Upsala J Med Sci 111 (1): 35–43, 2006

From Rosén von Rosenstein to HUGO (The Human Genome Organization)

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INTRODUCTION

The situation of health for children in Sweden in the middle of the 1700 century was very bad with an infant mortality of 50-60 %. Rosén von Rosenstein made outstanding contribution for better child health and sick care through research and teaching, which tremendously improved child care and social conditions in Sweden. One of the most important effects of this was a marked falling in infant death rate. He pointed out that a child was not an incomplete variant of the adult and that children had special needs and specific diseases, which required specific therapy and that deficiency states and diseases could be prevented. This is in line with clinical genetics, the ultimate goal of which is the prevention and management of genetic diseases.

Rosén von Rosenstein defended his thesis "*De historiis morborum rite consignandis*" (On the writing of case reports) in 1730,where he pointed out the importance of a detailed case and family history, which also is basic in clinical genetics.

MEDICAL GENETICS IN PERSPECTIVE

Inheritance patterns have been a subject of interest from time immemorial. The oldest pedigree is on horse breeding in Mesopotamia 5 000 years ago (Fig.1) It was prescribed in Talmud that the sons of women, who had given birth to a son who had bled to death after circumcision, as well as the sons of her sister, should exempt

Received 3 Octorber 2005
Accepted 17 October 2005

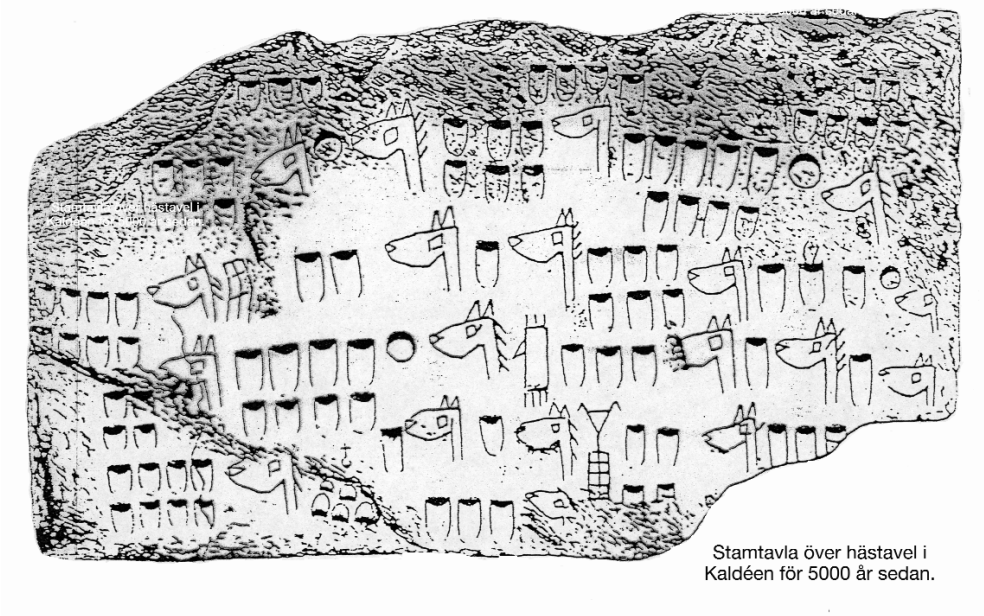
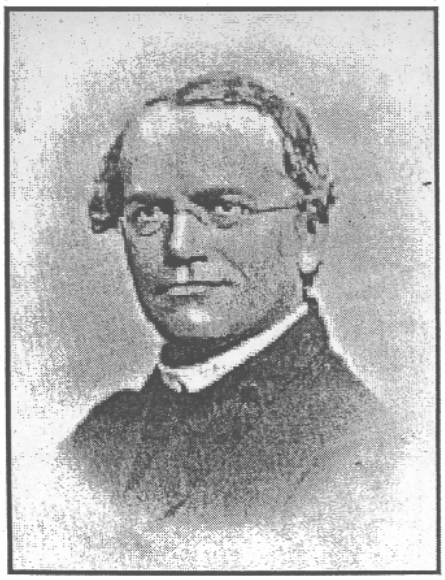


Fig 1. Pedigree illustrating horse breeding 5,000 years ago, from Kaldeén, Mesopotamia.

from the procedure. This may well be the first recorded example of genetic counselling. Thus, the Jews understood already many thousand years ago that haemophilia is a sex linked disorder only affecting males.



Gregor Mender_ Wikipedia, den fria encyklopedin

Fig 2. Portrait of Gregor Mendel.

The Austrian monk Gregor Mendel (Fig.2), the father of genetics, could by performing a series of cleverly designed breeding experiments on garden pees formulate the fundamental laws of heredity, published in 1865.His laws on the patterns of inheritance received no recognition until 1900 when they were rediscovered.

Probably the most important achievement in biologal research of the last century was the identification and deducing of the correct physical structure of DNA by James Watson and Francis Crick in 1953.This formed the basis for molecular genetics.

In 1956 M.J.Tjio and Albert Levan (Fig.3) showed the normal human chromosome number to be 46,which cleared the way for clinical cytogenetics.

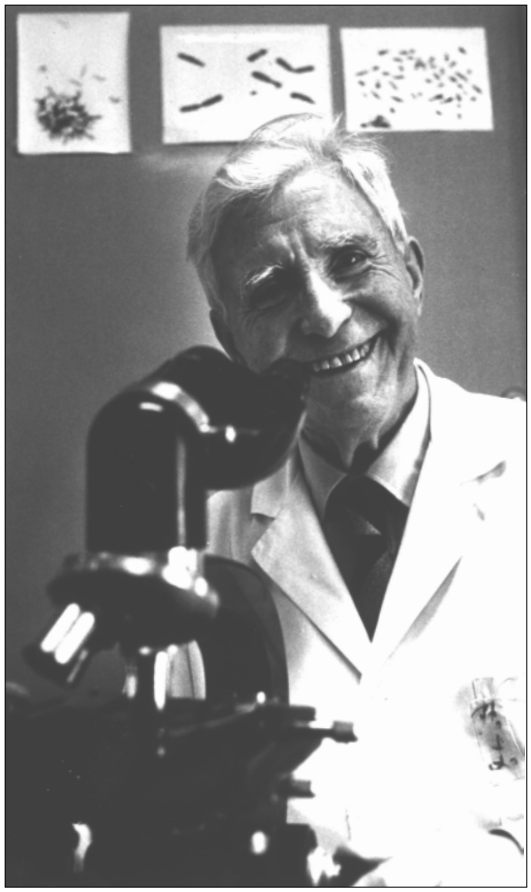


Fig 3. Albert Levan at the microscope.

In 1959 Jerome Lejeune and colleagues described the first chromosomal disorder in humans, trisomy 21 in Down´s syndrome. This was the beginning of clinical cytogenetics. The development of chromosome banding by Torbjörn Caspersson and Lore Zech (Fig.4) in 1968 increased the possibility to identify small chromosome abnormalities and by now more than 1000 different chromosome aberrations have been reported.

The most impressive advances have been in the area of molecular genetics. During the last 25 years several thousands of genes have been mapped to specific chromosomes, and molecular defects causing a great number of genetic defects and diseases have been identified. In 2003 the Human Genome Project provided the complete human DNA sequence. This is providing us with the first holistic view of our genetic heritage. The human genome contains 3 billion base pairs of DNA that contains approximately 30,000 protein coding genes.

During the course of the last century the disease panorama has very much changed. The importance of infectious diseases and malnutrition has diminished drastically, at least in developed countries, and the importance of genetic diseases has increased. Medical genetics was once confined to rare disorders seen by paediatricians and a few other specialists. It has now become a field of central importance for our understanding of most diseases. The diagnosis, prevention and treatment of many disorders have been influenced by molecular medicine. Most of the common disorders such as diabetes, allergic diseases, hypertension, and common birth defects as mental retardation, heart malformations, cleft lip and cleft palate have been shown to mainly have a multifactorial etiology and result from interplay of multiple genes with environmental factors. Genetic diseases are thus a significant cause of illness and death. Those individually rare conditions are in aggregate a large cause of morbidity and mortality. About 8 per cent of all children have a severe genetic disease or birth defect or will during their life develop a severe genetic disorder. Accordingly many children are nowadays recog-

nized as suffering from genetic conditions. It has been estimated that about a third of all admissions to paediatric hospitals are due to diseases with a genetic component.

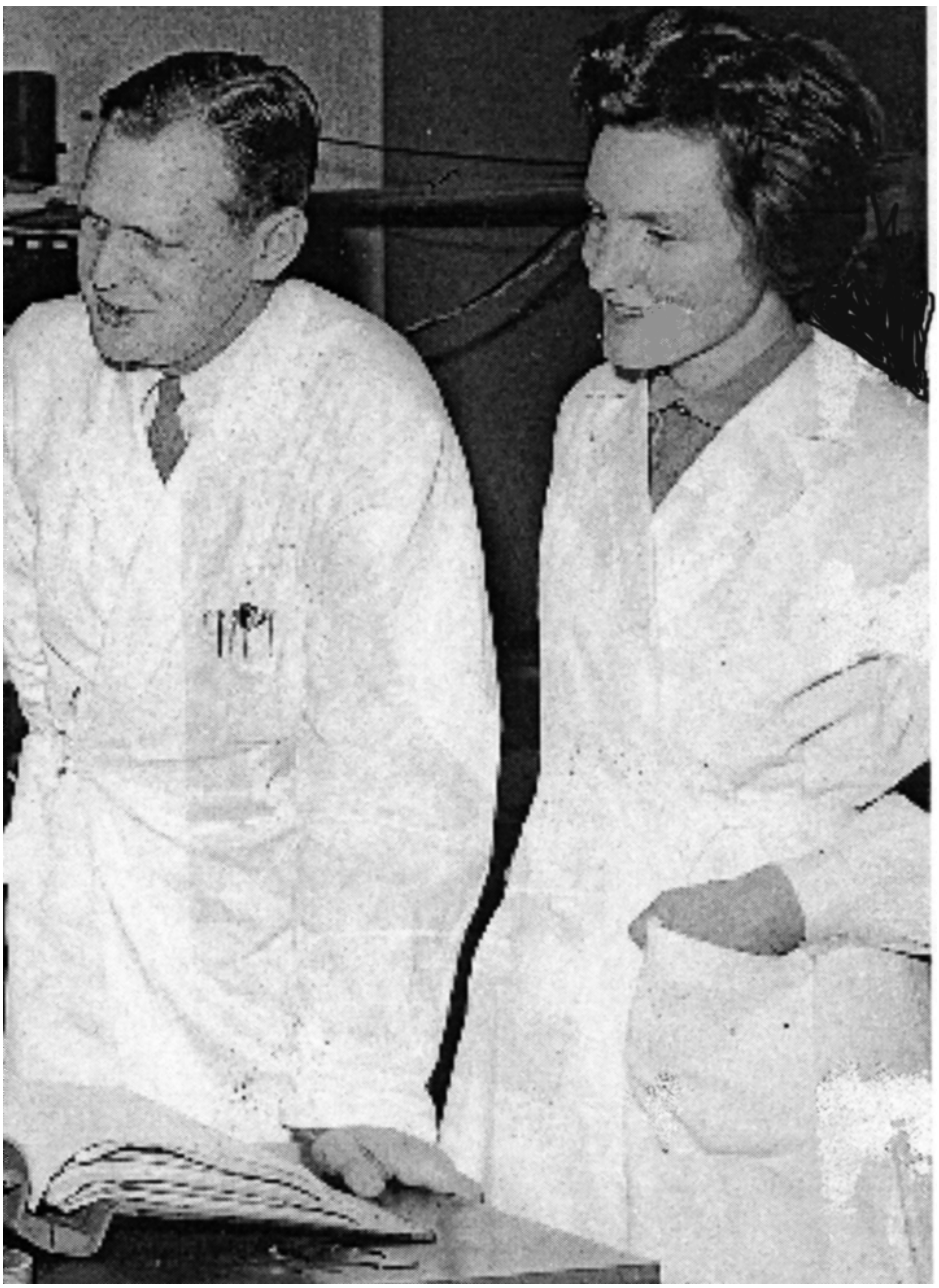


Fig 4. Torbjörn Caspersson and Lore Zech in the chromosome laboratory.

MAJOR TYPES OF GENETIC DISORDERS

Genetic disorders can be classified in 5 major categories; chromosome disorders, single gene defects, cancer, multifactorial disorders, and mitochondrial disorders.

Chromosome disorders

Chromosome abnormalities are a leading cause of mental retardation and pregnancy loss.

In Sweden about 60 of 10,000 live-born children have a chromosomal aberration, visualized under microscope.

Autosomal numerical aberrations are seen in 12 of 10,000 new-born infants. They have as a role an extra autosome, caused by nondisjunction. Most common is Down´s syndrome with an extra chromosome 21, seen in one of 800 new-borns. Autosomal monosomies are almost always lethal.

Twenty-four of 10,000 new-born infants have a microscopically observable structural autosomal aberration, usually a deletion. With the use of advanced molecular techniques, especially fluorescence in situ hybridisation(FISH) and metaphase based comparative genomic hybridisation(metaphase-CGH)of the chromosomes it is possible to visualize genetic alterations directly on interphase nuclei and metaphase chromosomes. They are powerful but relatively labour intensive techniques that allow detection of deletions, duplications, rearrangements and mapping of translocation break points. A new technology, microarray based comparative genomic hybridization (array-CGH), allowed the resolution of the analysis to increase enormously. In this method a chip has been dotted with DNA from many thousands of genes. These genes function as probes for detecting which genes are missing or active in different tissues or cells. This method has permitted detection of a large number of micro-deletions and some micro-duplications that are too small to be observed microscopically. The use of cDNA clones as array targets has the advantage of assessing both DNA copy number and gene expression on the same platform. These techniques have often made it possible to specify the critical region of the chromosome that has to be deleted or duplicated to cause a specific syndrome. Many of these microdeletion syndromes have earlier been regarded as monogenic conditions.

Twenty-six of 10,000 new-born boys and 13 of new-born girls have a sex chromosomal aberration.

Chromosome abnormalities are seen in 50% of first-trimester and 20 % of second-trimester spontaneous abortions.

Monogenic disorders and some ethical considerations

Monogenic disorders show Mendelian inheritance. The majority of monogenic disorders are caused by single base mutations resulting in structurally abnormal proteins. In September 2oo5 the on-line edition of McKusick´s Mendelian inheritance in man lists more than 15,000 known human monogenic traits. Of these 14,000 are located on auto-

somes, 800 on the X chromosome and 43 on the Y chromosome. The mutated genes have in many cases been mapped to specific locations on the chromosomes, cloned, sequenced and the protein identified. This research has lead to new important knowledge not only in genetics but also in the basic pathophysiology of the diseases.

To the monogenic disorders also belongs a group of disorders, called trinucleotide repeat disorders, where the mutation involves the amplification of a DNA sequence that contains repeats of three nucleotides. About 20 diseases caused by such repeat expansions are known, among them the fragile-X syndrome, Huntington´s disease, myotonic dystrophy and Friedreich´s ataxia. The repetitive sequences are also present in the genes of normal individuals but they are amplified many times in the genes of affected persons. The lengths of the trinucleotide repeat tends to increase as the gene passes from parent to offspring, by which the disease gets progressively more severe through successive generations, so called anticipation.

The diagnosis of a genetic disorder is only justified if it is of benefit for the patient or the family. The development of DNA-based genetic tests is tremendously rapid and the growing gap between genetic testing and treatment possibilities constitutes an ethical dilemma. The molecular genetic research will further accentuate this, but generates also new knowledge and treatment possibilities, which are necessary to correct this imbalance.

Many children are suffering from monogenic disorders and it is usually important to make an early diagnosis of a genetic disorder. That the disease affecting a child is genetic may, however, have far-reaching consequences for the family, which require careful consideration. It is important for the paediatrician to help the child and the family to adjust to the new circumstances, once the diagnosis of a genetic disease is made.

With the development of DNA-based genetic testing, pre symptomatic diagnosis has become available for many inherited disorders. By informing individuals that they are carriers or not carriers of a genetic disease-causing mutation, carrier testing can aid in making reproductive decisions. Predictive genetic testing is usually appropriate if the child at risk for the disease can be successfully treated early. However, if the disease does not present itself until adulthood and there is no useful treatment to be made, a predictive testing could have deleterious effects. The principles of genetic integrity and the right of self-determination are crucial in these circumstances. If the child is tested then it loses the opportunity to make its own decisions as an autonomous adult. A predictive testing could also have adverse consequences for insurance or employment in the future.

Who is to be counted as a child in relation to genetic information? It is obvious that a child of preschool age is not competent to make decisions on genetic risk and genetic tests.

I believe that it is wrong to adopt a sharp age-related criterion to draw a line between childhood and adulthood. Some 15-year-old individuals are as intellectually and emotionally mature as some 18-years-old.

Cancer

Mutations of cell regulatory systems, usually gain or loss of chromosomes or chromosomal segments in somatic tissues, with loss of the normal controls over growth and differentiation, are the primary basis of carcinogenesis. Familial cancers make up 5-10% of the most common solid tumours with debut in adulthood. However, most solid tumours in childhood as well as leukemias and lymphomas are not hereditary (non-familial).

Identification of genes involved in cancer and classification according to genetic defects have often been useful to predict response to specific treatments and clinical outcome. Thus, DNA microarray tools are now extensively used for study of the molecular bases of cancer. Gene expression profiles can also be used for identifying subtypes of the cancer to achieve specific and better treatment.

Multifactorial disorders

Multifactorial inherited traits and conditions result from interplay of multiple genes with multiple environmental factors, where a combination of genes from both parents, in addition to often unknown environmental factors, produce the trait or condition.

Many quantitative traits, such as intelligence, height and weight are multifactorial. Because they are caused by additive effects of many genes and environmental factors, each of which having a relatively small effect, these traits tend to have a normal distribution in the population.

Most of the common major malformations, such as cleft lip and/or palate, club foot, neural tube defects are multifactorially inherited. Often one gender is affected more frequently than the other in multifactorial traits. There appears to be a different "threshold of expression", which means that one gender is more likely to show the malformation over the other gender. For example, hip dysplasia is many times more common in females than males and pyloric stenosis is more likely in males.

Most of the multifactorial disorders such as diabetes and psychoses are seen primarily in adolescents and adults. Multifactorial traits do recur in families, because they are partly caused by genes. The recurrence risks are usually based on empirical data. The risk to siblings or offspring is lower than Mendelian risks, often falling somewhere near 3% when there is one affected person in the family. The risks increase when more family members are affected and if the parents are related. The risk for a multifactorial trait or condition to happen again depends also upon how closely the family member with the trait is related to you. For example, the risk is higher if your brother or sister has the trait or disease, than if your first cousin has the trait or disease.

There are often small subsets of the population where the disorder may be caused by a single gene with a large effect and environmental factors with small individual effects and show monogenic inheritance. Identifying specific genes responsible for common disorders is an important goal, since only then we can understand the pathogenesis of the disease.

Mitochondrial disorders

Human mitochondria are cytoplasmatic organelles which have their own unique DNA(mDNA). Mitochondrial DNA has a high mutation rate. Each cell contains sever-

al hundreds or more mitochondria. Several copies of a small, double-stranded, circular mDNA molecule exist within each mitochondrion. The mitochondria are transmitted in the ovum from the mother to all her children (maternal inheritance).Through oxidative phosphorylation the mitochondria produce adenosine triphosphate(ATP),the energy source essential for cellular metabolism. Mitochondria are thus very important for cell survival. Different tissues vary in the extent to which they depend on this energy production. Mitochondrial diseases are complex multi-system disorders. The phenotypic effect depends on the location and type of mutation and also on the proportion of mutated mitochondria which are involved during the course of the individual.

The mutations cause diseases, which in older children and adults, are characterized by neuromuscular symptoms such as ataxia, ophtalmoplegia, myoclonic epilepsy, dementia, stroke-like episodes, heart failure and myopathia. There is a very severe form in infants (Pearson´s syndrome), which is characterized by pancreatic insufficiency, pancytopenia, and lactic acidosis.

Mitochondrial mutations can also be seen in some common human diseases as deafness, non-insulin-dependent diabetes and schizofrenia.

CONCLUDING REMARKS

Although most genetic disorders can still only be treated symptomatically and with supportive care, recent progress in research has lead to effective treatment for many genetic diseases. Current research, particularly in the areas of enzyme replacement and gene therapy gives promise for future treatment possibilities.

The main goal for clinical genetics is true primary prevention, which is in line with Rosén von Rosenstein´s goals, presented in his Textbook on Paediatrics published in 1764.

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