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Genetics and biotechnology in medicine
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(Part II)

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Articoli/*Articles*

GENETICS, BEHAVIOUR AND PSYCHIATRY: HISTORICAL BURDENS AND PERSPECTIVE

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SUMMARY

Familiar, twin, adoption and linkage studies represent the usual tools for assessing the possible role of genetics in mental disease. These genetic approaches have been refined in the last years and a number of methodological problems are absent in recent approaches. While there is no doubt that schizophrenia, mood disorders and autism are characterized by a genetic component no linkage study has been successful up to date, apart, probably, the case of autism. The existence of a genetic component does not minimize the role of the environment and of critical life events. It is also evident that no major genes are responsible for these psychiatric diseases: thus, quantitative trait loci analyses might prove fruitful in future research to track the role of different genes contributing to the outcome of different psychopathologies. The main problem, however, is the difficulty of carrying out quantitative analyses since the today's diagnostic tools do not allow a quantitative approach to these phenotypes.

Francis Galton is often considered the pioneer in the field of human behaviour genetics. In his book *Hereditary genius*, Galton tried to persuade his readers that a strong genetic component accounted for the success of people: to his opinion, success reflected mainly individual intelligence, not other factors[1]. His approach was quite simplistic since he did not account for a number of environmental factors contributing to individual success such as cultural level, wealth or social role of family members. Despite many criticisms, he was the first to use systematically the family method in order to try to demonstrate that genetic factors are also responsible for some behavioural phenotypes, in

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this specific instance intelligence valued through social success. Galton lived in the Nineteenth century, an age in which genetic did not still exist as a science: also sociology moved its first steps and we cannot blame him too much for his approach which reflects the attitudes of his time.

In his studies, Galton did not show much interest for mental disorders even if one of the oldest psychiatric institutions in England, London's Bethlem Hospital already paid attention to their possible familiar roots. Though Bethlem Hospital was founded in 1247 and had one of the longest traditions in mental hospitalisation it is from about 1820 only that its records account for a possible familiar component of mental disease. However, we must wait almost one more century before the first research group on genetic psychopathology is established in Munich under the responsibility of Emil Kraepelin, also known for a successful textbook who exerted a strong influence on European psychiatry. In the Thirties of the last Century, one of the members of this genetic unit was Eliot Slater, a young member of the Maudsley Hospital: when he returned to London, Slater founded in 1959 the Medical Research Council's Psychiatric Genetics Unit, where great care was paid to the possible familiar roots of mental disease. In 1971 Slater, in association with Valerie Cowie, published the first text of genetic psychiatry, *Genetics of Mental Disorders*, a reference book in the history of this field and, more generally, of behaviour genetics[2]. Since then, there has been a dissemination of research on the genetics mental disease, a field at centre of many ideological and scientific discussions. As we will see, part of the debate relates to the reliability of some correlative approaches, in particular on the meaning of family studies, while others question the consistency of the phenotype, in this instance the fact that some mental diseases are considered in binary, qualitative terms: either they are present or absent since despite many attempts it is very difficult to evaluate them on a quantitative scale.

Schizophrenia

The largest part of genetic studies focalise on schizophrenia, rather than other psychopathologies, because of its gravity and

also because of its diffusion: its risk in the general population is in the order of about 1% throughout individual life. In the USA alone, more than one million people is rated as affected by schizophrenic disorders.

Family studies. About 40 familiar studies unequivocally indicate that schizophrenia has a strong familiar character[3]. While the risk of developing schizophrenia is around 1% in the general population, the risk for the relatives of schizophrenics proportionally increases with the level of kinship: it is around 4% and 9% for second degree and first degree relatives respectively. In 14 familiar studies which comprehend more than 8000 schizophrenics the average risk was about 6% for parents, 9% for siblings and 13% for children. The low (6%) risk for the parents of schizophrenic subjects is probably due to the fact that marriage is less frequent in schizophrenics and that those who marry have less children. For this reason the parents of schizophrenic subjects result schizophrenics in a percentage lower than expected. On the contrary, when schizophrenics become parents the risk for their children is quite high (13%). This risk is the same independently on the fact that it is the mother or the father to be affected by this disease. When both parents are schizophrenic the risk soars to 46%. The risk for the siblings of schizophrenics is in the order of 9%, half way between the risk calculated for parents and children: however, though this risk is quite high (about 9 times higher than in the general population) we must remember that the majority of schizophrenics does not have a first degree relative affected by this disease.

One of the most quoted studies on the familiarity of schizophrenia, carried out in Denmark at the beginning of the Sixties of the last century[4] indicated that children of schizophrenic mothers are at high risk. In a very accurate study 200 children were followed up to their fortieth birthday: within this high-risk group 16% were diagnosed as schizophrenics against 2% of the low-risk group. The mothers of those children who developed this conditions were affected by a most serious form of schizophrenia: thus, these children experienced a very unstable familiar environment and early hospitalisation, a fact that points to a serious bias of familiar studies, the difficulty to separate envi-

ronmental and genetic influences while this is possible in adoption studies. A similar methodological problem casts shadow on a very large and often quoted study on the genetic risk of schizophrenic relatives[5]: this study indicates that children of schizophrenic parents are characterized by a high number of personality disorders when they are young adults but, as other familiar studies, fails to separate genetic and environmental factors. These pitfalls are often minimized, thus perpetuating still today a wrong approach to the possible genetic causes of schizophrenia or, more generally, of mental disease.

Twin studies. While studies are more unreliable, twin studies are more controlled, though they are more difficult since it is not that easy to find a large twin sample. A number of twin studies indicate, in a more reliable way than familiar studies, that schizophrenia has a genetic component: in couples of monozygotic twins (MZ) there is correlation ranging between 41 and 65% while in dizygotic twins the value drops to lower levels (0-28%)[6]. Though the range of correlation coefficients is rather wide depending on the study considered, there is no overlapping between the lower values of MZ twins and the higher values of DZ couples. The merit of epidemiological twin studies is to go beyond the anecdotic suggestions of single case histories, such as the impressive, popular case of the Genain twins, four MZ girls who developed schizophrenia, though of different gravity[7]. Less anecdotic, though not numerically consistent, are the observations related to 14 twin couples raised apart at least two years before one of the twins developed schizophrenia: despite separation, 9 couples (64%) were concordant[8].

As for familiar studies, also twin studies point out to the role of the environment: as a matter of fact, the mean correlation within MZ twins is 0,5 only, while one should expect values closer to 1: the fact that twin correlations are higher in MZ than DZ couples does not allow to minimize the fact that half of MZ couples are not concordant, pointing out to the fact that non-genetic factors play a significant role. Since the differences evident in MZ twins cannot be due to genetic factors, the co-twin method may be useful to understand why one member of the couple develops schizophrenia and the other member is instead resilient.

For example, two different studies indicate that there were no major differences in the life events of discordant twins, apart from an history of difficulties at birth, sometimes resulting in structural brain differences[9].

Adoption studies. Adoption studies represent another approach since Leonard Heston carried out the first extensive study in adoptees in 1966[10]. The results of this research indicated that the risk of developing schizophrenia in adopted children born from biological schizophrenic mothers was in the order of 11% (5 cases out of 47), much higher than that close to zero evident in 50 adoptees whose biological mothers did not manifest mental disease. A risk of 11% is very similar to that evident for children raised by their biological schizophrenic parents, a fact that indicates that growing in a family in which a close relative is schizophrenic does not increase the risk of developing this disease beyond the threshold set by heredity.

One of the most impressive studies on the role of adoption was conducted in Denmark and still represents an important landmark[11]. This study, based on a population of 5500 adoptees and on 10000 of their 11000 biological parents, was possible because the Danish Adoption Record allowed the identification of the biological parents of the adoptees many years after they gave away their chidren to adopting families. Since children are generally given into adoption when their biological parents are adolescents or very young but schizophrenia generally develops later on, it is very important to check if biological parents did develop the disease when their children were already adopted. Thanks to the Danish Adoption Record, Rosenthal and his group were able to account for the real psychiatric condition of the biological parents of the adoptees. It was therefore possible to identify 44 biological parents who developed schizophrenia after adoption: their 44 adopted children were compared with 67 adoptees whose biological parents did not present mental problems. This study, based on a double-blind method, indicated that 7% of the adoptees born from schizophrenic parents developed schizophrenia while none of the controls presented psychiatric problems. Though this study presents some pitfalls, mostly related to an insufficient attention to the psychiatric conditions of

non-biological parents, it shows that there is a significant genetic influence on the development of schizophrenia. When non-biological parents were more rigorously screened in terms of their psychiatric conditions, a part of them was diagnosed as mentally disturbed (as it was in a follow-up of the first study[12]): however, no evidence was reached in favour of an environmental effect, since none of the disturbed foster parents had a schizophrenic adopted child. Thus, the positive correlations between biological parents and their adopted children evident in the Rosenthal et al. study were even more significant.

In a second study, carried out by Kety and his co-workers in 1994 on chronic schizophrenics[13], the diagnosis more reliable than that upon which is based the study of Rosenthal et al. in which acute psychotic episodes were also included. However, also the Kety et al. study indicates that 5% of the adoptees who were diagnosed as chronic schizophrenics had a first-degree relative affected by the same disease while none of the schizophrenic adoptees had an adoptive schizophrenic relative, a fact that should minimize the role of the environment and stress out the role of genetics.

As already indicated, one of the main problems with the genetics of schizophrenia is the ability to classify, understand and quantify this disease: is it a unique condition or a heterogeneous collection of different diseases, a syndrome that it is difficult to diagnose? If different typologies exist, as suggested by many psychiatrists[14], they presumably involve a continuum, ranging from milder to more severe forms of the same disease: this makes more difficult a quantitative genetic approach and might leave us with the only possibility of a qualitative approach -presence or absence of schizophrenia- even if psychiatrists are able to assess its severity. Of course, it is always possible to base genetic analyses on "mild" or "severe" forms but the quantification of the phenotype would still be problematic. Another strategy might be the search for markers, called "endophenotypes" by Gottesman and Shields[15]. For example, it has been suggested that behaviours such as "smooth-pursuit eye tracking" (following with the eyes an object while it moves) might help in the discrimination of the milder forms of schizophrenia or even a pre-

disposition to this disease but no agreement exists on the reliability of this and similar markers. Thus, while there is today general agreement on the fact that in many instances genetic factors play a role in schizophrenia there are also many cases in which the environmental component plays a critical role in apparent absence of familiarity or of other genetic determinants: this fact, in absence of an evident Mendelian mode of inheritance, has been explained in multifactorial terms and has spurred research on possible gene candidates.

Linkage studies. The possibility to identify a linkage between schizophrenia and genes responsible for this disease would have a meaning beyond the problem of its inheritance since such a linkage would suggest possible pathological pathways in the brain and give a hint for the use of more selective drugs. Despite many attempts and many optimistic announcements, no reliable linkage has been attained up to date. The history of the search for possible linkage is rather frustrating: for example, in 1988 Sherrington et al. identified an autosomic dominant gene located on chromosome 5 in Dutch and British family but unfortunately five other studies did not confirm it[16]. The presence of a locus on the short arm of chromosome 6 (*6p*24-22), identified in a linkage study involving 265 families with more than one schizophrenic member[17] was not confirmed by other studies[18]. Other linkage candidates relating to chromosomes 13 (*13q*14.1-*q*32) and 22 (*22q*12-*q*13) did not attain more success. All these –negative- attempts have consolidated the idea that schizophrenia is a multigenic disease, no gene playing a major role in its outcome: this hypothesis is in line with a recent study carried on 196 couples of schizophrenic brothers: its results exclude the existence of any gene conferring a relative risk higher than 3 or more in about 80% of human genome[19]. This had shifted the attention on genes exerting small effects: some of these are related to the dopaminergic system since drugs that block dopamine –or serotonin- receptors exert a positive effects on some symptoms of schizophrenics. In different studies the polymorphisms of the dopamine receptor gene (*DRD3*) and of serotonin receptor gene (*5HT2a*) seem to indicate a little but significant role of these receptors in the genesis of the disease: while it is to early

to claim for a specific genetic effect, these findings may support experimental studies based on animal models of psychoses relying on the use of animal inbred strains and on other genetic strategies[20].

Mood disorders

This short survey on the genetics of schizophrenia anticipates a similar discussion on other mental diseases such as mood disorders (monopolar and bipolar syndromes), anxiety and autism: the genetic procedures are in fact similar and all involve familiar, twin and adoption studies, in addition to some linkage attempts.

While the diagnosis of monopolar disorders is not difficult, bipolar disorders, in which there is an alternation between the depressive and manic pole, require subtler diagnostic tools since in many instances it is not that easy to recognise a manic state: thus DMSIV makes a distinction between type 1 bipolar disorders (characterized by a clear episode of mania) and type 2 bipolar disorders in which the manic episode is less defined. In more general terms, bipolar disorders are less common than depression, the risk for the former being about 1%, for the latter about 17%.

The first comprehensive *familiar survey*, relative to 12 families affected by bipolar depression, suggested a risk of about 8% in first degree relatives against a 1% risk in the general population[21]. In other seven studies[22] on major depression the familiar risk was at a 9% level against a 3% risk. It has been hypothesised that the distinction between major unipolar and bipolar depression is a matter of gravity, bipolar depression being a more severe mood disorder[23]. The results of multivariate familiar analyses indicate that the relatives of unipolar individuals do not have a major risk of bipolar depression (less than 1%) while relatives of bipolar individuals face a higher risk (11%) of unipolar depression. If we assume that bipolar depression is the severest form, this analysis might explain the reason for a higher familiar risk for bipolar depression, for the higher number of unipolar relatives of bipolar individuals and the lower number of bipolar relatives of unipolar patients.

As for schizophrenia, also the familiarity of depression is a matter of shared environment and the age factor plays an important role. There are in fact many studies indicating that a familiarity of depression is more evident when the first depressive episode takes place in infancy, thus indicating that parental –depressed- behaviour may affect the mood of their children. On the contrary, when depression strikes a family member during adulthood or after, the familiar risk is lower since children are already grown-up or adolescents when their parents develop a bipolar disorder[24].

Twin studies are more reliable in that allow a better separation of genetic and environmental factors. One of the first studies, conducted by Allen in 1976 on hospitalised individuals –thus affected by a severe mood disorder- indicates a correlation of 0.40 and 0.11 for MZ and DZ twins respectively. When bipolar depression is considered, the average correlations were 0.72 and 0.40 but later studies indicated lower values in MZ twins, ranging from 0.18 (unipolar) to 0.08 (bipolar depression)[25]. Finally, a study on 12 twin couples reared apart in which at least one twin suffered of major depression indicates that eight couples out of twelve (67%) presented major depression[26]. When the condition of the children of identical twins discordant for bipolar depression is considered the situation is rather similar to that evident for schizophrenia. The risk of contracting mood disorders is similar (10%) in the children of twins affected or non affected by bipolar disorders: these findings suggest that the identical non-affected twin may transmit a predisposition for bipolar disorders as does his affected twin. However, we will see that no definite markers of unipolar or bipolar disorders are today available, thus it is still uncertain what characters are transmitted and what a "predisposition" means.

The higher incidence of depression in women has suggested that a dominant gene on X chromosome might be responsible for unipolar and bipolar disorders: further, detailed studies do not confirm this hypothesis[27]. Similarly, the much publicised hypothesis for a *marker* for bipolar disorder on chromosome 11 in a genetically isolated population of Amish in Pennsylvania[28], did not prove to be true[29]. Other possible chromosomal associations

involving chromosome 4 (4*p*16) , 12 (12*q*23-24), 16 (16*p*13) and 21 (21*q*22)[30] have been proposed but need to be confirmed. A number of candidate genes such as *hSERT*, are mostly connected to the serotoninergic hypothesis of depression dealing with reuptake of serotonin at the synaptic level. These synapses are the site of action of Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants and the hypothesis of a possible relationship between *hSERT* polymorphisms and mood disorders in conceptually sound, though, at the present time must still be proved.

Studies on anxiety are less numerous than those on schizophrenia or mood. The results of these studies are still very contrasting: in some instances a slight genetic component has been ascribed to panic disorder, obsessive-compulsive disorder and post-traumatic stress disorder: for these and other behavioural troubles, many problems arise from the changes of classification in the subsequent DSM versions (DSM-IV being more rigid than its previous versions in the subdivision and classification of various forms of anxiety) and from the difficulty to compare different studies based on unreliable o inconsistent diagnostic criteria[31].

Autism

Autism is a relatively rare disease since it affects 3-6 children every 10,000. While many years ago it was ascribed to the psychodynamics of mother-child relationships and its genetic component was minimized further studies indicated that this disease is of biological origin. However, it is rather difficult to assess the role of genetics in autism for different reasons: compounding the problems of rarity, another difficulty in detecting the genetic origins of autism is the lack of family pedigrees. Unlike people who inherit Huntington disease, a genetic disease that does not strike until after the affected person has reached reproductive age, persons affected with autism are so socially disabled that they never marry and have children. Thus, researchers do not have the extended family histories that have played a critical role in the identification of genes implicated in other diseases. Despite these problems, the first systematic twin study on autism, conducted in 1977 contributed to stress out its non environmental bases[32].

In the case of autism, the likelihood that the sibling of an affected child also would be affected is between three and six percent. This incidence is about 100 times greater than the rate at which autism affects unrelated people in the population. Twin studies have provided powerful evidence for the role of genetics in autism: one study showed that the likelihood that the identical twin of an autistic child also would be autistic was 82 percent, whereas the equivalent rate for fraternal twins was only 10 percent. With sophisticated statistical techniques and numerous twin studies, behavioural geneticists now believe that as much as 90 percent of the behavioural phenotype of autism is related to inherited genes.

Such a high genetic contribution appears to be the exception rather than the rule when considering complex behaviours. This is probably because a relatively small number of genes may be involved in autism whereas other behaviours may be influenced by many genes. Rutter considers autism as one of the most inheritable mental disease[33]. When linkage is considered, the International Genetic Study of Autism Consortium (1998) has also demonstrated the association with a locus on chromosome 7 (7*q*31-33)[34]: this finding has been confirmed by different groups[35].

The findings reviewed until now are based on a classical approach to the genetics of psychopathology, mostly based on Mendelian and linkage analyses. Although the current interest in molecular biology has produced a strong focus on testing a single-gene model of genetic transmission[36], attempts to fit data with a major-gene model have generally met failure. These failures may reveal the limitation of this approach for studying genetic influence on normal or disturbed behaviour that, as repeatedly pointed out, involves multiple genes, rather than one or two major genes, as well as non-genetic sources of variance[37]. One of the most interesting developments of behaviour genetics is the attempt to combine quantitative genetics with molecular approaches in order to move towards complex behavioural traits determined by many genes and depending on environmental factors. Convergence of quantitative and molecular genetics in order to deal with complex quantitative traits has resulted in the study of multigenic systems through Quantitative Trait Locus

(QTL) analyses. In recent years, increasing attention has been devoted to the involvement of stressful experiences (life events) in the development and expression of psychopathology. Moreover, a diathesis-stress hypothesis has been proposed, which suggests that environmental factors are not specific for a given pathology, whereas genetic factors (diathesis) are. Results obtained in animal models support to this hypothesis. For example, it has been shown that different strains of mice are equally susceptible to stress but develop different behavioural disturbances related to different alterations of neurotransmitter systems[38]. It is possible that through the QTL method, now applied to the study of the genetics of human psychiatric disease, may lead to a better description of the different phenotypes involved in a particular disease. As a matter of fact similar psychiatric symptoms may be due to different neural alterations, to complex genetic interactions and regulatory processes that more sophisticated genetic analyses, such as QTL, might reveal, thus overcoming some of the difficulties deriving from more simplistic one-dimensional approaches.

QTL approach reflects a shift of the genetic approaches to mental disease. As a matter of fact, several biological abnormalities have been implicated in family and high risk studies as possible intermediate phenotypes. Targeting such biological manifestations as "intermediate phenotypes" is a relatively new approach aiming to reduce a number of susceptibility genes and to clarify the biological mechanisms by which such genes increase the likelihood of emergence of a clinical mental illness. One of the most significant examples is the case of the relationship of catechol-O-methyltransferase (COMT) genotype with prefrontal function. Abnormalities in prefrontal information processing are well documented characteristics of patients with schizophrenia, a fact that has been correlated to a variant in the DNA sequence of the COMT gene that is associated with a change in activity of the enzyme and that had a predicted effect on prefrontal dopamine function[39]. It should be noted that inheritance of the COMT val itself accounts for a very small increase in risk in the general population, approximately 1.5-2 fold increase: however, as indicated by Weinberger (2002), the COMT data represent the first clear success since it has moved the genetics of psychiatric illness from the realm of statistics and probabilities to the concrete reality of biology mechanisms of susceptibility[40].

Final remarks

In conclusion, there is no doubt that schizophrenia, mood disorders and autism are characterized by a genetic component even though the existence of a genetic component does not minimize the role of the environment and of critical life events. Despite many analyses pointing out to a genetic component no linkage study has been successful up to date, apart, probably, the case of autism, in order to explain the range of symptoms characteristic of a specific mental disease. As a matter of fact, despite many studies there is no evidence for major genes being responsible for the psychiatric diseases considered. If no major genes play a critical role, quantitative trait loci analyses might prove fruitful in future research to track the role of different genes contributing to the outcome of different psychopathologies. The main problem, however, is the difficulty of carrying out quantitative analyses since today's diagnostic tools do not allow a quantitative approach to these phenotypes: in other words, there is still a gap between the consistency of diagnostic tools and the power of today's genetic analyses.

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