GENETICS AND PSYCHIATRY

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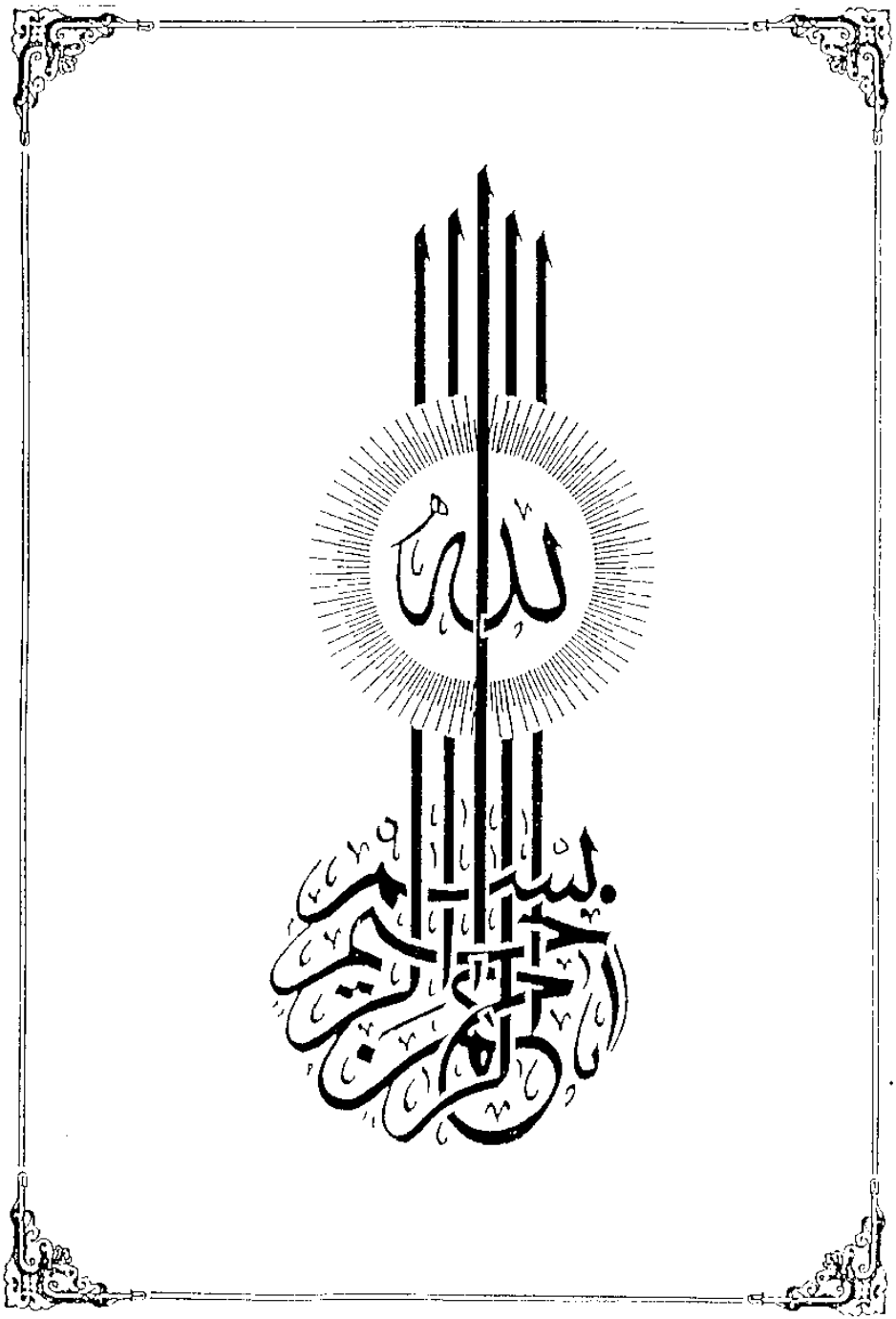

CONTENTS

INTRODUCTION

Genetic studies are important in research on psychiatric disorders because they have the potential for demonstrating the existence of a major locus that affects a psychiatric disorder , even when the cause of the disorder and the biologic function of the major locus are unknown .

The application of genetical informations to clinical problems in the mental health is both meagre and controversial . However , first steps on this way are evident in the studies by Chaudhari and Hahn on post-natal developmental changes in types of messenger RNA specific to mouse brain .

It is still not possible to associate mental disorders with a specific gene behaving in a Mendelian fashion , but one of the closest approaches to this goal is represented by the genetic linkage studies in manic-depressive psychosis .

Some persons have reported an excess of chromosomal aneuploidy among populations of schizophrenic patients or have described schizophrenia-like symptoms in individuals with extrachromosomes

particularly the X-chromosome , others have detected chromosomal mosaicism in populations of schizophrenic patients and possible clinical differences in those with chromosomal aneuploidy .

As regards the functional psychoses : genetic contribution in the aetiology is well evidenced but the exact mode of such contribution in the transmission of the functional psychoses is still a matter of great controversy .

With regard to criminality and psychopathy ; there are many unresolved questions associated with chromosomal influence , particularly those related to males with an extra Y-chromosome .

In male homosexuality : there seems to be no typical chromosomal disorder , although certain male patients with chromosomal aneuploidy exhibit various forms of atypical sexual behaviour .

The intriguing hints regarding the effect of chromosomal aneuploidy both on intellectual function (from the observation of decreased space-form discrimination in girls with Turner s syndrome) and on ego control (evidenced by impulsive behaviour in some XYY-males) only indicates how fragmentary still is the application of genetical informations to problems of human behaviour in psychiatric disorders .

It seems that the major problem in studying psychiatric

genetics is the presence of controversial data and different hypotheses suggested by many investigators . However , different data in psychiatric genetics are gathered in this thesis with an attempt to clarify and systematize these data , this may aid to point out areas in which future researches are needed . At first , an introduction to the science of human genetics will be presented , the following chapters are devoted to study genetics in different psychiatric disorders , then a hollow view of genetic counselling will be shown and finally a discussion to what had been emphasized throughout the different chapters will be presented .

AIM OF THE WORK

This thesis is done aiming at many goals ; firstly , to make a comprehensive review on the subject of psychiatric genetics which is becoming of increasing importance specially after the marked development of genetic engineering and genetic counselling , and the continuous changes of the methodological and diagnostic criteria of psychiatric disorders . Secondly , to clarify the role of genetics in the inheritance of psychiatric illnesses . Thirdly , to illuminate the way for further studies and researches with the aim of future prevention of many psychiatric disorders . Finally , that such review will be a current thought drawing from the past and looking forward the future .

CHAPTER 1

BASIC GENETICS

The nucleus of the human cell contains 46 chromosomes , namely 23 pairs , which are long fine filaments can be seen by special techniques as short thick structures because they are highly coiled . Twenty two of the 23 pairs are the same in males and females , those are called autosomes . The twenty third pair is called the sex chromosome, and is different from male to female . In female there are two X-chromosomes , while in male there are one X-chromosome and a much smaller Y-chromosome . The chromosomes carry the genes which are the hereditary elements , and the number of genes they bear in linear order is very large . [Slater & Cowie , 1974]

Genes have been postulated as the hypothetical units of genetical activity each with a specific locus on a chromosome . As the chromosomes exist in identical pairs with the exception of the XY pair in the male , the genes are correspondingly paired , and the partners of a particular pair of genes are called "alleles" . The total genetic constitution of an individual is called his "genotype" , while his appearance at any given time is called his "phenotype" . A person receiving a given gene from both parents is called a "homozygote" for that particular gene and he will be certain to show the characteristics of such genes . If a person receives the given gene from one parent and a different gene at the crresponding

locus from the other parent , he is known as a "heterozygote" . In some cases the heterozygote displays a trait as that represented by the homozygote . and now this trait is known as "dominant" . in other cases he does not display the trait , and now this trait is known as "recessive" . In still other cases the heterozygote displays traits intermediate between those represented by the homozygotes . [Rainer . 1981]

Biochemistry of genetic material

chromosomes are composed of deoxyribonucleic acid [DNA] and protein . this DNA is the primary genetic material . DNA contains deoxyribose [a five carbon sugar] , phosphate and four nitrogenous bases : two purines [adenine & guanine] and two pyrimidines [cytosine & thymine] . and the number of adenine molecules equals that of thymine . and the number of guanine molecules equals that of cytosine . DNA consists of two sugar-phosphate chains twisted around each others in the form of a double helix . From a sugar on one chain to a corresponding sugar on the other , there is a hydrogen bond linkage through either adenine on a chain and thymine on the other or guanine on a chain and cytosine on the other . So , sugar and phosphate components are constant and what confers individuality is the sequence of purine and pyrimidine bases . [Watson & Crick . 1953]

A typical gene consists of a long strand of DNA containing about 500 bases , the two strands are held togetner in a double helix . The

genetic informations can be regarded as confined to just one of the two strands and the essential unit is the "codon" which is a triplet of three successive bases . Each triplet codes for a particular amino acid , since there are four bases , taken three at a time , so there are 64 possible combinations . [Slater&Cowie,1974]

Protein Synthesis

The process of protein synthesis begins when a message from a portion of DNA is copied by messenger RNA (mRNA) which is a single stranded molecule , which then migrates into the cytoplasm of the cell (transcription) , where it is attached to ribosomes . The mRNA is the same as the DNA except that thymine is replaced by uracil. At the same time the amino acids (a.a.) in the cytoplasm are joined to a type of genetic molecule called transfer RNA (tRNA) , which is a long chain bent like a hair-pin. A given molecule of tRNA is able to be joined at its free end to one of the amino acids. At one bend of the hair-pin a sequence of three nucleotides is ready to attach itself to its unique complementary sequence on the mRNA as that sequence moves across the ribosomes. In this manner the mRNA serves as a template that specifies how a sequence of amino acids each accompanied by its appropriate tRNA molecule will line up (translation).These amino acids join together as the tRNA molecules separate off and the resulting polypeptide chain remains .

[Rainer , 1981]

Mutation

The basic chemical structure of the chromosome is remarkably stable since division results in the production of chromosomes identical to the parent one . When the chromosome divides at the hydrogen bonds which link the base pairs into two complementary strands , each base will pick up its corresponding partner from the surrounding chemical medium . Thus the end result is two chains identical with the parent chain . Although , the stability of the chemical structure of the chromosome is due to the effect of natural selection over a very long evolutionary period , yet changes apparently occur in the DNA from time to time with usually harmful effects . these changes are called "mutations" . This may arise from faulty replication of a small portion of DNA so that the sequence of bases is changed in that region and consequently the instructions from that part of the genetic code are changed . Larger changes may involve the actual loss or the deletion of a section of DNA . Mutation may occur spontaneously or after exposure to injurious materials as chemicals or irradiation . It is estimated that a mutation at any one given locus occurs about 1 in 100.000 gametes . The effects of mutation are deleterious and the condition arising is self limiting owing to its severity .

[Slater and Cowie , 1974]

Dominance and Recessiveness

Traits determined in the heterozygotes for a mutated gene and the

normal allele , where the individual need only receive a gene from one parent , are termed "dominant" . It follows that the trait is transmitted from generation to generation , if the transmission is regular and every heterozygote shows its effects , each affected person will have a detectably affected parents . Further , if one parents is affected and the other is not , on average , half of the offspring will be affected , Autosomal dominant traits usually show this type of inheritance .

Recessive gene traits are those expressed only in the homozygotes and strictly there should be no manifestation of the heterozygous genotype . However , the heterozygote is frequently recognizable and the indications are that , with increasing sophistication of biochemical and other techniques , an increasing proportion of heterozygotes will be identifiable

from the above it will be clear that it is not possible to draw a firm diving line between dominant and recessive gene traits and that indeed all these harmful visible effect gene traits are best described as "intermediate" or as "partial dominants" . As a matter of convenience in medical genetics it is customary to describe those traits usually coming to notice in heterozygotes as dominant and those commonly presenting in homozygotes as recessive .

[Stevenson & Davison , 1976]

Polygenic inheritance

Many traits have variations over a wide range with no sharp

distinction between normal and abnormal phenotypes . In these conditions the phenotypic characteristic is produced not by a single gene but by multiple genes . each of smaller or unequal effects . [Kreitman&Clayton,1978]

Sex-linked Inheritance

Sex-linked genes are those located on the X-chromosome or on the Y-chromosome .

[A] Y-linked Inheritance

A number of rare conditions have appeared in pedigrees as if transmitted from fathers to all their sons (holandric inheritance) . However, most of these conditions also appear in other families inherited in other ways . usually as irregularly expressed dominants and the significance of these pedigrees apparently exhibiting holandric inheritance is difficult to assess . [Stevenson&Davison,1976]

[B] X-linked Inheritance

A recessive mutation on the X-chromosome is not manifested in a female unless she is homozygous . However , it is explained that such recessive mutation on the X-chromosome of the hemizygous male determined the same specific phenotype as in homozygous female because there is no opposing or balancing allele . So . X-linked recessive traits are transmitted by heterozygous unaffected females to half of their sons who