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HEREDITARY DISEASES

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ABSTRACT

This article provides information about hereditary diseases, their origin, genetic changes and their differences from each other, differences in chromosomes.

Hereditary diseases - diseases caused by the violation of genetic information (hereditary information); It is mainly caused by mutations in chromosomes or genes and is passed down through generations. Mutations can occur as a result of external environmental factors (ionizing rays, some biologically active chemical compounds) and negative effects on the body and cells. Hereditary diseases are mainly studied by the clinical genealogical method, in which a family tree is drawn up. With the help of this method (autosomal-dominant, autosomal-recessive and sex-related diseases) it is determined that they are inherited in different ways. In autosomal dominant diseases, the disease is controlled by autosomal dominant genes. In this case, the disease occurs in more than 50% of cases in each generation.

. Brachydactyly, arachnodactyly, retinoblastoma, certain types of psoriasis, etc. in this way it is passed down to generation after generation. If the parents have autosomal recessive pathological recessive genes, there is a chance of having a sick child, so these diseases do not occur in every generation. However, this probability increases when a family is formed between close relatives carrying the altered gene. These include phenylketonuria, mioclonia, epilepsy, certain types of oligophrenia and others.

Certain autosomal-dominant and autosomal-recessive (for example, a certain type of daltonism, hemophilia A, sideroachrastic anemia, etc.) are transmitted to offspring depending on sex.The method of twins is also used to study some characteristics of hereditary characters. It is known that twins are identical or fraternal. Identical twins are characterized by the same genotype and appearance (phenotype) and belonging to the same sex. Identical twins have different genotypes and differ from each other in appearance and sex. The method of twins allows not only to study the laws of

transmission of certain diseases, but also to determine the susceptibility of the organism to certain genes. It differs by chromosome and gene. Chromosomal disorders are mainly caused by changes in the structure and number of chromosomes, which account for 1% of newborns. Serious changes in the chromosome often limit the life activity of the organism and lead to the death of the developing fetus. These diseases are caused by changes in autosomes and sex chromosomes. These include syndromes such as Shereshevsky-Turner (karyoti-pi — XO), Klinefelter (XXY), Patau (trisomy 13), Down, "cat's scream" syndrome.

In general, in many chromosomal diseases, the structure of the human skeleton and nervous system changes, congenital defects of external and internal organs, retardation of growth, nervous, endocrine, etc. disorders of systems are observed, the generative activity of patients decreases.

Gene diseases are associated with metabolism caused by point mutations. Now more than 30 of them have been identified. For example, a disorder of fat metabolism is accompanied by a change in the activity of the central nervous system. The most severe of these is Tay-Sachs amaurotic idiocy, which is characterized by decreased visual acuity, dementia, and neurological symptoms.

Galactosemia triad associated with changes in carbohydrate metabolism. In this case, the enzymatic process that converts galactose into glucose changes, galactose and its products accumulate in cells and damage the activity of the central nervous system and organs. Diabetes is also associated with carbohydrate metabolism disorders.

In Bruton's disease, the synthesis of immunoglobulin fractions is disturbed, the disease mainly occurs in boys. In this case, children are born almost healthy, but it is determined that they are prone to infectious diseases already at the age of 3-4 months. Blood related hemolytic disease of the newborn. This is mainly due to the rhesus factor in the blood of the mother and the child, as well as the incompatibility of the blood groups of the couple.

Down syndrome is caused by an increase in the 21st chromosome. Today, one out of every 1,000 babies is born with this syndrome. Edwards syndrome is caused by an increase in the 18th chromosome. Mostly girls suffer from this disease. Many babies die before birth. Only 5-10 percent reach one year old. One in 5000 children is born with this syndrome. Patau syndrome - the 13th pair of chromosomes becomes trisomic. 80% of children born with this syndrome die before reaching one year of age. The probability of meeting is 1: 10,000 and 1: 21,700. Varkani syndrome is caused by an increase in the 8th chromosome. In 97.5% of cases, mental retardation occurs, and there are many other symptoms. It occurs in the ratio of 1: 50,000 (5000).

Schmid-Fracco syndrome is caused by the trisomy of the 22nd pair of chromosomes. It is also known as cat's eye syndrome. A rare disease.

Autosomal monosomic and deletion syndromesschhorn syndrome is caused by the absence of certain genes on the small arm of the 4th pair of chromosomes. The sex ratio is 1:2 – male:female. Relatively rare, 1: 50,000. Lives up to 30 years. Cat scream syndrome is caused by monosomic 5th pair of chromosomes. One in 50,000 children is born with this syndrome.

Williams syndrome is caused by the deletion of 27 genes from the 7th pair of chromosomes. In this syndrome, all children are born with mental retardation. IQ level will be below 50. One child out of 20,000 is born with this syndrome.

Jacobsen syndrome is caused by the deletion of certain genes on the 11th pair of chromosomes. In this case, 5-16 million DNA nucleotides will be deleted from this chromosome. Most children die before the age of 2. It is estimated that 1 in 100,000 children suffer from this disease. Smith-Magenis syndrome is caused by the deletion of certain genes in the small arm of the 17th pair of chromosomes. It causes mental weakness. It occurs in the ratio of 1: 15,000 and 1: 25,000.

This list can be continued for a long time. Chromosomal syndromes show many symptoms and result in many diseases. In most cases, these syndromes sharply reduce the viability of a person, and he dies in the early stages of ontogenesis. There may be a condition related to the pathology of white blood cells - leukocytes. For example, it is known that gene mutations play a role in the development of leukemia. Hemophilia is also a hereditary disease of the blood system, in which, mainly, blood clotting properties decrease; the synthesis of some proteins involved in blood coagulation is disturbed.

Medical genetics deals with its detection and prevention. Its main task is to determine its spread, the possibility of the birth of a child with a hereditary disease in the family. The cytogenetic method has a special place among other methods in the study of human genetic pathology. With the help of this method, it is possible to study the foundations of heredity, the norm and pathology of the human karyotype, certain laws of mutational and evolutionary processes.

DNA testing only became commercially available in the 1980's. Before that, identity or paternity testing in that sense, used to be tedious. Testing last century relied on fairly inaccurate indirect laboratory techniques such as blood grouping, eye or skin colour, and until the late 1980's not much had changed. The invention of the polymerase chain reaction (PCR) allowed a technique where incredibly small samples of DNA could be detected and amplified in a test tube to give sufficient yield for DNA testing. Lengths of DNA segments similar to supermarket 'bar codes' could be run out on agarose gels using techniques including Southern blotting and more recently microsatellites and single nucleotide polymorphisms ('SNiPs'), allowing comparison of the samples from (ideally) a child, the mother and the so called 'putative father'. Matching of the samples can now fairly confidently confirm or exclude paternity. Older techniques where mismatch of blood groups made paternity less likely, did not allow reasonable proof of paternity to be achieved. Samples using forensic techniques can now be obtained from microscopic smears of DNA from crime scenes, dental floss, beer glasses and other personal items. The offence of unlawful DNA theft was introduced into legislation in 2004 and the law now prevents unlawful theft of DNA through the 2005 Human Tissue Act where it is an offence to remove DNA 'without permission' so if you want to test a neighbour's dental floss retrieved from their rubbish bin (for example) to see what genetic disorders they may have, you now should obtain their permission first. Employers cannot test employees for

hereditary disorders either – they have a duty to make the workplace sufficiently safe, so if an employee has a genetic tendency to asthma, their working environment should have sufficient air quality to allow them to work adequately.

When I started working in genetics in the 1980's, Duchenne muscular dystrophy – a sex-linked recessive disorder - was uniformly fatal and diagnosed fairly late at around six years of age in boys. They had rapid progression to long leg bracing and death in adolescence from respiratory failure. Identification of the dystrophin gene in 1987 was the first major advance in allowing family screening and earlier diagnosis. In cases where the mother could be confirmed as a carrier, reproductive choice became possible, and accurate carrier testing became available for other family members. Especially those who could now be defined as having a low risk, who previously could not be reassured with certainty. Testing of affected boys now results in a molecular diagnosis in most cases, allowing confirmation without muscle biopsy. Biopsy in the latter part of last century was usually open and required an anaesthetic, neither of which parents of affected boys were particularly keen on. The dystrophin gene unfortunately is one of the largest genes in the human body with 79 exons, so testing was tedious and time consuming. Early studies suggested that frameshift mutations caused the severe Duchenne phenotype, and in-frame deletions caused a milder Becker phenotype. We now know that there is a continuum of mild to severe phenotype rather than two distinct ends of a spectrum. Numerous mutations occur and alter the dystrophin transcript and resulting protein expression in several ways. We now know that 'leakage' occurs where some patients with large gene deletions still express low levels of high molecular weight and semi functional dystrophin. Therapy with antisense oligomer induced exon skipping in patients with leaky mutations allows an increase of the dystrophin above baseline levels and helps restore muscle function to patients with a Duchenne phenotype . Diagnosis is now possible in utero and using pre-implantation diagnosis can allow an unaffected embryo to be implanted into the mother. Cell free non-invasive DNA blood testing at around 8 weeks gestation can help a mother find out (by analysing small cell fractions of fetal material in the maternal venous circulation) if she is carrying a male or female fetus, and if female, she can relax for the rest of the pregnancy knowing she does not carry a male fetus that could be potentially affected.

Down syndrome was described by Dr John Langdon-Down in his article on the ethnic classification of idiots. I know some of you may still employ this classification for the grading of NHS managers. It is well recognised that patients with trisomy 21 have greater muscle fatigue than normal individuals. It has long been suspected that the extra genes on chromosome 21 interfere with regulation of muscle expression. Usually babies with trisomy 21 are tested at birth, not to confirm the diagnosis as it is usually fairly obvious clinically, but to check if they are the 95% of Down syndrome babies born due to non-dysjunction (which is more common with increased maternal age), the 2% that are mosaic with abnormal cell division occurring post-zygotically (a small proportion of certain cells may be Down syndrome and these children are typically very mild with few features), or most importantly, the 3% that are

translocation Down syndrome where a balanced rearrangement of a parental chromosome may recombine to cause a familial type of Down syndrome with a risk of recurrence. The parents of translocation Down syndrome have a high risk of recurrence – often around 10%, whereas mosaic cases usually have a negligible risk as they occur as a post-zygotic event. In all but the mosaic cases, muscle fatigue is well documented. Recent physiological studies confirm that there is a 40-70% decrement in knee extensor strength, typically giving a 20 year old with Down syndrome the equivalent muscle strength of a 70 year old. Transgenic mice models have often given clues as to whether genes are downregulated or upregulated in certain genetic disorders and the Ts65Dn mouse has shown that of the 159 genes equivalent to the human, on chromosome 21, 106 are downregulated and 53 are upregulated. When genes with known function regulating muscle physiology are looked at – several genes with a role in neuromuscular transmission are down regulated as are genes in skeletal muscle structure and function. Experimental muscle physiologists have concluded that overall in Down syndrome, there is normal muscle in the non-fatigued state, but abnormal post-exercise fatigue occurs and this is mediated by clear mitochondrial limitation. Evidence shows that exercise training including circuit training helps improve the recovery phase and reduces inflammatory cytokine activity so children with Down syndrome should be encouraged to lead as active a life as possible. In years gone by, often such children were put in an institution and suffered early death and intellectual deficiency as would we all if we were forbidden to exercise and given no formal education. The inference from mouse model studies suggests that if children with Down syndrome have good levels of fitness and are educated in the best schooling possible, then their educational attainment and life expectancy will considerably improve. We now find that lifespan has increased sufficiently that adult rheumatology clinics are utilised by 80% of adults with Down syndrome due to progressive arthritis and some often have earlier onset of dementia because of abnormal regulation of an extra amyloid beta precursor protein gene on chromosome 21.

In conclusion, We have seen great advances in genetic testing from early karyotyping to the latest DNA technology. Whole genome screening is already possible and the technology available and the costs to utilise it are improving in a similar way to the speed of computer chips over the last decade. Several famous individuals have had their genome analysed including Black Sabbath singer John Michael 'Ozzy' Osbourne whose ADH4 gene allows him to metabolise alcohol very speedily and combined with his CLTCL1 gene giving him the propensity for addictive behaviour, and his increased proportion of Neanderthal DNA, means he can still sing and provide entertainment for the public for many more years to come. He presumably also has a gene for musicality and this may someday be identified on a further analysis of his DNA.

Commercial companies such as 23andMe can provide over the counter or web based mouth swab tests for all sorts of curious genes including telling you if your lower or upper back is hairy or not, and if your ear wax is wet (European ancestry) or dry (South East Asian ancestry). You may

not necessarily impress your friends with such test reports on yourself as they may say you could have saved your money by either looking at the reflection of your back in the mirror or sticking a finger in your ear. Whole genome technology does open the exciting prospect of having your personal genome checked on an admission to hospital, if not at birth, and the attending clinician can then check your predisposition to genetic diseases, microbiological and pharmaceutical sensitivities and responses, and personally tailor your treatment with what we now call 'precision medicine'.

Whether being told what genetic predispositions you might die of, will adjust individual behaviour any more than the advice we give today, I think is still unlikely. In twenty years' time we will be much better at the diagnosis and treatment of patients admitted to this hospital, but prevention may still remain very much an individual choice as it is today.

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