Deficiency of the enzyme leads to the accumulation of phenylalanine; untreated PKU results in severe and irreversible intellectual disability, seizures and other neurological problems, whereas early diagnosis through newborn screening and a phenylalanine-restricted diet allow normal development [9]. PKU was the first disorder for which population newborn

screening was introduced, and it remains a model of successful prevention of the consequences of a genetic disease.

Cystic fibrosis is an autosomal recessive disease caused by variants in the CFTR gene, which encodes a chloride channel of epithelial cells. Thick secretions lead to chronic lung infection, pancreatic insufficiency and other complications [11]. After the discovery of the CFTR gene, the survival of patients increased considerably owing to newborn screening, specialised care and, more recently, small-molecule CFTR modulators that improve the function of the defective protein [10]. Sickle cell disease and β-thalassaemia are caused by variants in the β-globin gene; they lead to chronic haemolysis, vaso-occlusive crises or dependence on transfusions and remain a leading cause of childhood mortality in countries without screening and treatment programmes [14, 15]. Duchenne muscular dystrophy, caused by variants in the very large DMD gene on the X chromosome, results in progressive muscle weakness in boys [12].

6. Chromosomal diseases

Chromosomal diseases are caused by numerical changes (aneuploidies), such as trisomy 21 (Down syndrome), trisomy 18 and trisomy 13, and sex chromosome aneuploidies such as 45,X and 47,XXY, as well as by structural changes — deletions, duplications, translocations and inversions. Down syndrome is among the most common severe congenital disorders, and advanced maternal age is a well-known risk factor for chromosomal abnormalities [5]. Small deletions and duplications that cannot be seen under the light microscope are detected by chromosomal microarray, which has replaced the conventional karyotype as the first-tier test for patients with developmental delay or congenital anomalies; its diagnostic yield in this group was about 15–20%, compared with about 3% for G-banded karyotyping [21].

7. Multifactorial and mitochondrial diseases

Most common diseases, including congenital heart defects, cleft lip and palate, neural tube defects, type 2 diabetes, hypertension and coronary heart disease, do not follow Mendelian patterns. They result from the combined effect of many genetic variants, each of which has a small effect, and of environmental factors such as nutrition, smoking, infections and medications [2, 3]. For such conditions, the risk for relatives is higher than in the general population but much lower than in monogenic diseases, and it increases with the number of affected relatives, the closeness of the relationship and the severity of the disease in the family. Empirical risk figures derived from family studies are therefore used in counselling.

The modern understanding of multifactorial diseases is based on the polygenic model, in which a person develops the disease when the total burden of genetic and environmental risk factors exceeds a certain threshold. Large genome-wide studies have identified thousands of common variants associated with these conditions, and population databases make it possible to compare the frequency of each variant in patients and healthy people [6]. Polygenic risk scores are being studied as a tool for identifying people at higher risk, but their clinical use is still limited.

Mitochondrial diseases form a special group. Mitochondria contain their own small circular genome, which encodes components of the respiratory chain. Variants in mitochondrial DNA are transmitted only from the mother, and a cell may contain a mixture of normal and mutant mitochondrial DNA. The proportion of mutant molecules (the degree of heteroplasmy) varies between tissues and between children of the same mother, which explains the great clinical variability and the difficulty of predicting the risk for offspring [2, 3]. Organs with high energy demand — the brain, muscles, heart and retina — are most often affected.

8. Modern laboratory diagnosis

The choice of laboratory test depends on the suspected type of disorder (Table 2). Karyotyping and fluorescence in situ hybridisation remain useful for aneuploidies and balanced rearrangements; chromosomal microarray detects copy-number variants; targeted gene panels are used when the clinical picture points to a defined group of disorders. Exome sequencing, which analyses the protein-coding part of the genome, has become the main tool for discovering new disease genes and for diagnosing Mendelian disorders [22]. Genome sequencing also covers non-coding regions and structural variants.

Table 2

Comparison of the main methods of genetic diagnosis

Method	What it detects	Main indications
Karyotyping	Aneuploidies, large structural rearrangements (balanced and unbalanced)	Suspected Down, Turner, Klinefelter syndromes; recurrent miscarriage
FISH	Specific microdeletions, rapid detection of aneuploidies	Confirmation of a suspected syndrome (e.g. 22q11.2 deletion)
Chromosomal microarray [21]	Copy-number variants (deletions and duplications)	First-tier test in developmental delay, autism, multiple anomalies
Targeted gene panel	Sequence variants in a defined group of genes	Disorders with clear phenotype and genetic heterogeneity
Exome sequencing [22]	Variants in protein-coding regions of almost all genes	Undiagnosed suspected Mendelian disease
Genome sequencing [23]	Coding and non-coding variants, structural variants	Critically ill infants, complex cases; highest diagnostic yield

The diagnostic advantage of sequencing has been confirmed by meta-analysis. In 37 studies comprising 20,068 children with suspected genetic diseases, the diagnostic utility of whole-genome sequencing was 0.41 and that of whole-exome sequencing 0.36, compared with 0.10 for chromosomal microarray (Figure 5); testing of parent–child trios further increased the likelihood

of diagnosis, and the authors concluded that genome and exome sequencing should be considered first-line tests in this group of patients [23].

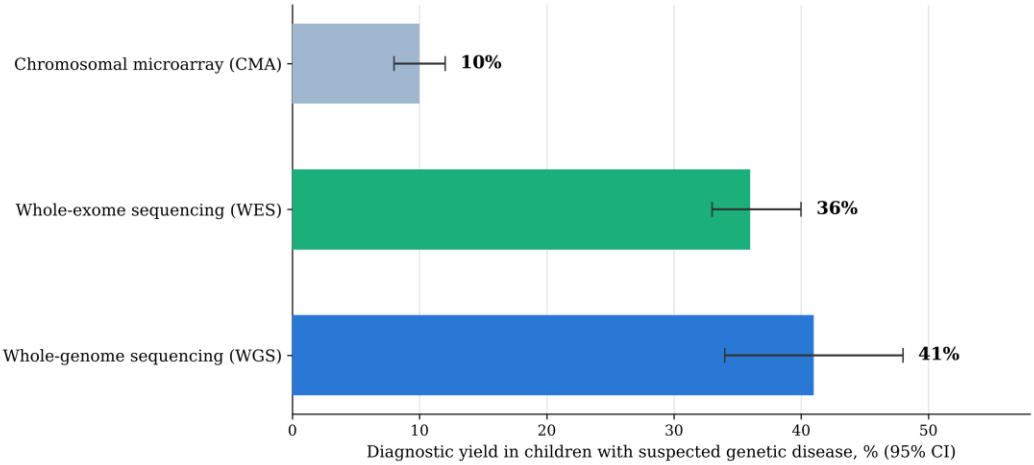

Figure 5. Diagnostic yield of chromosomal microarray, exome and genome sequencing in children with suspected genetic disease (based on [23]).

Correct interpretation of the results requires close cooperation between the laboratory and the clinician. The same variant may be classified differently by different laboratories, variants of uncertain significance are frequent, especially in populations that are under-represented in international databases, and the classification of a variant may change as new data accumulate [6, 19]. For this reason, reports of sequencing should be discussed with a clinical geneticist, the phenotype of the patient should be described as precisely as possible, and testing of parents (trio analysis) should be used whenever possible to determine whether a variant is inherited or has arisen de novo [23]. The development of national genomic databases is an important task for countries of Central Asia, whose populations are still poorly represented in global resources.

A genetic diagnosis is not only of academic interest. It ends the “diagnostic odyssey” of the family, allows the prognosis to be predicted, changes treatment in a significant proportion of patients, enables testing of relatives and provides the basis for prenatal or preimplantation diagnosis in future pregnancies [2, 23].

9. Prevention: screening and genetic counselling

Prevention of hereditary diseases is based on several complementary measures. Newborn screening identifies treatable disorders such as PKU, congenital hypothyroidism, cystic fibrosis and haemoglobinopathies before symptoms appear; by 2015, newborn screening programmes of different scope operated in many countries of the world, although coverage in low- and middle-income countries remained limited [24]. Carrier screening of couples, especially in populations with a high frequency of a particular disease or with consanguineous marriages, allows the risk of autosomal recessive disorders to be identified before or during pregnancy [15, 18]. Prenatal diagnosis by ultrasound and genetic testing and, where available, preimplantation genetic testing provide further options for families at risk [5].

The technical basis of newborn screening has also changed. Early programmes tested one disorder at a time with simple biochemical methods, whereas tandem mass spectrometry makes it possible to detect dozens of inborn errors of amino acid, organic acid and fatty acid metabolism in a single dried blood spot [24]. Some countries are now studying the use of genomic sequencing in newborns, but this approach raises questions about the interpretation of variants, the detection of untreatable or adult-onset conditions and the cost of follow-up care [19, 23]. The key principle of screening remains the same: a disorder is included only if early detection leads to effective intervention that improves the outcome for the child.

Genetic counselling links all these measures. Its tasks are to establish the diagnosis, explain the nature of the disease and its mode of inheritance, estimate the risk for relatives and future children, discuss the available options and support the family in making its own decision. Counselling should be non-directive and respect the values and beliefs of the family. Primary prevention of multifactorial congenital disorders, such as folic acid supplementation to prevent neural tube defects and vaccination against rubella, complements genetic measures [5].

10. Treatment: from diet to genome editing

For a long time, the treatment of hereditary diseases was limited to symptomatic care. Today several levels of therapy are available. Metabolic disorders can be controlled by diet, as in PKU; for some lysosomal storage diseases, enzyme replacement therapy is used; small molecules can correct the function of a defective protein, as CFTR modulators do in cystic fibrosis [9, 11]. Haematopoietic stem cell transplantation can cure some haemoglobinopathies and immune deficiencies but depends on the availability of a compatible donor.

Gene therapy aims to correct the cause of the disease at the level of DNA. Two main approaches are used: delivery of a functional copy of the gene with viral vectors, most often adeno-associated viruses for in vivo therapy, and ex vivo modification of the patient's own stem cells, which are then returned to the patient [7]. In a landmark trial, 15 infants with spinal muscular atrophy type 1 received a single intravenous dose of an adeno-associated viral vector carrying the SMN1 gene; all patients were alive and event-free at 20 months of age, compared with a survival rate of 8% in a historical cohort, and of the 12 children who received the high dose, 11 sat unassisted and 2 walked independently [17].

Other gene-targeted approaches act at the level of RNA. Antisense oligonucleotides are short synthetic nucleic acid molecules that bind to a specific messenger RNA and change its splicing or stability; this principle has been used, for example, to increase the production of functional protein from a back-up gene in spinal muscular atrophy and to skip mutated exons in some forms of Duchenne muscular dystrophy [7]. Unlike viral gene therapy, such drugs do not change the genome and usually require repeated administration. The choice between these approaches depends on the mechanism of the disease, the target tissue and the possibility of delivering the therapeutic molecule to the affected cells.

The CRISPR-Cas9 system, described as a programmable RNA-guided DNA endonuclease, has made precise editing of the genome possible [25, 26]. In the first clinical application for haemoglobin disorders, the patient's haematopoietic stem cells were edited at the erythroid enhancer of the BCL11A gene, which represses fetal haemoglobin; about 80% of alleles at the target locus were modified, and more than a year after treatment both the patient with transfusion-dependent β-thalassaemia and the patient with sickle cell disease had high levels of fetal haemoglobin and no longer needed transfusions [16]. These achievements open new perspectives, but they also raise questions of long-term safety, very high cost and equitable access, as well as ethical questions about germline editing [7, 26].

11. Ethical and social aspects

Advances in genetics raise ethical questions that every medical professional should understand. Genetic information concerns not only the patient but also his or her relatives, so the confidentiality of test results and the right of family members to know about their own risk must be balanced. Predictive testing for adult-onset diseases without effective treatment, such as Huntington disease, is carried out only after careful counselling and with the informed consent of an adult, and testing of children for such conditions is generally postponed until they can decide for themselves [2]. Results of exome and genome sequencing may include incidental findings unrelated to the reason for testing, and patients should be informed in advance about how such findings will be handled [19].

Social aspects are equally important. Families of children with hereditary diseases often face stigma, financial difficulties and limited access to specialised care, and the burden is heaviest in low- and middle-income countries, where nine of ten children with serious congenital disorders are born [5]. New therapies, especially gene therapy, are extremely expensive, which creates a risk of inequality between countries and social groups [7]. Germline genome editing, which would change the genetic material passed on to future generations, remains ethically unacceptable for clinical use according to most international scientific bodies, and the debate on its regulation continues [26].

12. Importance for dental practice

Many hereditary diseases have manifestations in the oral cavity, and the dentist is often the first specialist to notice them. Hereditary defects of enamel and dentine, such as amelogenesis imperfecta and dentinogenesis imperfecta, ectodermal dysplasias with missing and conical teeth, cleft lip and palate as part of genetic syndromes, and the dental features of Down syndrome — delayed eruption, hypodontia and a high prevalence of periodontal disease — require knowledge of their genetic background [2, 3]. Patients with haemophilia need special preparation before tooth extraction, and children with metabolic diseases on special diets may have a higher risk of caries. Recognising such patients, taking a family history and referring the family to a geneticist are therefore part of the professional competence of a modern dentist.

CONCLUSIONS

1. Hereditary diseases include gene (monogenic), chromosomal and multifactorial disorders. Of 6,172 rare diseases, 71.9% are genetic and 69.9% begin exclusively in childhood; together, rare diseases affect 3.5–5.9% of the world population.

2. The frequency of individual gene diseases differs greatly between populations: the birth prevalence of phenylketonuria ranges from 1:4,500 to 1:125,000, and about 312,000 newborns with sickle cell anaemia are born every year. Consanguinity increases the risk of autosomal recessive disorders.

3. The mode of inheritance determines the recurrence risk (50% in autosomal dominant inheritance, 25% for carrier parents in autosomal recessive inheritance, 50% for sons of a carrier mother in X-linked recessive inheritance), and a correctly drawn pedigree is the basis of genetic counselling.

4. Genome and exome sequencing have a diagnostic yield of 41% and 36% in children with suspected genetic disease, about four times higher than chromosomal microarray, and should be considered as first-line tests.

5. Newborn and carrier screening, genetic counselling and new methods of treatment, including gene replacement and CRISPR-Cas9 genome editing, are changing the prognosis of many hereditary diseases. Knowledge of medical genetics is also necessary for dentists because of the frequent oral manifestations of hereditary syndromes.

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