EUROBRAIN

Genes and the brain

GENES AND THE BRAIN

INTRODUCTION

Each year, the European Dana Alliance for the Brain (EDAB) organises a public lecture on topical area of neuroscience in a different European country.

The first was held in 1999 in London in honour of Professor D. Marsden, a specialist in Parkinson's disease.

The second, of which a digest is included in this leaflet, took place in December 2000 at the University of Bern on the theme "The genome and the brain". Two specialists, Professor Christian W. Hess, Head of the Service of Neurology at the Inselspital at Bern and Professor Gérard Waeber, of the Department of Internal Medicine at the Centre Hospitalier Universitaire Vaudois (CHUV) at Lausanne, spoke on this occasion. One dealt with hereditary aspects of neurological pathologies, while the other turned his attention to possible interactions between psychiatry, neurology and metabolic diseases, although still from a genetical point of view. Both speakers explained how the decoding of the human genome last year has opened up new perspectives for the diagnosis and possible therapy of certain disorders, especially those involving the nervous system.

The next conference will be hosted by Germany on the 6th June 2001 at Göttingen, during the meeting of the German Neuroscience Society, followed by one in Paris in July 2002, during the Forum of the Federation of European Neuroscience Societies (FENS).

These EDAB public lecture are the opportunity for the interested public, not necessarily well-informed in the medical field, to hear about the most recent progress in fundamental research in the field of the neurosciences and its relationship to the clinical situation.

Béatrice Roth, PhD
EDAB, Lausanne

CONTACT

Béatrice Roth, PhD
Institut de Physiologie
7, rue du Bugnon
CH–1005 Lausanne
Switzerland
Tel./Fax: +41 21 692 55 25
dana1997@iphysiolsg1.unil.ch
www.unil.ch/edab

Elaine Snell
Vicarage House
58-60 Kensington Church Street
London W8 4DB, U.K.
Tel.: +44 207 937 7713
Fax: +44 207 937 4314
edab@which.net
www.edab.net

The European Dana Alliance for the Brain

Diabetes, psychiatry and neurological disease: Is there a genetic relationship?

Gérard Waeber

EPIDEMIOLOGICAL LEVEL

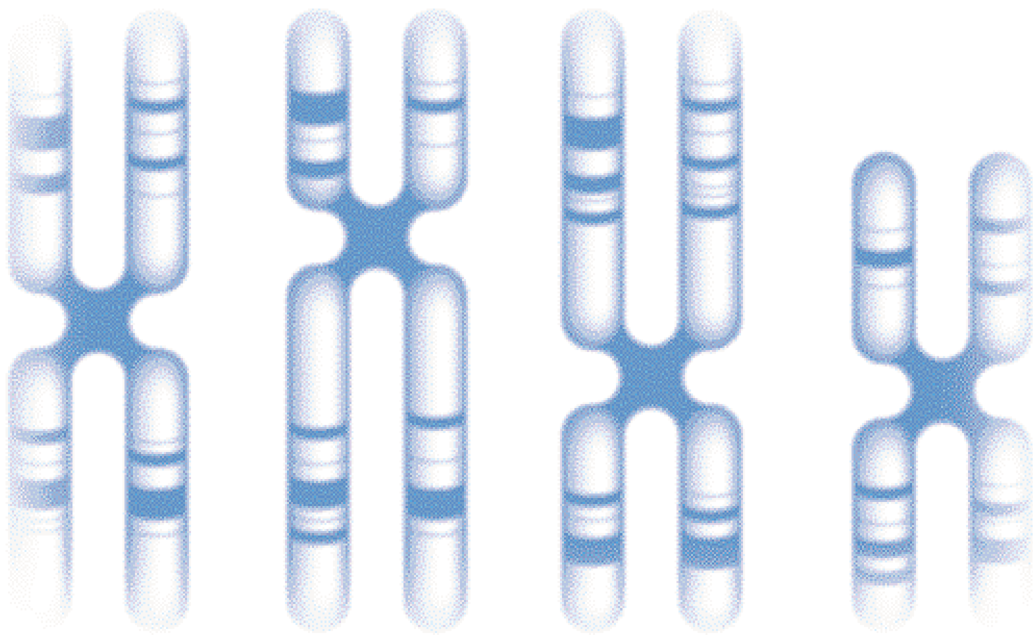
At the epidemiological level, psychiatric, neurological and metabolic diseases have many similarities. Several disorders involving these fields of medicine have a polygenic origin and a high prevalence. By way of an example, it is estimated that more than 15 million Americans suffer from an addiction, including alcohol addiction, that epilepsy affects more than 2.5 million Americans and that multiple sclerosis affects more than 350,000 people. Deafness, considered as a neurological disorder, affects more than 10% of the American population.

At the metabolic level, the World Health Organisation (WHO) has publicised the equally disturbing figures that 6 to 7% of the world population suffers from diabetes, i.e. approximately 16 million people in the United States. Approximately 800,000 new cases of diabetes are diagnosed each year in the United States and the number of people affected in the next ten years is going to increase to 23 million. The WHO has granted diabetes the moot privilege of being the first non-infectious disorder meeting the criteria for epidemic dissemination. Deaths due to cancer, stroke or cardiovascular diseases are on the decrease, whereas mortality due to diabetes has increased by 30 percent in the last 12 years. Globally, psychiatric, neurological and metabolic diseases represent a very high cost in human and economic suffering.

In addition to these disturbing figures, there is another common denominator in all of these disorders, in that they are all diseases with a polygenic origin, the phenotypic expression of which results from the interaction between conditions disposing to susceptibility, i.e. genetically determined, and environmental factors. Now that the human genome has been entirely sequenced, it is possible to determine whether a single gene is responsible for both metabolic and neurological disorders. It is currently estimated that our genomic repertoire is made up of approximately 40,000 genes. In 2001, only 12,000 genes have been well described in terms of their structure and they code for proteins with a known function. However, only 1,129 of these genes are currently formally associated with a human disease. This means that, although the first genes for monogenic disorders have been identified in man, almost none of the genes contributing significantly to polygenic disorders have been identified.

COULD THERE BE A GENETIC RELATIONSHIP BETWEEN PSYCHIATRIC, NEUROLOGICAL AND METABOLIC DISORDERS?

At the epidemiological level, certain prevalence figures are intriguing. For example, the prevalence of depression in the United States is estimated to be 4% in the general population and greater than 17% in diabetic patients. In addition, in a series of publications evaluating patients suffering from manic-depressive psychoses, it was estimated that the prevalence of diabetes is 3 times higher in manic-depressive patients than in an age-controlled group. These figures are difficult to interpret, since the high prevalence of diabetes in depressive

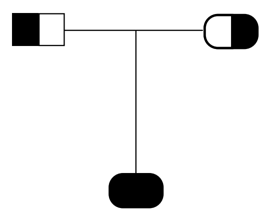


patients or those suffering from manic-depressive psychosis could perhaps result from psycho-social factors specific to the basic disease, the biological consequences of diabetes, or even from side effects of certain medications. However, we cannot exclude the possibility that a common organic abnormality, especially a genetic abnormality, plays a part as a susceptibility factor.

This can be illustrated by a few examples from medical genetics. In 1998, the team of Professor Allen Permutt described the identification of a gene called wolframin on chromosome 4 which, when mutated, is responsible for Wolfram syndrome. This is a neuro-degenerative disorder, known since 1938, which combines diabetes, optic atrophy and deafness. The wolframin gene codes for a membrane protein found in the central nervous system and also in the islets of Langerhans, which produce insulin. Interestingly, children who are homozygous carriers of a mutation of the wolframin gene present the dramatic picture of Wolfram syndrome, whereas the parents, who are heterozygous carriers of the mutations of the gene in question, do not have the Wolfram syndrome phenotype. These heterozygous carriers of the wolframin gene are 26 times as likely to be hospitalised for psychiatric disorders, especially manic-depressive psychosis-type diseases (fig. 1). These data indicate that total haploinsufficiency for the wolframin gene results in a dramatic syndrome including diabetes, whereas partial haploinsufficiency (heterozygote) is a major risk factor for a psychiatric disease. This example illustrates the fact that a common gene can have very different phenotypic manifestations, which can be neurological and psychiatric as well as metabolic.

WOLFRAM SYNDROME

Figure 1: Wolfram syndrome leads to a severe phenotype when the carrier is a homozygote. In contrast, heterozygous carriers of the mutation of the wolframin gene do not have the Wolfram syndrome phenotype, but instead have a high risk of developing a psychiatric disease.



Nature Genet, 20, 1998 – Am J Psy, 148, 1991 – Lancet, 336, 1990

AT THE EXPERIMENTAL LEVEL

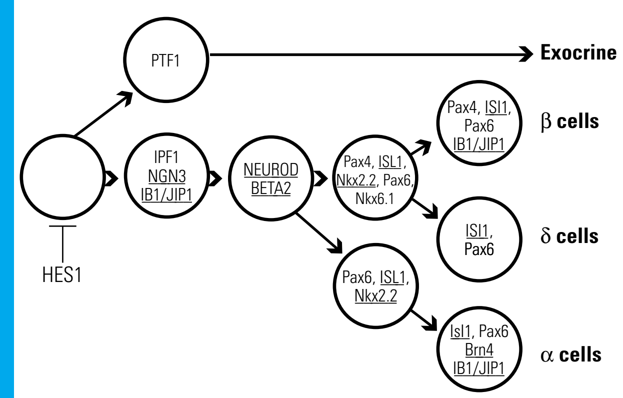
At the experimental level, there are indications that certain common genes could contribute significantly to different neurological and metabolic clinical pictures. For example, the development of the endocrine pancreas requires a series of transcriptional factors that permit stem cells to proliferate and differentiate into a highly specialised cell producing insulin. Interestingly, as shown in figure 2, many of the genes involved in this differentiation code for transcriptional factors found in the central nervous system and, in particular, neurones. In animal studies, selective incapacitation of these genes (knockout) makes it possible to establish a causal relationship between a missing gene and a phenotype. NeuroD or BETA2 is a transcriptional factor expressed specifically in the central nervous system and the islets of Langerhans. *In vitro,* BETA2 is involved in the induction of neuronal differentiation. Selective knockout of this gene leads not only to diabetes, but also to abnormalities of central nervous system development. Again, a transcriptional factor controls multiple genes and can contribute to different phenotypic manifestations, both at the level of the central nervous system and in the development of the endocrine pancreas. Other examples can be cited, such as the gene coding for the protein Islet-Brain-1 (IB1) or JIP1 that is expressed at high levels in the hippocampus and in cortical neurones, and also in the islets of Langerhans. This protein plays a key role in cell protection. It is an anti-apoptotic molecule involved in MAP kinase cellular signalling. Point mutations of the gene coding for IB1/JIP1 have been described in some forms of diabetes in man and, experimentally, the gene plays a key role in hippocampal function. It thus becomes a candidate gene for neurodegenerative diseases.

These examples illustrate the possible genetic relationship between diabetes and psychiatric and neurological diseases. Carbohydrate metabolism is complex and involves a series of organs, transporters and enzymatic processes. Cerebral energy metabolism requires glial-neuronal interactions. Molecular studies on the physiopathology of these different disorders are crucial. Such studies can identify candidate genes common to the occurrence of these disorders, define therapeutic strategies acting on the common signalling pathways and help in setting up pharmacogenetic studies.

The main lines of research in these disciplines have many similarities. The first genes for diabetes were identified in the form of MODY, responsible for the monogenic forms of diabetes. The identification of these genes was of great importance, as it made it possible to understand the molecular physiopathology and to establish a list of candidate genes for type 2 diabetes. As an example, IPF1 is an homeobox transcriptional factor involved in the differentiation of the endocrine pancreas. Drastic mutations of this gene lead either to agenesis of the pancreas or to the appearance of dominant autosomally transmitted diabetes (MODY4). Less drastic point mutations of IPF1 are associated with late forms of type 2 diabetes, a phenotype less dramatic than that seen with MODY4. This is similar to the situation described above in which abnormalities in the Wolfram syndrome gene lead to severe monogenic disorders in the homozygote, whereas heterozygous carriers of these mutations are more susceptible to develop manic-depressive psychosis-type psychiatric disorders.

NEURONAL TRAITS IN PANCREATIC BETA CELLS

Figure 2: The differentiation of the endocrine and exocrine pancreas requires a cascade of events controlled by a network of transcriptional factors. By way of an example, a series of nuclear factors, shown underlined, are especially highly expressed in the central nervous system and in the cells of the endocrine pancreas.



IN SUMMARY

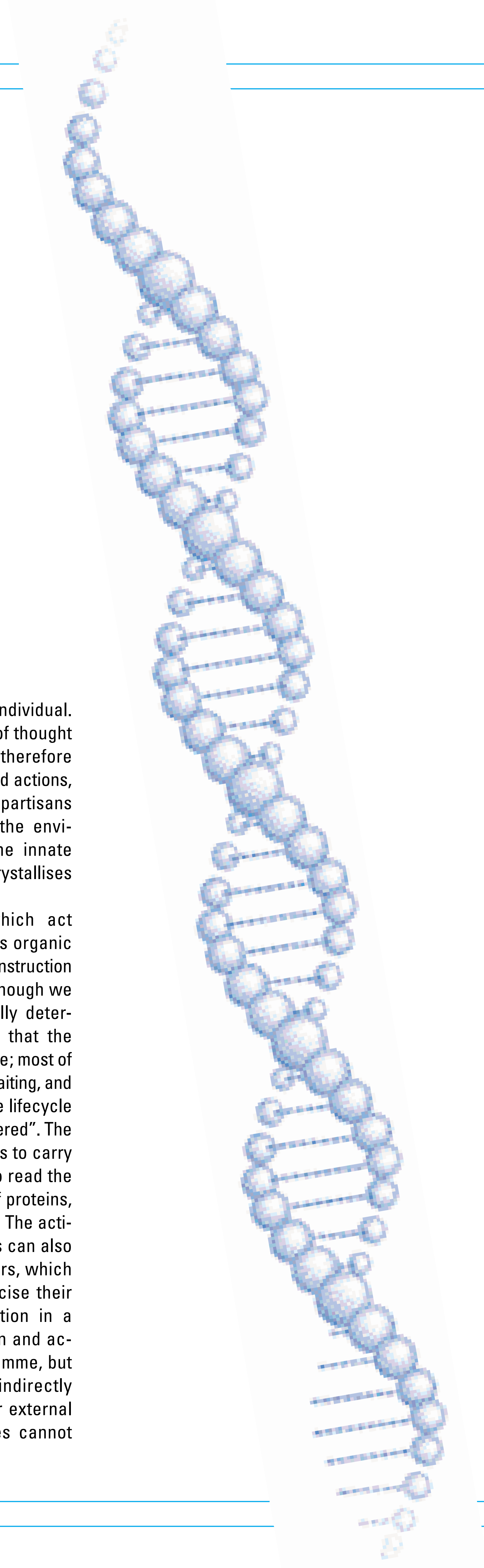
In summary, epidemiological studies suggest, but do not prove, that there is a genetic association between metabolic disorders and psychiatric and neurological disorders. There are several rare examples of genetically determined disorders that are responsible concomitantly for metabolic, psychiatric and neurological disorders. The availability of the human genome sequence information should contribute significantly to the identification of zones of interaction between, or zones common to, cerebral and carbohydrate metabolism.

By **Gérard WAEBER**
Professor Department of Internal Medicine
Centre Hospitalier Universitaire Vaudois (CHUV)
Lausanne, Switzerland

EuroBrain Vol. 3, Nos 1-2 – June 2001

Neurological diseases and genetic susceptibility

Christian W. Hess



DEVELOPMENT OF THE BRAIN – NATURE AND NURTURE

Nowadays, we learn in school that the blueprint and functional programmes of every living organism, including man, are genetically determined and that the genes responsible are transmitted from parents to offspring. This is especially true for the brain, the organ which uses the largest part of the genetic information, a reflection of the enormous complexity of this organ with its 100 billion cells, a complexity unrivalled in any other part of the body. It is therefore not surprising that, despite the considerable progress made in this field, especially over the last few decades, we are still very far from a complete understanding of the genetic mechanisms that regulate it.

Although we generally find it fairly easy to accept the concept that attributes such as height, facial appearance, blood group and skin, eye or hair colour can be inherited, the idea that the same applies to the brain and its properties, although scientifically evident, often gives rise, both among specialists and laymen, to controversy coloured by philosophical considerations. The idea that the "seat of the soul and intellect" could be genetically determined is sometimes denounced in polemic tones as an unacceptable diktat of the genes, all aimed at having a positive effect on the mental and emotional faculties of the individual. It is around the brain, the seat of thought and emotion and the organ therefore responsible for our behaviour and actions, that the debate between the partisans of the genome and those of the environment, the supporters of the innate versus those of the acquired, crystallises most intensely.

Synthesising the proteins which act either as enzymes or directly as organic constituents, genes direct the construction and functioning of the body. Although we say that the brain is genetically determined, it must be understood that the genes are not continuously active; most of the time, they are dormant and waiting, and it is only at certain phases of the lifecycle that they are expressed or "triggered". The activation required for the genes to carry out genetic transcription, i.e. to read the code governing the synthesis of proteins, is itself directed by other genes. The activation and inactivation of genes can also be influenced by external factors, which means that genes do not exercise their directing and regulatory function in a completely autonomous fashion and according to an immutable programme, but that their activity can be indirectly modulated by learning or other external circumstances. Although genes cannot be modified by the environment (except for rare cases of induced mutations), their activity is very dynamic and susceptible to external influences.

We now know that the genes and the environment (living conditions and learning) both influence an individual's character and intellect. Comparative psychometric tests carried out on monozygotic and heterozygotic twins have shown that many behavioural characteristics are half inherited, half acquired. However, the interactions between genes and the environment are much too complex for them to be considered in a purely linear additive way. Furthermore, the relationship between the two varies depending on the mental characteristics and individuals studied, ranging from monogenic brain diseases, transmitted by a single defective gene and expressed with full penetrance (i.e. everyone carrying the gene will develop the disease), to simple hereditary predispositions, strongly influenced by the environment and not necessarily resulting in disease.

HEREDITARY DISEASES OF THE BRAIN

Huntington's chorea is one example of a monogenic disease. It is a severe brain disease of adults, which starts as involuntary movements and psychiatric disorders and develops into dementia. The effects of the gene, which is localised on chromosome 4 and inherited by dominant autosomal transmission, are manifested with a penetrance and expressivity close to 100%. This means that 50% of the children of an affected parent will develop the disease or that monozygotic twins (with the same genome) show 100% concordance, i.e. both or neither develop the disease. The offspring have a tendency to develop the disease at an increasingly early age, the defective gene forming what are known as trinucleotide repeats which increase slightly with each generation, each time aggravating the abnormality of the gene. Since it is not possible to cure the disease, but only alleviate the symptoms, the question must be raised whether it is good to make the diagnosis, with the attendant heavy consequences, before the disease appears, unless the person concerned is an at-risk individual who wants to have children, in which case genetic screening is very important.

Another monogenic brain disease is fragile X syndrome, which only affect boys and in which the defective gene is found on the X chromosome, one of the sex chromosomes. Another well known example of mental deficiency with a genetic origin is trisomy 21 (Down's syndrome), a disease with highly variable expressivity and due to the presence of three copies of

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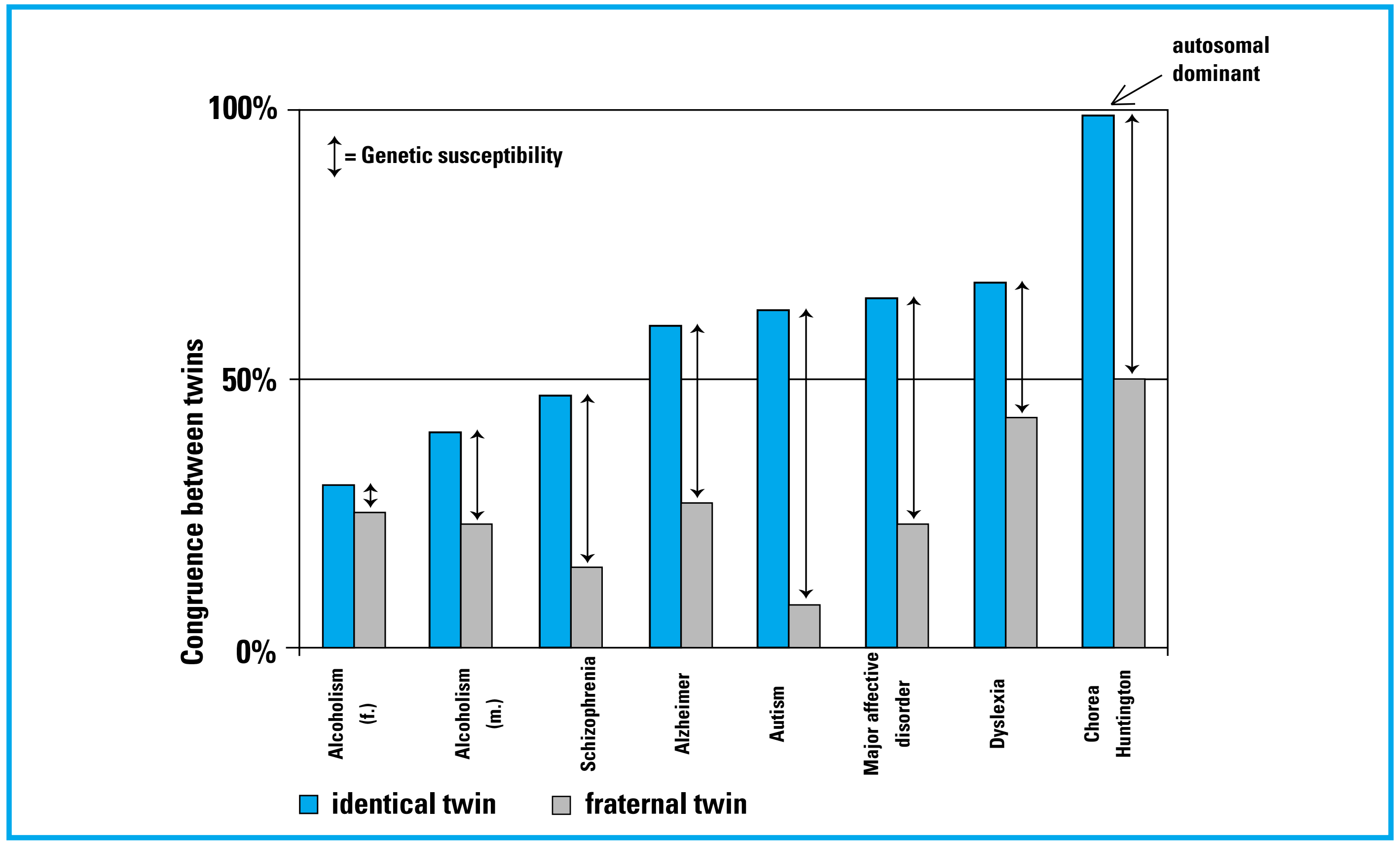

Comparison of the concordance of several mental diseases in monozygotic and heterozygotic twins, the difference indicating the degree of heredity of the disorder in question. Of the diseases shown, only Huntington's chorea is monogenic, the others having a multifactorial origin. Modified from Plomin et al. 1994.

chromosome 21 instead of the normal two. This is the most common chromosomal aberration, the disease translating clinically as mental deficiency associated with certain external manifestations of dysplasia, e.g. physical appearance.

HEREDITY OF INTELLECT, CHARACTER AND MOOD

It is also possible to inherit abnormal character traits. This is the case in hyperekplexia, a monogenic disorder with generally dominant transmission which results in a highly exaggerated startle response. In many hereditary brain diseases, transmission is polygenic and therefore more complex, similar to the situation for eye colour, which also depends on several genes. The hereditary nature of infantile autism or Gilles de la Tourette's disease (tic disorder) is not in doubt, although a simple monogenic lineage has not been demonstrated. Moreover, the penetrance and expressivity are much lower than in monogenic hereditary diseases. Genetic predispositions that manifest themselves as diseases or abnormalities under unfavourable environmental conditions are much more common. Studies carried out on twins have shown that schizophrenia, endogenous depression (major) and dyslexia are diseases of this type. In the case of schizophrenia, the risk for the affected person's brother or sister is about 10%, but increases to about 15% for a heterozygotic twin and about 50% for a monozygotic twin, who has the same genes as the affected brother or sister (see the figure).

The great difference in percentage between heterozygotic and monozygotic twins shows that there is an important hereditary component, whereas the fact that the risk is only 50% for monozygotic twins suggests that additional environmental factors play a very important role in the genesis of this disease, especially since twins are normally brought up in the same home.

Given the large number of hereditary abnormalities, it was logical to think that normal character traits and intellectual abilities must also have a hereditary basis, and this has now been demonstrated. We know, for example, that heredity is very important in character traits such as curiosity and timidity or those factors that make up an individual's temperament, is a little less important in intelligence (IQ) and has practically no effect in juvenile delinquency. In studies on twins and adopted children, it has been much easier to demonstrate a hereditary component that an environmental influence for most abilities and personality traits. Thus, for many things, adopted children, even those adopted as babies, resemble their biological parents more than their adoptive parents. This surprising observation can be explained in several ways.

Firstly, these characteristics apparently have a relatively strong genetic dependence.

Secondly, even as a baby, the child starts to construct its own individual environment, which has the effect of secondarily amplifying the genetic influence.

Thirdly, the intra-uterine world, so important in the child's development, largely escapes our control.

Fourthly, the assumption that adoptive parents make no distinction between their own children and adopted children is not always true.

Finally, studies tend to be carried out in a relatively "normal" environment in which negative environmental influences are fairly rare; however, environmental influences have a greater effect when they are extreme.

By analogy with animal experiments, we know that serious privation of one or several sensory modalities during early infancy can lead to structural modifications, some of which are irreversible, in the brain, which is trying to adapt. Even though their genetic material is intact, children systematically left on their own can, for example, remain permanently backward. Perhaps the same applies when one develops to the extreme an ability (e.g. for music), which is not often the case in ordinary families and thus has no effect on the studies described here.

In conclusion, we can say that, although genes play a very major role in the imprinting of the brain and its functions, it must also be stressed that life circumstances are also important and that, above all, negative influences must be checked, existing abilities encouraged and weak points corrected.

By **Christian W. Hess**
Professor and Chairman University Dept of Neurology
Inselspital, Bern, Switzerland