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GENETICS IN PSYCHIATRY
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WORDS OF WELCOME

Loga Slobodan, MD, PhD, Corespodent member of ANUBiH

Dear colleagues, dear friends, Ladies and Gentlemen!
I am delighted to welcome all those of you who have chosen accepted our invitation to be part of this Symposium "Genetic in Psychiatry".
It is my great privilege to greet all of you in behalf of Academy of Sciences and Arts of Bosnia and Herzegovina.
The Department of Medical sciences of ANUBH, more precisely, the Board for Neurological and psychiatric investigation, took over the responsibility for organising first scientific conference in Dubrovnik about very important, and up-to-date topic – genetics in Psychiatry. There is a growing need in our society for good experts in the field of genetics in psychiatry. As a matter of fact, ANUBIH is a member of IUC in Dubrovnik and this event represents our first joint activity. We are very grateful to ANUBiH, especially its president Božidar Matić for that decision and support that he gave us in organising this conference.

I am very thankful for all lectures, respected people, who have found time to come here and give very important lectures during this conference. We are especially happy for the fact that our partner at this conference is prof. Maier, the head of Department of Psychiatry, University of Bonn. Greetings for prof. Mayer.

We are also thankful to all participants for their coming to this conference.

We hope that you will find time, in the course of our not too condensed program, for visiting Dubrovnik, one of most beautiful places in the world. I hope that your stay in Dubrovnik will be a pleasant one.

Together with my colleagues in Organising committee I warmly welcome you and wish you all a lot of success.

INTRODUCTION TO SYMPOSIUM "GENETICS IN PSYCHIATRY"

Slobodan Loga
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The field of genetics is very huge and if we try to describe it in short: mapping the human genome, cloning animals, and identifying new disease genes. For many of us who are in every day psychiatric practice, the problem is putting this information into context of our work and understanding what recent genetic findings really mean in terms of mental health. To help answer these questions, we have organized this symposium primarily to help our understanding how advances in genetics can help in the treatment of psychiatric diseases.

With the human genome decoded, researchers in field of psychiatric genetics have the task through the newly discovered genes in search of those that lead to disease. The field of psychiatric genetics has become one of the most interesting areas of psychiatric research. These efforts we hope will change the way how we see diseases and their treatment in psychiatry.

The Human Genome Project recently announced that they had sequenced all of the human chromosomes — about three billion bases long. In itself, this is a huge achievement, but knowing the sequence doesn't tell us what the 30,000 to 50,000 genes actually do in the body. Their next step is to figure out what the genes do, and what role these genes may play in disease.

Complex genetic conditions, such as diabetes, heart disease, most common cancers, autoimmune conditions, and psychiatric conditions are result from the interplay of environment, lifestyle, and the effects of many genes. They may be present in more than one family member but don't follow the characteristic inheritance pattern seen with Mendelian conditions.

Familiar, twin, adoption and linkage studies represent the usual tools for assessing the possible role of genetics in mental disease. 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. 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 arrying out quantitative analyses since the today's diagnostic tools do not allow a quantitative approach to these phenotypes.

There now exists growing evidence of candidate gene sites for a variety of psychiatric disorders ranging from schizophrenia to reading disability.

Genetic researches in the field of psychiatry try to find the impact on:

- diagnostic
- risks assessment
- prevention and treatment strategies

We are taking family medical history for patients is our everyday task. This helps us to tell if there are genetic factors that may influence a patient's health. But a family history does not provide us with the complete picture of a person's risk. Some people may be at risk for an early-onset disease, as schizophrenia for example, even if they do not have a family history of that disease. Also, we know from many cases that not every person with a strong family history of a disease will inherit the risk factors.

We are now just at beginning to be able to screen people for genetic risk factors present in their family (Tab. 1). In the future, it may be possible for psychiatrist to screen their patients for many genetic-based risks. We hope that individual risk assessments will be created for each our patient based on that patient's set of genes.

In case when we know which genes are involved in a disease, it would be possible develop a test to screen people who are at risk and also start looking for a cure. A diagnostic test by itself will not cure the disease, but it can help identify high-risk people who may require more intensive screening or preventative action. Knowing what genes cause a given disease can also help us understand what goes wrong in that disease, which can help drive the search for drugs that counteract the problem.

Knowing personal risk of potentional patients makes it possible to decrease their chance developing the disease through lifestyle changes, and preventative medical treatments. We know in field of mental health that risk for almost any condition is a function of both our genes and our environment. While we can't change genes, we can apply our knowledge of family medical history to predict risk for specific problems. This, in turn, allows us to focus on the things we can change — diet, lifestyle, screening, treatment — to ensure a long, healthy life.

TABLE 1. *Recurrence risks for psychiatric disorders (1)*

	Life prevalence	Risk to first degree relatives of affected individuals
Schizophrenia	1.0 -1.9%	4.4 -13.8%
Bipolar Affective disorders	0.8 -1.1	4.0 – 9.0%
Severe Unipolar Depression	4%**b** 8%**c**	9%**b** 18%**c**
Panic disorder	1.5 -3.5%	15% -24.7%
Alcohol dependence	14%**b** 3%**c**	27%**b** 5%**c**

b risk to males **c** risk to females

Despite the progress in molecular genetics, the genes responsible for the development of bipolar disorder (BPD) and schizophrenia have not yet been identified. This failure can be attributed to an ambiguous phenotypic description and several variations in the genetic transmission of these diseases. There is a growing consensus that an endophenotype approach may be utilized to overcome the difficulties regarding the phenotypic description and facilitate the identification of the susceptibility or protective genes. The endophenotypes which can be defined as subclinical vulnerability markers may assist in the identification of the genetic underpinnings of psychiatric disorders regardless of the disease status.

Twin studies have demonstrated that the rate of autism is much higher in identical than in non-identical twins of individuals with autism. This is taken to support the opinion of a strong genetic contribution of autism. Siblings of the children with autism have a much increased risk of themselves having autism. About one in twenty of full siblings of individuals diagnosed as suffering from autism have autism (in general population: one in thousand). This is a high risk

given that genetic stoppage occurs in autism. Genetic stoppage means that families who have a child with a severe disorder – such as autism – tend to have fewer children than do those who have normal children (2).

Genetic regulation of immune response showed that it is apparent that genes on at least three chromosomes can contribute to antigen recognition by T cells. Three highly polymorphic gene families are likely to play a role in any autoimmune disease of the nervous system: human leukocyte antigen (HLA) genes, T-cell receptor genes, and immunoglobulin genes (3).

Preliminary results of research into the pharmacogenetics of psychotropic drug response suggests that specific genes may influence phenotypes associated with psychotropic drug administration. These results require further validation.

Genetic advances pose new and unique ethical dimensions to the familiar issues of privacy, confidentiality, access to and justice in health care, and informed health decisions. This means ensuring privacy and confidentiality of all genetic information.

References:

1. Adapted from Moldin SO. Psychiatric genetic counselling. In: Guze SB, ed. Washington University adult psychiatry. St. Louis: Mosby, 1997;
2. Gillberg, C (1995) Clinical child neuropsychiatry, Cambridge, Canbridge Univ. Press
3. Steinman, L. (1993)Autoimmune disease, Scientific American, Sept. 1993, 107 -112

INTERNATIONAL SYMPOSIUM GENETICS IN PSYCHIATRY

Organized by
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And
The Department of Psychiatry
University of Bonn
IUC Dubrovnik, August 28th – 30th 2004

CONCLUSIONS

The Symposium on "Genetics in Psychiatry" highlighted the currently rapid progress in unraveling the molecular and genetic basis of major psychiatric disorders and their treatment. Less than two years before the first three susceptibility genes for schizophrenia (dysbindin, neuregulin 1, and G72/30 together with DAAO) were discovered by systematic search including linkage and association studies, and confirmed, the first susceptibility gene for bipolar disorder for bipolar disorder also emerged, most interestingly, a gene which also presents as susceptibility gene for schizophrenia. Neither of the implicated genes or any of its products have been previously postulated to be implicated in the etiology of psychoses. Another conclusion is that both disorders are polygenic with multiple modulate effect genes but without a major gene. Thus this success story demonstrates that our knowledge on the up till now widely unknown pathophysiology of these disorders can rapidly expand in fully unexpected directions. The understanding of action of effective pharmacologic treatment will also greatly increase.

The plenary lectures by Wolfgang Maier and Marcela Rietschel at the Symposium illustrated these innovative developments in an historical context. It became apparent that the relationship between at-risk haplotypes of susceptibility genes and the targeted disorders are substantially more complex than expected. Apparently, neurobiological correlates of the disorder (like hippocampal volume reduction) and candidate core symptoms (like persecutory delusions) are more directly related to the predisposing genetic variations than the clinical diagnostic entities as defined by DSM IV and/or ICD 10. It was also indicated that the bottleneck for further progress is in the availability of informative samples.

The Symposium focused on the contribution of research groups form Bosnia and Herzegovina, Bulgaria, Croatia and Slovenia to this exciting development: Berberović, the leading quantitative geneticist from Sarajevo together with Bojan Šošić, demonstrated the strong genetic heritability of the complex

disorder, schizophrenia by reference to biometrical multifactor models, which have been greatly confirmed by the recent molecular genetic progress.

Radka Kaneva from Sofia demonstrated the utility of isolate populations for finding disease genes in bipolar disorder. She collected multiple Gipsy families with multiple affected and performed a genome wide linkage analysis with very strong linkage signals which are revealing substantial agreement with other genome wide scans. The major advantage of her approach is the homogenous population, genetic background, which might accelerate the identification of not yet uncovered susceptibility genes.

Population genetics in Bosnia and Herzegovina was the topic of a very carefully conducted study by Pojskić and Kapur from Sarajevo who demonstrated that the geographical variation of genetic markers is even stronger than the interethnic variation in Bosnia and Herzegovina. This result allows to consider the genetically influenced disorders in Bosnian population independent of ethnic background.

The ambitious recruitment program by Oruč in Sarajevo focusing on trio-families of bipolar disorder can therefore rely on a demonstrated homogenous population genetic background. This recruitment program will be a very promising starting point to study the molecular genetic basis of affective disorders in Bosnia and Herzegovina. This project is important, as it will allow to discussing the variability of genetic basis of complex diseases across population.

A population specific view on complex genetic disorder is also required because of gene and environmental interaction; environment is strongly dependant on cultural factors and the society as Marušič from Ljubljana demonstrated by reference to suicidal attempts and completed suicide. It is now evident that suicidal behavior is genetically influenced. Although specific susceptibility genes have not yet been identified with certainty, environmental factors are known. Particularly alcohol availability and consumption increases suicidal risks, which is also reflected by differential incidence rates across countries. But environment is obviously not the only source of variation in national suicide frequencies; similar genetic background (Fino-Ugrian) produces a comparable excess in suicide risk in spite of different cultural backgrounds.

The beneficial effects of the progress in genetic research for our patients will come from the understanding of genomic effects of available efficacious treatments. The currently growing knowledge will, as Jakovljević from Zagreb

demonstrated – help o better predict treatment outcome and to identify the crucial molecular targets of treatment which are essential for successful outcome. Thus it can be expected within the upcoming years to use genetic markers to select the most appropriate drug for an individual patient and to develop new, more causal and therefore more effective treatments.

Genetic markers may also help to predict the conversion to psychosis in subjects presently with prodromal symptoms as Džubur-Kulenović from Sarajevo demonstrated. Thus early treatment will become possible targeted to prodromal subjects with high, genetically mediated risk for schizophrenia. Neurodegeneration which might occur early in the course of schizophrenia might be prevented by these means and the clinical long - term course of psychosis can be modified too the benefit of the patient.

Spahić-Mihajlović from Chicago discussed the relationship between schizophrenia and diabetes and the metabolic syndrome. Both conditions are genetically influenced as well as this might be the case for their excess co-morbidity. Atypical antipsychotics have specific impact on this relationship, but this is even more the case for conventional antipsychotics. However, the variety of risk factors is also operating.

The Symposium also discussed humanistic and conceptual views that are challenged by the molecular genetic revolution. Kulenović from Sarajevo reminded the audience to the origins of molecular understanding of life by reference to the great biologist and most innovative scientist and thinker in the filed: Jacques Monod. Life and evolution of nature and humans is not only under the control of causal mechanisms, the necessity principle. There is also space for Randomness and Freedom. Thus, our future is not predetermined.

However, there are serious concerns and fears that the human nature might be manipulated by gene technological interventions. With unpredictable – but in any case dangerous outcome as Novaković from Bijeljina argued. Thus it is evident that the ethics of molecular genetic research in disorders and of the dissemination of research results to affected and the public require substantially more attention than it currently receives.

The participants of this high-quality exciting conference hope that genetic research in psychiatry is stimulated particularly in South East Europe. It becomes evident that the success chances in this field are high.

PROGRESS ON THE GENETICS OF SCHIYOPHRENIA AND BIPOLAR DISORDER

Wolfgang Maier and Marcella Rietschel

Introduction

The distinction between schizophrenia and bipolar disorder was historically based on distinct phenomenologies and long-term courses. A differential nosology and etiology was postulated, however never convincingly proven. The dichotomic postulate was maintained despite of striking similarities in prevalence rates and risk factors between both "lifetime" disorders: Lifetime prevalence rates are similar (- 1%) and stable across countries and cultures, male-to-female ratios of affected subjects are balanced, age at onset reveals a broad overlap in the age period of 18-30 years. However, there is also evidence for differences in risk factors (Mortensen et al., 2003): e.g., premorbid IQ score presents a risk factor for schizophrenia but not so for bipolar disorder (Zammit et al., 2004).

Both disorders are under genetic control with very similar recurrence rates of 5-10% for siblings and parents, similar concordance rates (- 10% for DZ and > 50% for MZ twins), and about 60-80% of the variance being influenced by genetic variants in both disorders, and the remainder being due to individuum-specific environmental factors which are not shared among the twins; a monogenic, Mendelian transmission cannot be observed for any of both disorders; both also reveal genetic-familial bonds to unipolar depression; variation of prevalence/incidence rates by season of birth seems also to be a characteristic of both disorders.

The similarity in risk factors between both disorders is now extended by neurobiological communalities: There is rapidly growing evidence that the psychopathology or/and the nosologically based disease entities are not based on distinct pathogenic processes. For example, both disorders share morphometric features as enlarged ventricles and reduced hippocampal volumes, neurophysiological patterns as reduced amplitudes of evoked potentials (as P300), and various memory dysfunctions. Recently, common cellular and molecular patterns were observed: e.g., glutamate-mediated excito-toxicity in the cingulum (woo et al., 2004). Similar patterns of gene expression in post-mortem hipoocampal tissues (e.g., reduced GABA-ergic markers or neurotrophic factos as BDNF; Knable et al., 2004) pointing at similar oligodendrocyte dysfunction (Tkacher et al., 2003), or similar alterations in MRNA of receptors in crucial

prefrontal and hippocampal areas pointing at similar dysfunctions in signal transduction (Lopez-Figueroa et al., 2004) are common between schizophrenia and bipolar affective disorders. Furthermore, in both disorders similar abnormalities of intracellular molecules linking different neurotransmitter systems with intracellular enzymes (like PSD95) that mediate signaling and provide links between different neurotransmitter systems were found, e.g. in key areas of the thalamus (Clinton and Meador-Woodruff, 2004). These neurobiological communalities are supplemented by the recent progress in genetic research.

We review the current evidence of a genetic relationship between schizophrenia and affective disorders on an epidemiological and molecular level.

Family and twin studies

For many decades familial aggregation of schizophrenia and bipolar disorder without cosegregation of both disorders was cited as a strong argument for the dichotomic position. The empirical proof of this argument requires family and twin studies covering simultaneously bipolar disorder and schizophrenia in comparison to controls. Only a very few family studies fit these criteria. The empirical evidence in favor of a nosological dichotomy of schizophrenia and bipolar disorder emerging from these studies is not in agreement with a dichotomic position. A hallmark stdy, the lowa-500 study by Tsuang et al. (1980), revealed an excess of bipolar disorder in families of probands with schizophrenia. Other controlled family studies observed a link of Schizophrenia as well as of bipolar disorder to unipolar depression (Gershon et al., 1988; Maier et al., 1993), or an aggregation of psychotic affective disorders in families of probands with schizophrenia and bipolar disorder (Kendler et al., 1993). More recent family reports producet an even more distinct overlap of bipolar disorders in families of schizophrenic patients and vice versa (Valles et al., 2000; Maier et al., 2002). The most recent extended study in siblings was conducted trough case registers in New Zealand (Osby et al., 2003, verbal communication) reporting a relative risk (odds ratio) of 3.6 (2.9-4.4) for bipolar disorder among first-degree relatives of probands with schizophrenia, and of 4.4 (3.5-5.4) for schizophrenia among first-degree relatives of probands with bipolar disorder (comparator: unaffected controls). In comparison, the recurrence risks for schizophrenia in relatives was increased by a factor of 7.4 (6.8-8.1), and for bipolar disorder in relative by a factor of 12.8 (10.6-15.3). given that diagnoses were derived from registers, misclassifications cannot be excluded and possibly influenced the magnitude of reported results However, other studies with extremely carefully

validated diagnostic rocedures are pointing in a qualitatively similar direction. High-risk studies in offspring of probands with schizophrenia in comparison to probands with affective disorders demonstrated excess cosegregation: more cases with psychotic disorders in kids of affective disorder probands, more cases with affective disorders in kids of schizophrenia parents compared to the general population (Erlenmeyer-Kimling et al., 1997). The reanalysis of the Maudsley twin series demonstrated that the overlap of familial vulnerabilities is due to genetic factors shared between schizophrenia and mania (Cardno et al., 2002): diagnosis-specific additive genetic variance was reported as 33% for schizophrenia, and as 19% for mania, compared to 49% and 68% respectively of common additive genetic variance.

There is also symptomatic overlap between bipolar disorder and schizophrenia: psychotic affective disorders share both symptom clusters. It might be suggested that this symptomatic subgroup combines the two disorders and carries the genetic vulnerabilities to each of them. Thus, clustering of psychotic symptoms in families of patients with psychotic affective symptoms have to be explored. This possibility might at least partly explain excess risk for schizophrenia in relatives of bipolar probands; the empirical evidence for this constellation, however, is controversial (Tsuang et al., 2004).

Furthermore, aggregation of bipolar disorder in families of schizophrenic patients could be restricted to psychotic bipolar disorder which might put psychotic bipolar disorder in a distinct nosological position. Empirical evidence for these possibilities is available (e.g., Kendler et al., 1993; Maier et al., 2002) but not consistently so.

Despite of this inconsistency, there is now growing evidence of a cosegregation between affective disorders (including bipolar disorder) and schizophrenia.

Search strategies for disposition genes

Both, schizophrenia and bipolar disorder are genetically complex diseases driven by genetic as well as environmental factors. The search of disposition genes can be accomplished by linkage and association studies: Linkage studies identify candidate regions which are likely to host disposition genes. Candidate regions might cover broad areas on the genome (10-30 cMorgans corresponding to 10-30 milion base pairs).

Association studies identify smaller regions with markers in linkage disequilibrium including those for disposition genes Linkage disequilibrium describes dependency between the distribution of two genetic markers on the same chromosome; it is dependent on the sampled population and ranges up to 100.000 base pairs in the mean in Caucasian populations, however, meaningful genetis analyses assume linkage disequilibrium of 15.000 (Schulze et al., 2004). Thus, the associated marker is not necessarily the directly influential variant; the marker is, however, in linkage disequilibrium with the pathogenic mutation. Association studies can be parformed only with preselected specific candidate genes or can be performed across limited regions on a chromosome; genome-wide association studies require high through-put technologies with a very high number of markers (> 1 milion) and are currently not yet feasible. Given the high risk for false positives, replication of postulated linkage and association findings are obligatory for their validity.

Currently, there are confirmed linkages between schizophrenia and markers in specific candidate regions and confirmed association findings in some candidate regions; some of them were also found to be linked to bipolar disorder. We are exploring the possibility of genetic variants whicht exert pleitropis effects by influencing both schizophrenia and bipolar disorder. How can linkage and association studies contribute to the clarification of this possibility? Is the overlap between candidate regions for bipolar disorder and for schizophrenia informative to this question? Is the association of a marker to schizophrenia as well as to bipolar disorder able to provide evidence for common genetic determinants?

Linkage analyses

Genome-wide linkage analysis is a most efficient tool in detecting causal disease genes in monogenic disorders. This technique is less efficient in genetically influenced complex diseases with multiple contributing genes. Initially, a high degree of inconsistency was noted among implicated candidate regions in about 20 schizophrenia and about 18 bipolar disorder scans, and the appropriateness of this strategy for genetically complex disorders was critically discussed (DeLisi et al., 2002). Most investigated samples, however, were underpowered to be able to replicate postulated linkages to candidate regions. Metaanalyses combining all published genome-wide scans provide a feasible opportunity to circumvent this limitation.

Two meta-analyses were performed for schizophrenia as well as for bipolar disorder; fortunately, the data analysis was perfomed in parallel for

schizophrenia and bipolar disorder allowing conclusions on the overlap of candidate regions. Overall, both metaanalyses conclude that there is substantially more consistency than expected on the basis of a comparison between suggestive linkage results of specific linkage studies. However, the analytic technique for a metaanalysis of linkage studies is not straightforward: Given the variation of linkage disequilibrium between nearby markers across populations the positional information of a linkage signal is not accurate. We have two sources of evidence for linkage on the basis of multiple studies: (a) the actual linkage scores combined across various studies at a specific marker locus, and (b) the aggregation of linkage signals in a small region with multiple markers in linkage disequilibrium. The various techniques of metaanalyses give differential weight to these alternative rationales resulting in different candidate regions. Yet, as both modes of reasoning are appropriate, all metaanalytic conclusions based on different analytic techniques might be true. Yet, two different analytic methods were applied resulting in different confirmed linkage findings:

Badner and Gershon (2002) used only a subset of published genome scans and found strong evidence for linkage

(a) for schizophrenia on 13q31 and 22q11-13, with the 13q-linkage showing strongest evidence ($p < 6x10 -6$),

(b) for bipolar disorder on 8p22, 13q31 and 22q 11-13, with the 13q-linkage showing the maximal evidence ($p < 7x10-5$).

Thus, most of the identified candidate regions (22q and 13q) with strongest evidence (i.e., genome-wide statistical significance) reveal an overlap between both disorders.

The more comprehensive meta-analyses by Lewis et al. (2003) for schizophrenia and by Segurado et al. (2003) for bipolar disorder found strong evidence for linkage only for schizophrenia; evidences for linkage to bipolar disorder were only moderate. Ignoring this difference the strong and/0r moderate evidence for linkage was found in the following chromosomal regions:

(a) for schizophrenia primarily on 2q, but also on 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q and 14p,
(b) for bipolar disorder on 10q 11.21-22, 9p22-21, 14q24-32.

Thus, just considering the strongest p-values for candidate regions no overlap of candidate regions between schizophrenia and bipolar disorder can be concluded

according to this more comprehensive analyses. Yet, there is still aconsidrable number of overlapping candidate regions if nominal p-values (P avgRnk > 0.05) are also considered:

- 2q22. 1-q23.3 for both disorders,
- 8p22 (8pter-p22 for bipolar disorder, and 8p22-p21-p21. 1 for schizophrenia),
- 14q13.1 (14q13.1-q24. 1 for bipolar disorder, and 14pter-14q31.1 for schizophrenia).

These are three overlapping candidate regions among 12 candidate regions for schizophrenia and 21 candidate regions for bipolar disorder with nominally significant pvalues.

Previously, a systematic review of the published genome scans exploring regions of overlap between replicated diagnosis-specific candidate regions prposed five common linked regions (Berrettini, 2003): 18p 11.2, 13q32, 22q 11-13, 8p22, 10p14.

Thus , although the combined analysis of available genome-wide linkage analyses provided different results depending on the applied method, a considerable overlap of validated candidate regions between schizophrenia and bipolar disorder can be observed – for all modes of biometric analyses.

Pleiotropis genetic effects with a specific DNA-sequence variation influencing the manifestation of tvo different disorders can only be proven if the pathogenic mutation is known. Linkage to the same candidate region and association to the same marker can only propose the possibility of common genetic determinants.

Cytogenetic abnormalities

Several defined cytogenetic alterations of the DNA string reveal major psychiatric syndromes. Most extensively explored are a translocation on chromosome 1q, and chromosome 22q microdeletions. It is most noteworthy that both abnormalities are associated with the occurrence of schizophrenia as well as of affective disorders in the same families.

A balanced reciprocal translocation (1;11) (q42; q14.3) was found to cosegregate with psychotic syndromes in a large Scottish family (Blackwood et al., 2001). Strong linkage at this region q42; q14.3) was found to cosegregate with psychotic syndromes in a large Scottish family (Blackwood et al., 2001).

Strong linkage at this region q42 was calculated for schizophrenia (LOD score = 3.6), and even higher for affective disorders (LOD score = 4.5); linkage can be maximized by considering all kinds of psychotic and affective disorders as affected (LOD score = 7.1). A refined clinical analysis reveals that the DISC phenotype includes schizophrenia, schizoaffective disorder, bibolar disorder and recurrent major depression but also neurophysiological abnormalities in absence of clinical diagnoses; particularly, the most common abnormality among carriers of the balanced t (1; 11) translocation shows a reduced P300 amplitude in response to an oddball discrimination task which occurred in carriers with the various mentioned diagnoses as well as in unaffected carriers (Blackwood and Muir, 2004). This neurophysiological abnormality is also consistently observed in schizophrenia but also in affective disorders (friedman and Squires-Wheeler, 1994; Pierson et al., 2000).

The translocation disrupts two genes which were called DISC1 and DISC2; they might be involved in the cytoskeletal regulation which is relevant for neuronal development, neuronal architecture and intracellular transport. In particular DISC1 interacts with a variety of cytoskeletal proteins, some of them are associated with cortical development (Ozeki et al., 2003). The translocation is up to now only observed in a single family. Could the family-specific linkage be of more general relevance? The answer is yes, as the translocated 1q region is closely located to markers showing linkage to schizophrenia in two Finnish samples (Hovatta et al., 1999; Ekelund et al., 2001). Thus, the DISC 1 and DISC2 genes are hot candidates for susceptibility genes of major disorders. Yet, the pathogenic mutations still have to be identified.

The Velo-Cardio-Facial syndrome (VCFS) – also called DiGeorge syndrome – is a monogenic disorder caused by interstitial deletions in a specific region of chromosome 22:q11. This syndrome is characterized by facial malformations and congenital heart disease. It reveals a sharp excess of prevalence in major psychiatric syndromes with more than 25% (Bassett et al., 2001) – mainly with severe psychotic and affective disorders which are similar to both schizophrenia and bipolar disorder (Carlson et al., 1997). These
disorders are also segregating and cosegregating in the VCFS families.

Given the very small prevalence (> 1%) of VSFS in the general population, the impact of this syndrome-specific genetic association on schizophrenia as vell as on bipolar affective disorders might be negligible. Yet, the 22q 11 microdeletions are also slightly more common in unselected samples of patients With schizophrenia (2% compared to 1% among 4000 in the general population) (Scambler, 2000); similar figures for bipolar disorder are not

available. Although linkage of schizophrenia to 22q11 did not show up in a recent large-scale multicenter study (Mowry et al., 2004), it revealed to be one of the most consistent and strongest findings emerging in another meta-analysis covering all published genome-wide scans (Badner and Gershon, 2002). Thus, it is possible that the same gene in 22q22-q22 is impacting on schizophrenia and bipolar disorder in the VCFS families as well as in larger samples of multiplex families. There is considerable dispute which of the genes in the 22q 11 region presents as disposition gene; e.g., there is some but still insufficient evidence for COMT (Shifman et al., 2002) and PRODH2 (Liu et al., 2002) in schizophrenia; the COMT gene is also discussed as disposition gene for bipolar disorder (Shifman et al., 2004) (s.below).

Susceptibility genes

There is rapidly growing evidence for DNA-sequence variations in specific genes to be implicated in the manifestation of schizophrenia. A substantial proportion of these genes are apparently also involved in the etiology of bipolar disorder. Currently, it is quite evident that the neuregulin-1 gene, dysbindin gene, G72/G30 gene and possibly also the COMT gene are involved in schizophrenia (Chumakov et al., 2002; Shifman et al., 2002; Straub et al., 2002; Schwab et al., 2003; Stefansson et al., 2002, 2003). Subsequently, it was recognized that the G72/G30 gene and possibly also the COMT gene are also involved in the etiology of bipolar disorder evidenced by identical markers for both disorders (Hattori et al., 2003; Schumacher et al., 2004).

Complex behaviours as psychotic and affective disorders are influenced by multiple genes, and an influencing gene generally affects multiple behavioural components at various physiological functions (Kas and van Ree, 2004). In this context it is of interest that each of the idenfitied genes is involved in multiple physiological pathways; simultaneously, the physiological targets are, however, very similar between the identified susceptibility genes (with the exception of the COMT gene): They are involved in the glutamatergic transmission (Collier and Li, 2003), in the development and the survival of neurons and glia cells. However, the functional consequences of each of these genes are currently only poorly understood.

G30/G72 gene:

The strongest support for specific susceptibility genes common to schizophrenia and bipolar disorder comes from the G30/G72 gene in the 13q candidate region (Hattori et al., 2003; Addington et al., 2004; Chen et al., 2004; Korostishevsky et al., 2004; Wang et al., 2004). There is a curiosity with this gene locus: G30 and G72 are two overlapping genes with G30 including G72; the over-transmitted marker variants and naplotypes differ between populations (Koorostishevsky et al., 2004). A haplotype in this gene was found to be associated with schizophrenia in a Russian and a Canadian sample, and was subsequently replicated in several other samples including a German one (Chumakov et al., 2002; Schumacher et al., 2004). Associations of other G30/G72 haplotypes were also reported for schizophrenia in the Ashkenazi population (Korostishevsky et al., 2004) and for childhoodonset schizophrenia (Addington et al., 2004). The pathogenic mutations are not yet identified but might be located in the vicinity of this gene complex or in the regulatory region (Korostishevsky et al., 2004).

The overlap of the candidate regions in this chromosomal section between schizophrenia and bipolar disorder motivated the genetic association studies in bipolar disorder with the identical G30 haplotype being found to be associated with bipolar disorder and schizophrenia. However, in some populations the at-risk haplotypes are shared between schizophrenia and bipolar disorder (Schumacher et al., 2004). The function of both genes is not yet known. However, G30 is in vitro interacting with the DAOA gene (D-amino-acid oxidase activator); gnetic variants of this gene were also found to be associated with bipolar disorder and schizophrenia (Schumacher et al., 2004) but not consistently so (Hattori et al., 2003). DAOA is of particular interest as it degrades serine which is modulating the glutamaergic NMDAR1 receptor which is differently expressed in both disorders, schizophrenia and bipolar disorder (Law and Deakin, 2001).

Leboyer et al. (1998) discussed the possibility that the more basic symptoms might be in a stronger relationship to susceptibility genes than those symptom patterns which are defining disorders which are validated through clinical conventions. They proposed the concept of candidate symptoms; a refined phenotype analysis by schulze et al. (in preparation) applied this idea and searched for symptoms in strong relationship to the G30 at-risk haplotype among subjects with bipolar disorder. Persecutory delusions were the only symptom with this property; this finding is unlikely to be a false positive as it could be replicated in an independent sample. As a consequence a distinct

etiological status of bipolar disorder with this specific psychotic symptom can be concluded.

BDNF gene:

The brain-derived neurotrophic factor (BDNF), the gene being located on chromosome 11p13 outside of confirmed candidate regions, is belongin to the family of neurotrophic factors and is involved in neuronal development, migration, growth and survival of neurons, but also in active-dependent neuronal activity and learning processes as long-term potentiation (Green and Craddock, 2003). BDNF transcripts are reduced in the hippocampus of both bipolar disorder and schizophrenia (Knable et al., 2004). The gene is expressed in hippocampus and neocortex, and reveals several polymorphisms; one of them results in an amino-acid substitution with functional impact in cell models on activity-dependent secretion (Val66Met); the more common variant of this polymorphism is also associated with enhanced episodic memory achievement (Egan et al., 2003). Two other polymorphisms in nonexpressed sections of the gene are also known. Thus, the BDNF gene presents as an apriori ideal candidate gene for foth bipolar disorder and schizophrenia. And indeed, two convincing family-based association studies proposed an association of the common Val-variant with bipolar disorder in Caucasian populations (Neves-Pereira et al., 2002; Sklar et al., 2002) which could, however, not be replicated in Japanese populations (Nakata et al., 2003).

An unexpressed dinucleotide repeat (GT)n polymorphism located close to the promoter region of the BDNF gene was also reported to be associated with schizophrenia in one but not in several other samples (Muglia et al., 2003). Furthermore, in a single study another polymorphism using a novel nucleotide substitution (C270T) was investigated in a recent case-control sample with cases with schizophrenia, and provided a positive result (Szekeres et al., 2003).

Taken together, the positive association results with multiple polymorphisms are difficult
to interpret in the context of negative reports both for schizophrenia and bipolar disorder. The BDNF gene, thus, remains a very promising candidate gene which might have a modest effect on each of both disorders.

COMT gene:

The catechol-O-methyltransferase (COMT) gene is located in the 22q 11 candidate region for schizophrenia and bipolar disorder which is confirmet in

meta-analysis. The gene product is a dopamine-degrading enzyme; dopamine is involved in the pathophysiology of schizophrenia and bipolar disorder. The COMT gene carries multiple polymorphisms with at least one of them is of functional relevance: Val158Met. The Met-variant causes a substantially reduced enzyme activity inducing an increased level of dopamine in the prefrontal area which is involved in working memory (which is impaired in schizophrenia as well as in bipolar disorder); consequently, carriers of this more common Val-variant are less efficient in working memory tasks independent of their affection status (Egan et al., 2001).
The Val-variant was also proposed to be over-transmitted in subjects with schizophrenia, but up to now the cumulative evidence is only spurious with maximally a very small effect size (Glatt et al., 2003). However, haplotypes tapping three other polymorphisms turned out to be more strongly associated with schizophrenia (Shifman et al., 20029. The same haplotype turned out to be also associated with bipolar disorder (Shifman et al., both disorders, but the functional Val 158Met variant is probably not of pathogenic impact.

PIPK2A gene:

A most interesting candidate regionin this context is 10p12. Linkage to schizophrenia has been confirmed in several family studies (Faraone et al., 1998; Schwab et al., 1998: Foroud et al., 2000). Linkage to bipolar disorder was also reported (Rice et al., 1997). These linkage results are complemented by associations to a variant of the PIP5K2A gene, both of schizophrenia and bipolar disorder (Stopkova et al., 2003). Schwab et al. (1998) also detected variants of the closely nearby placed PIPK2 gene for schizophrenia. Remarkably, both genes are involved in the phosphate inositol metabolism. Phosphoinositol pathways are involved in intracellular signal transmission, particularly in the context of long-term potentiation, a mechanism relevant for episodic memory which is impaired in schizophrenia; furthermore, phosphoinositol is modulated by lithium. It is speculated that an inositol deficit contributes to bipolar disorder. The phosphoinositol-related findings might introduce a hypothetical common neurobiological basis for schizophrenic and manic syndromes with therapeutic implications. Yet, the implication of phophoinositol-related genes still have to be confirmed. In this context it is particularly relevant to noticethat PIP5K2A is a critical component of the phosphoinositide and inositol phosphate pathways are modulated by lithium, an effective drug for bipolar and schizoaffective disorders.

Other candidate genes can also be discussed to be related to schizophrenia as well as to bipolar disorder, particularly DNA-sequence variants in genes coding for proinflammatory factors: the interlleukin-1ß in the interleukin-1 cluster on chromosome 2q13 (outside of the candidate region 2q22) (Papiol et al., 2004), and the tumor necrosis factor alpha gene located in the schizophrenia candidate region 6p close to the HLA region (Schwab et al., 2003; Pae et al., 2004); the empirical basis, however, is limited and far from being convincing, further replications are required.

Conclusion

There is emerging evidence that schizophrenia and bipolar disorder define no etiologically distinct disorders. A Series of family and twin studies as well as molecular-genetic studies propose some etiological overlap which is at least partially due to genetic factors. In conclusion there is overlapping inheritance which might be due to shared polygenic mutations in the same disposition genes in terms of cosegregation in families and twins..

A first common disposition gene (G30/G72) was identified for both disorders, and it can be expected that other disposition genes of this kind will follow given the overlap of candidate regions detected by linkage analysis and common functional and molecular neurobiological features. Although some association studies observed the same at-risk haplotype associated with both disorders. As the pathogenic variants are not yet identified it still remains unclear if both disorders are driven by the identical genetic variants and mechanisms (e.g. , in the gene G30/G72). Given the strong DNA-sequence variability observable in many genes two nearby located but different variants within the same gene coding specifically for each of both disorders remain a possibility.

Diagnostic entities are based on clinical conventions which might lack etiological and pathophysiological validity. Therefore, the observed genetic overlap between schizophrenia and bipolar disorder might have different meanings. The most plausible alternatives are:

(a) Both or one of both disorders are etiologically and pathophysiologically heterogeneous, e.g., there is a distinct subtype (e.g., psychotic bipolar disorder) explaining the overlap but not being considered as a separate diagnostic entity.

(b) Both disorders share common symptomatic and or neurophysiological features which have their own genetic underpinning which is consequently shared between both disorders

(c) Complex behaviour is driven by multiple genes, and each variant in these genes is predisposing to different aspects of behaviour depending on spatial distribution of geneexpression patterns which might be triggered by environment (pleiotropy); thus, the same genetic factor might induce schizophrenia as well as bipolar symptoms depending on the context.

Although some arguments were discussed in favor of possibility (b), the current status of knowledge does not allow a conclusive decision.

References

Addington AM, Gornick M, Sporn AL, Gogtay N, Greenstein D, Lenane M, Gochman P, Baker N, Balkissoon R, Vakkalanka RK, et al. (2004) Polymorphisms in the 13q33.2 gene G72/G30 are associated with childhood-onset schizophrenia and psychosis not otherwise specified. Biol Psychiatry 55: 976-980.

Badner JA, Gershon ES (2002) Meta-analysis of whole-genome linkage scans of bipolar disorder and schizophrenia. Mol Psychiatry 7: 405-411.

Bassett AS, Chow EW, Waterworth DM, Brzustowicz L (2001) Genetic insights into schizophrenia. Can J Psychiatry 46:131-137.

Berrettini W (2003) Evidence for shared susceptibility in bipolar disorder and schizophrenia. Am J Med Genet 123C: 59-64.

Blackwood DH, Fordyce A, Walker MT, St Clair DM, Porteous DJ, Muir WJ (2001) Schizophrenia and affective disorders – cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. Am J Hum Genet 69: 428-433.

Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P (2002) A twin study of genetic relationships between psychotic symptoms. Am J Psychiatry 159: 539- 545.

Carison C, Papolos D, Pandita RK, Faedda GL, Veit S, Goldberg R, Shprintzen R, Kucherlapati R, Morrow B (1997 Molecular analysis of velo-cardio-facial syndrome patients with psychiatric disorders. Am J Hum Genet 60: 851-859

Chen Y-S, Akula N, Detera-Wadleigh SD, Schulze TG, Thomas J, Potash JB, DePaulo JR, Mclnnis MG, Cox NJ, McMahon FJ (2004) Findings in an independent sample support an association between bipolar affective disorder and the G72/G30 locus on chromosome 13q33. Mol Psychiatry 9: 87-92.

Chumakov I, Blumenfeld M, Guerassimenko O, Cavarec L, Palicio M, Abderrahim H, Bougueleret L, Barry C, Tanaka H, La Rosa P, et al. (2002) Genetic and physiological data implicating the new human gene G72 and the gene for D-amino acid oxidase in schizophrenia. Proc Natl Acad Sci U S A 99: 13675-13680.

Clinton SM, Meador-Woodruff JH (2004) Abnormalities of the NMDA receptor and associated intracellular molecules in the thalamus in schizophrenia and bipolar disorder. Neuropsychopharmacology 29: 1353-1362.

Collier DA, Li T (2003) The genetics of schizophrenia: glutamate not dopamine? Eur J Pharmacol 480: 177-184.

DeLisi LE, Craddock NJ, Detera-Vadleigh S, Foroud T, Gejman P, Kennedy JL, Lendon C, Macciardi F, McKeon P, Mynett-Johnson L, et al. (2002) Update on chromosomal locations for psychiatric disorders: report of the interim meeting of chromosome workshop chairpersons from the VIIth World Congress of Psychiatric Genetics, Monterey California, October 14-18, 1999. Am J Med Genet 96: 434-449.

Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR (2001) Effect of COMT Val 108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A 98: 6917-6922.

Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev A, Gold B, Goldman D, Dean M, et al. (2003) The BDNF val66met polymorphism affects activitydependent secretion of BDNF and human memory and hippocampal function. Cell 112: 257-269.

Ekelund J, Hovatta I, Parker A, Paunio T, Varilo T, Martin R, Suhonen J, Ellonen P, Chan G, Sinsheimer JS, et al. (2001) Chromosome 1 loci in Finnish schizophrenia families. Hum Mol Genet 10:1611-1617.

Erlenmeyer-Kimling L, Adamo UH, Rock D, Roberts SA, Bassett AS, Squires.Wheeler E, Cornblatt BA, Endicott J, Pape S, Gottesmann II (1997) The New York High- Risk Project. Prevalence and comorbidity of axis I disorders in offspring of schizophrenic parents at 25-year follow-up. Arch Gen Psychiatry 54: 1096-1102.

Faraone SV, Matise T, Svrakic D, Pepple J, Malaspina D, Suarez B, Hampe C, Zambuto CT, Schmitt K, Meyer J, et al. (1998) Genome scan of European-American schizophrenia pedigrees: results of the NIMH Genetics Initiative and Millennium Consortium. Am J Med Genet 81:290-295.

Foroud T, Castelluccio PF, Koller DL, Edenberg HJ, Miller M, Bowman E, Rau NL, Smiley C, Rice JP, Goate A, Et al. (2000) Suggestive evidence of a locus on chromosome 10p using the NIMH genetics initiative bipolar affective disorder pedigrees. Am J Med Genet 96:18-23.

Friedman D, Squires-Wheeler E (1994) Event-related potentials (ERPs) as indicators of risk for schizophrenia. Schizophr Bull 20: 63-74

Gershon ES, DeLisi LE, Hamovit J, Nurnberger JI Jr, Maxwell ME, Schreiber J, Dauphinais D, Dingman CW 2nd, Guroff JJ (1988) A controlled family study of chronic psychoses. Schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 45: 328-336.

Glatt SJ, Faraone SV, Tsuang MT (2003) Association beteen a functional catechol Omethyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. Am J Psychiatry 160: 469-476.

Green E, Craddock N (2003) Brain-derived neurotrophic factor as a potential risk locus for bipolar disorder: evidence, limitations, and implications. Curr Psychiatry Rep 5: 469-476.

Hattori E, Liu C, Badner JA, Bonner TI, Christian SL, Maheshwari M, Detera-Madleigh SD, Gibbs RA, Gershon ES (2003) Polymorphisms at the G72/G30 gene locus, on 13q33, are associated with bipolar disorder in two independent pedigree series. Am J Hum Genet 72:1131-1140.

Hovatta I, Varilo T, Suvisaari J, Terwilliger JD, Ollikainen V, Arajarvi R, Juvonen H, Kokko-Sahin Ml, Vaisanen L, Mannila H, et al. (1999) A genomewide screen for schizophrenia genes in an isolated Finnish subpopulation, suggesting multiple susceptibility loci. Am J Hum Genet 65:1114-1124.

Kas MJ, Van Ree JM (2oo4) Dissecting complex behaviours in the post-genomic era. Trends Neurosci 27: 366-369.

Kendler KS, McGuire M, Gruenberg AM, O Hare A, Spellman M, Walsh D (1993) The Roscommon Family Study. IV, Affective illness, anxiety disorders, and alcoholism in relatives. Arch Gen Psychiatry 50: 952-960.

Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF (2004) Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem fundigs from the Stanley Neuropathology Consortium. Mol Psychiatry 9: 609-620.

Korostishevsky M, Kaganovich M, Cholostoy A, Ashkenazi M, Ratner Y Dahary D, Bernstein J, Bening-Abu-Shach U, Ben-Asher E, Lancet D, et al. (2004) Is the G72/G30 locus associated with schizophrenia? Single nucleotide polymorphisms, haplotypes, and gene expression analysis. Biol Psychiatry 56: 169-176.

Law AJ, Deakin JF (2001) Asymmetrical reductions of hippocampal NMDAR1 glutamate receptor mRNA in the psychoses. Neuroreport 12: 2971-2974.

Leboyer M, Bellivier F, Nosten-Bertrand M, Jouvdent R, Pauls D, Mallet J (1998)
Psychiatric genetics: search for phenotypes. Trends Neurosci 21: 102-105.

Lewis CM, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Wiliams NM, Schwab SG, Pulver AE, Faraone SV, et al. (2003) Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. Am J Hum Genet 73: 34-48.

Liu H, Abecasis GR, Heath SC, Knowles A, Demars S, Chen YJ, Roos JL, Rapoport JL, Gogos JA, Karayiorgou M (2002) Genetic Variation in the 22q11 locus and susceptibility to schizophrenia. Proc Natl Acad Sci U S A 99:16859-16864.

Lopez-figueroa AL, Norton CS, Lopez-Figueroa MO, Armellini-Dodel D, Burke S, Akil H, Lopez JF, Watson SJ (2004) Serotonin 5-HT1A, 5-HT1B, and 5-HT2A receptor mRNA expression in subjects with major depression, bipolar disorder, and schizophrenia. Biol Psychiatry 55: 225-233.

Maier W, Lichtermann D, Minges J, Hallmayer J, Heun R, Benkert O, Levinson DF (1993) Continuity and discontinuity of affective disorders and schizophrenia. Results of a controlled family study, Arch Gen Psychiatry 50: 871-883.

Maier W, Lichtermann D, Franke P, Heun R, Falkai P, Rietschel M (2002) The dichotomy of schizophrenia and affective disorders in extended pedigrees. Schizophr Res 57: 259-266.

Mortensen PB, Pedersen CB, Melby M, Mors O, Ewald H (2003) Individual and familial risk factors for bipolar affective disorders in Denmark. Arch Gen Psychiatry 60: 1209-1215.

Mowrz BJ, Holmans PA, Pulver AE, Gejman PV, Riley B, Williams NM, Laurent C,Svhwsb SG, Wildenauer DB, Bauche S, et al. (2004) Multicenter linkage study of schizophrenia loci on chromosome 22q. Mol Psychiatry 9:784-795.

Muglia P, Vicente AM, Verga M, King N, Macciardi F, Kennedy JL (2003) Association between the BDNF gene and schizophrenia. Mol Psychiatry 8: 147-148.

Nekata K, Ujike H, Sakai A, Uchida N, Nomura A, Imamura T, Katsu T, Tanaka Y, Hamamura T, Kuroda S (2003) Association study of the brain-derived neurotrophic factor (BDNF) gene with bipolar disorder. Neurosci Lett 337:17-20.

Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL (2002) The brainderived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am J Hum Genet 71: 651-655.

Ozeki Y, Tomoda T, Kleiderlein J, Kamiya A, Bord L, Fuji K, Okawa M, Yamada N, Hatten ME, Snyder SH, et al. (2003) Disrupted-in-Schizophrenia-1 (DISC-1): mutant truncation prevents binding to NudE-like (NUDEL) and inhibits neurite outgrowth. Proc Natl Acad Sci U S A 100: 289-294.

Pae CU, Lee KU, Han H, Serretti A, Jun TY (2004) Tumor necrosis factor alpha gene- G308A polymorphism associated with bipolar I disorder in the Korean population. Psychiatry Res 125: 65-68.

Papiol S, Rosa A, Gutierrez B, Martin B, Salgado P, Catalan R, Arias B, Fananas L (2004) Interleukin-1 cluster is associated with genetic risk for schizophrenia and bipolar disorder. J Med Genet 41: 219-223.

Pierson A, Jouvent R, Quintin P, Perez-Diaz F, Leboyer M (2000) Information processing deficits in relaltives of manic depressive patients. Psychol Med 30: 545-555.

Rice JP, Goate A, Williams JT, Bierut L, Dorr D, Wu W, Shears S, Gopalakrishnan G, Edenberg HJ, Foroud T, et al. (1997) Initial genome scan of the NIMH genetics initiative bipolar pedigress: chromosomes 1, 6, 8, 10, and 12. Am J Med Genet 74: 247-253.

Scambler PJ (2000) The 22q 11 deletion syndromes. Hum Mol Genet 9: 2421-2426.

Schulze TG, Chen Y-S, Akula N, Hennessy K, Badner JA, Mclnnis MG, DePaulo JR, Schumacher J, Ckichon S, Propping P, et al. (2004) Can long-range microsatellite data be used to predict short-range linkage disequilibrium? Hum Mol Genet 11: 1363-1372.

Schumacher J, Jamra RA, Freudenberg J, Beckr T, Ohiraun S, Otte AC, Tullius M, Kovalenko S, Bogaert AV, Maier W, et al. (2004) Examination of G72 and D-amino-acid oxidase as genetic risk factors for schizophrenia and bipolar affective disorder. Mol Psychiatry 9: 203-207.

Schwab SG, Hallmayer J, Albus M, Lerer B, Hanses C, Kanyas K, Segman R, Borrman M, Dreikorn B, Lichtermann D, et al. (ll998) Further evidence for a susceptibility locus on chromosome 1014-p11 in 72 families with schizophrenia by nonparametric linkage analysis. Am J Med Genet 81: 302-307.

Schwab SG, Knapp M, Mondabon S, Hallmayer J, Borrmann-Hassenbach M, Albus M, Lerer B, Rietschel M, trixler M, Maier W, et al. (2002) Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. Am J Hum Genet 72: 185-90.

Schwab SG, Mondabon S, Knapp M, Albus M, Hallmayer J, Borrmann-Hassenbach M, Trixler M, Gross M, Schulze TG, Rietschel M, (2003) Association of tumor necrosis factor alpha gene-G308A polymorphism with schizophrenia. Schizophr Res 65: 19-25.

Segurado R, Detera-Wadleigh SD, Levinson DF, Lewis CM, Gill M, Nurnberger JI jr, Craddock N, DePaulo JR, Baron M, Gershon ES, et al. (2003) Genome scan metaanalysis of schizophrenia and bipolar disorder. Part III: Bipolar disorder. Am J Hum Genet 73: 49-62.

Shifman S, Bronstein M, Sternfeld M, Pisante-Shalom A, Lev-Lehman E, Weizman A, Reznik I, Spivak B, Grisaru N, Karp L, et al. (2002) A highly significant association between a COMT haplotype and schizophrenia. Am J Hum Genet 71: 1296-1302.

Shifman S, Bronstein M, Sternfeld M, Pisante A, Weizman A, Reznik I, Spivak B, Grisaru N, Karp L, Schiffer R, et al. (2004) COMT: a common susceptibility gene in bipolar disorder and schizophrenia. Am J Med Genet 128B: 61-64.

Sklar P, Gabriel SB, Mclnnis MG, Bennett P, Lim YM, Tsan G, Schaffner S, Kirov G, Jones I, Owen M, et al. (2002) Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. Mol Psychiatry 7: 579-593.

Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, Brynjolfsson J, Gunnarsdottir S, Ivarsson O, Chou TT, et al. (2002) Neuregulin 1 and susceptibility to schizophrenia. Am J Hum Genet 71: 877-892.

Stefansson H, Sarginson J, Kong A, Yates P, Steinthorsdottir V, Gudfinnsson E, Gunnarsdottir S, Walker N, Petursson H, Crombie C, et al. (2003) Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. Am J Hum Genet 72:

Stopkova P, Saito T, Fann CS, Papolos DF, Vevera J, Paclt I, Zukov I, Stryjer R, Strous RD, Lachman HM (2003) Polymorphism screening of PIP5K2A: a candidate gene for chromosome 10p-linked psychiatric disorders. Am J Med Genet 123B: 50-58.

Straub RE, Jiang Y, MacLean CJ, Ma Y Webb BT, Myakishev MV, Harris-Kerr C, Wormley B, Sadek H, Kadambi B, et al. (2002) Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am J Hum Genet 71: 337-348.

Szekeres G, Juhasz A, Rimanoczy A, Keri S, Janka Z (2003) The C270T polymorphism of the brain-derived neurotrophic factor gene is associated with schizophrenia. Schizophr Res 65: 15-18.

Tkachev D, Mimack ML, Ryan MM, Wayland M, Freeman T, Jones PB, Starkey M, Webster MJ, Yolken RH, Bahn S (2003) Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 362:798-805.

Tsuang MT, Winokur G, Crowe RR (1980 Morbidity risks of schizophrenia and affective disorders among first degree relatives of patients with schizophrenia, mania, depression and surgical conditions. Br J Psychiatry 137: 497-504.

Tsuang MT, Tazlor L, Faraone SV (2004) An overview of the genetics of psychotic mood disorders. J Psychiatr Res 38: 3-15.

Tsuang MT, Taylor L, Faraone SV (2004) An overview of the genetics of psychotic mood disorders. J Psychiatr Res 38: 3-15.

Valles V, Van Os J, Guillamat R, Gutierrez B, Campillo M, Gento P, Fananas L (2000)Increased morbid risk for schizophrenia in families of in-patients with bipolar illness. Schizophr Res 42: 83-90.

Wang X, He G, Gu N, Yang J, Tang J, Chen Q, Liu X, Shen Y, Qian X, Lin W, et al. (2004) Association of G72/G30 with schizophrenia in the chinese populatinon. Biochem Biophys Res Commun 319: 1281-1286.

Woo TU, Walsh JP, Benes FM (2004) Density of glutamic acid decarboxylase 67 messenger RNA-containing neurons that express the N-methyl-D-aspartate receptor subunit NR2A in the anterior cingulate cortex in schizophrenia and bipolar disorder. Arch Gen Psychiatry 61: 649-657.

A GENOME 4-WIDE LINKAGE SCAN OF BIPOLAR DISORDER IN BULGARIAN AND ROMA FAMILIES

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INTERPLAY OF GENES AND ENVIRONMENT AS CONTRIBUTORY FACTORS IN SUICIDAL BEHAVIOUR

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Family studies show that the risk of suicide is increased when there is a suicide in the family, particularly when a violent method is used (Linkowski et al. 1985). One of the limitations of family studies is that they do not differentiate between genetic and other factors, as family members share both genetic as well as environmental factors. Classic research methods, which differentiate between that which is genetic and that which is acquired within the family, are the "natural experiments" of twin and adoption studies. In the case of identical twins the concordance of suicide is much greater than is the case with fraternal twins (Roy et al. 1991). Genetic model fitting on one of the largest studies of twins showed that 43 percent of the variability of suicidal behaviour can be explained by genetics (McGuffin et al. 2001).

If so, how can genetic factors increase the probability of suicidal behaviour in an individual? Suicide does not of course show a simple Mendelian pattern of transmission; there is not a 'suicide gene'. As in the case of other complex behaviour patterns, it is likely that the predisposition towards suicide consists of numerous genetic and environmental factors, which manifest themselves as suicidal behaviour only when a certain threshold of liability is crossed. In other words, we can talk about a polygenetic multifactorial aetiological model of suicidal behaviour.

How do we locate and identify genes that are involved in suicidal behaviour? The most practicable approach currently is to focus on so-called candidate genes, that is genes involved in metabolic pathways in the brain that could plausibly have something to do with suicidal behaviour. As it is thought that the variability of serotonergic neurotransmitters plays a pivotal role in individual differences in mood, impulsiveness and aggression, it is no surprise that molecular genetic studies of suicide and suicidal behaviour focus on serotonergic genes. Candidate genes can be classified into three subgroups:

- gene involved in synthesis of serotonin (*tryptophan hydroxylase – TPH* is the rate -limiting enzyme in serotonin synthesis);
- genes involved in serotonergic neurotransmission (*serotonin transporter - 5-HTT* regulates re-uptake of serotonin into pre-synaptic neuron and different *serotonin receptors* that also regulate neurotransmission), and
- genes involved in serotonin catabolism (*monoaminoxidase – MAO*).

One of the problems that has pervaded association studies in psychiatry, and indeed studies of many other common forms of disease, has been that attempted replications have been on so small a scale as to have little power to confirm original positive findings (Owen et al. 1997). In an attempt to overcome such shortcomings and problems of genetic studies of suicide, recently first meta-analyses of association studies of suicide behaviour were reported. Lalovic and Turecki (2002) reported negative results for intron 7 based on publications with an overall number of 1290 cases and 2295 controls. On the other hand, an analysis by Rujescu et al (2003) including only those studies that were performed on samples of similar ethnic origins and geographic closeness provides strong evidence for an association of suicide-related behaviour with an A218 nucleotide polymorphism in the TPH gene in Caucasians.

So far little attention has been paid to the possible interplay of genes with environmental factors. As such, a simultaneously performed candidate gene analysis and a study of life events and social support might be a way forward. As a nice example of such simultaneously performed research, Caspi et al (2003) tested why stressful experiences lead to depression in some people but not in others, by using a prospective-longitudinal study of a representative birth cohort. The functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. This epidemiological study provides evidence of a gene-by-environment interaction, in which an individual's response to environmental insults is moderated by his or her genetic makeup.

Until we know more about the genetic factors significant in the development of suicidal behaviour, most of the work related to suicide prevention will be directed at improving environmental conditions, particularly with respect to those individuals where the tendency towards suicidal behaviour is most pronounced. One should not however forget that identifying people at risk already has some societal implications and, therefore, raises a number of etical issues regarding public policy (Meltzer 2000). First of all, it will soon become very important to protect the confidentiality of data on individuals, from whom

material for molecular genetic research on suicide will have been taken. Secondly, we must make sure that potential subjects can provide informed consent. Thirdly, the question of to whom, when and how to present information once genetic testing becomes more commonplace will have to be addressed.

References

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A and Poulton R (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science* 301: 386-9.

Lalovic A and Turecki G (2002). Meta-analysis of the association between tryptophan hydroxylase and suicidal behavior. *American Journal of Medical Genetics*, 114 , 533-540.

Linkowski P, de Maertelaer V, Mendlewicz J (1985). Suicidal behavior in major depressive illness. *Acta Psychiatrica Scandinavica*, 72, 233–8.

McGuffin P, Marušič A, Farmer A (2001). What can psychiatric genetics offer suicidology? *Crisis,* 22, 61–5.

Meltzer HY (2000). Genetics and etiology of schizophrenia and bipolar disorder. *Biological Psychiatry*, 47, 171-3.

Owen MJ, Holmans P, McGuffin P (1997). Association studies in psychiatric genetics. *Molecular Psychiatry,* 2, 270-3.

Roy A, Segal NL, Centerwall BS, Robinette CD (1991). Suicide in twins. *Archives of General Psychiatry,* 48, 28–32.

Giegling I, Sato T, Hartmann AM, Moller HJ (2003). Genetic variations in tryptophan hydroxylase in suicidal behavior. Analysis and meta-analysis. *Biological Psychiatry*, 54 , 465-73.

POPULATION GENETICS AND EPIDEMIOLOGY – SCHIZOPHRENIA AS A THRESHOLD CHARACTER

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Most behavioural traits fit into the category of quantitative characters and are believed to be subject to a complex system of genetic determination, and simultaneously highly influenced by environmental factors (polygenic model of multifactorial inheritance). Accordingly, there is a set of several or many genes (a polygene), each having a relatively small contribution to the hereditary basis of a quantitative trait. The most important form of interaction between the genes of a polygene is considered to be addition. However, notwithstanding their equal mendelian nature, genes constituting a polygene do not have equal effect in the determination of a trait. The polygenic model has long been the fundamental model of quantitative (biometrical) genetics, although a "single locus with two alleles" model can in some instances account for a continuous phenotypic variation.

Heritability defined as genetic/nongenetic variance ratio can be estimated depending on the nature of the character and its variation in an array of different ways. Many methods have been developed for this purpose. But it is still fairly exceptional to apply population genetics techniques in the procedures of estimating heritability of psychiatric nosologic entities.

A case of heritability/liability estimation, using the specific data from several schizophrenia studies is presented. The aim is to explore the possibility of applying population genetics and its models in the epidemiological investigation of schizophrenia and related diseases which can be regarded as "threshold characters".

GENETIC POLYMORPHISMS INFLUENCING RESPONSE OF ANTIDEPRESSANTS

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Pharmacogenetic studies in mood disorders were performed only during recent years involving short term antidepressant response. Antidepressant drugs are the first line treatment for major depression but the therapeutic response in clinical practice is expected in about two thirds of patients. The large inter-individual variability in the pharmacological response pattern has been partially ascribed to heritable factors. We investigated the possible influence of a set of candidate genes as possible genetic predictors of antidepressant response efficacy. The functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR), the A218C gene variant on the tryptophan hydroxylase gene (TPH), the G-protein beta3-subunit (Gbeta3) C825T gene variant and the Circadian Locomotor Output Cycles Kaput (CLOCK) gene variants were independently associated with short term SSRIs antidepressant efficacy. The effects of 5-HTTLPR and TPH polymorphisms were more pronounced in subjects not taking pindolol, while this effect was not observed for Gbeta3 and CLOCK. CLOCK variants were associated with insomnia time course during treatment. We observed a significantly higher presence of insomnia throughout the trial in homozygotes for the C variant. A Neural network approach was developed for analyzing multiple gene polymorphisms simultaneously. The inclusion in the model of baseline depressive scores, polarity, presence of psychotic features and fluvoxamine plasma levels did not influence the observed association. DRD2, DRD4, Mao-A and 5-HT2A gene variants were not associated with outcome. These results shed further light on the genetically determined component of the response to pharmacological treatments.

GENETICS AND ETHICS

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"Do not wish death to the enemy, but long life to yourself"

Arabian adage

Today the most difficult thing to do is to study genetics and regain ethics. One does both things in order to provide better to the others. It is difficult to reach the aim.

Genetics, as a science, studies inherited factors, which affects the human development. Lesser degree of scientific knowledge emphasis higher degree of "no ones fields" in which many diseases are attributed to hereditary. Modern science tries to get inside all factors of human continuum and behaviour, and genetics gets more and more its exact position, which naturally belongs to it.

Multidisciplinary is deteological position of approach to all modern scientific studies, even those studying genetics. Some sciences are radically involved into human beginning among which are; psychology, sociology, economics, ethics. Other sciences are also in multidiscipline touch with beginning: biology, biochemistry, eugenic, medicine. Great number of sciences observes moral development and human beginning: andrology, politics, economics, law, philosophy to Freud's tautology.

Introduction

Genetics is a science about inherited. In philosophic sense, genetic refers to the beginning-genesis, concerning the history of beginning and development of plants and animals, heredity or science of heredity. Human genetics is a scientific discipline studying the influence of inherited factors on human development.
Moral and deteological in science are replaced with standards and regulations. In this way, one shows his/hers creativity, but within the limits which exist in modern medicine and psychiatry. In this normative part, the truth is ultimate, and

in the junction of two cannons there is multidiscipline. Today it is exactly scientific and legal need.

Ethical (moral) end of human action remains in all aspects, but the question is: Is the influence real or more frequently archaic and scholastic?

Researches Genetics

Biological factors in etiology of many diseases in psychiatry understand the influence of: anatomical-morphological, biological, physiological and biochemical factors.

Genetic factors are roughly investigated in the beginning of mental diseases, in investigation of epidemiological genetics and molecular biology.

Epidemiological genetics accepts the knowledge that dominant disease in psychiatry "schizophrenia occurs more frequently in certain families. Multimorbidity risk for members of patient's family (close relatives) is between 4% and 9%, not so close relatives have less chance to develop the disease" (S.Loga).

There are several assumptions how the disease can be inherited Monogenetic - certain gene is responsible for the development of the disease Poligenetic- many genes are responsible for the development of the disease Heterogenetic- the disease is not simple; it is heterogeneous, caused by the influence of many different factors.
Lowering of number of mutual genes lessens the risk of developing the disease
This disorder occurs on both, mother and father, sides

Mental disorders are inherited poligenetically and multifactorally. Voulnerability to mental disease is normally distributed in the family, but it is manifested only in those in which it passes the threshold of reaction.

Molecular genetics is performed at the level of chromosomal analysis with biological markers. In this way, the search for known genetic markers in families in which mental disease occurs is performed. Also, in this way we find the field of lingag analysis, which tells us that sensitive places are differently disseminated in the genome. There are positive findings on chromosomes 13q, 22q, 6p, 8p.

There are :1.linkage analysis researches, 2. gene cloning researches and 3. mRNA brain expressiveness researches.

Behaviour genetics studies the influence of inherited factors on psychological characteristics and behaviour. This genetics is based on the studies of families with psychological characteristics (mental backwardness) or illness. During past three centuries, heredity has been observed in "exotic mental illnesses", according to MKB-10.

Genetic psychology is genetic structuralism or Geneva school with great French influence. The school is an interesting collection of expansive psychoanalysis, Soviet objectivistic school and Anglo-Saxon behaviourism. In these scientific places results have emerged and become visible during 1950-s and they influenced psychological idea (thought) of that period.

Genetic psychology emphasizes the connection between genetic model and development of psychological functions. Genetic code is showed according to the development sequence during the lifetime, and with that process, complex psychological functions are developed. From the psychological point of view, the school prefers cognitive functions in mental development of the human being and gives it the name of cognitive orientation. (20).

Intellect is developed by senso-motoric period, which lasts 18 months and ends by controlling of the first symbols and development of abstract schemes. It is continued by the "preparation period" (until 6 to 7 years) in which symbolically development of speech happens together with process of abstraction and understanding of classification. Then a child than begins to make concrete conclusions, operates with negations, identity, reciprocity and it is able to close the value.

In period from 10 to 12 years formal-operational period starts and full thinking normalization, and ability of "superoperational" performing are achieved. This period lasts after the puberty. This is the characteristic of abstract thinking of an adult human being, which is very important for the development of moral reasoning. Logical reasoning is a base for moral reasoning, and ethics is the logic of human acts. In that way fundaments for moral reasoning and acting are formed.

In later phases of development under the behavioural influence, one cedes a lot of things to the moral judgment. On the bases of this one compromises basic moral principles (compromise compromitans). One actually lives between two

basic wombs, mother's and ground's, keeping the part of what he/she inherited and with(out) obligation to accept what the environment imposes.

Two latest great awards in the world in the field of the most finest researches of the brain structures tell us about the biggest expansion of genetic researches of the brain tissue. Daily information about human cloning (without knowledge about its legality) brings the human race into the reality: *Where is the human genetics going?*

Etics

Eugenic is one of the most important branches of social politics. It is also called race hygiene, the science about the conditions, which lead to production of physically and mentally healthy posterity. It prevents production of unhealthy and incapable posterity. It is a tendency of creating certain benevolent conditions.

Data suggest that F. Galton founded eugenic in 1870. He divided it into: positive, which improves human race by stimulating reproduction. Negative prevents the situation in which human being dies early. Blood relation helps appearance of physical and mental deficiencies. Applied eugenic could provide avoidance of reproduction if both parents are at risk. There can be found some legal problems of regulation of eugenic issues.

French law in January 1975 says: "a pregnant woman can bring her condition in unwanted situation; she can ask her doctor to perform an abortion. This abortion can be performed only before the completion of 10 weeks of pregnancy. Law allows the abortion in case when it is known that a fetus is abnormal."(12).

Today there are possibilities of interventions during the pregnancy with embiopathy caused by immunological postinfective dysfunction. Multiple pregnancies in which a mother and fetus are in danger represent indication for eugenic abortion. In past three decades an intentional abortion can be performed if two doctors, after the physical examination, reach unique attitude about it. This approach depends on the country legislation.

So, human and scientific factors determine the lasting of the human life after the conception in ordered societies. The World Health Organization finds that birth rate is reciprocally proportional to conditions of life and it brings a man closer to nature. In psychiatric sense according to MKB-10, probable psychiatric

consultations will remain in "exotic mental disorders." *Is this a new conflict between exotic and nature?*

New-old ethical dilemas

"Moral principles are easy to understand, but very difficult to apply in practice"

J. Maric

Does the man know to respect patient's personality?
Does the man know to respect personality of other man before the conception?
Does the man know to respect human and medical secret?
Does the man know to respect the person of a doctor inside him/herself?
Does the man know when, how and where to create a new human being?

Attitude towards the patient is the basic obligation in doctor's work. Psychiatric attitude can be more specific with more understanding for suffering of the body and soul of the patient. But, there is a Freud's thesis which says: " Three things cannot be learnt: to be a good parent, psychotherapist and nations leader." Empathy is small obligation of each doctor; above this are obligations of psychiatrist and psychotherapist. Who knows what are other obligations-one will remain human or human will disappear.

Conception is a real beginning of a human life, but modern man thinks that it is some kind of intrigue in which something bad will happen to him (more frequently) or something good (less frequently). Rarely one thinks that it is planned conception of a new life. Conception cannot be destroyed. If there is real contraception monsters will not be born. (20).

Abortion is an act of ceasing the pregnancy, death of homo novus. Abortionist kills the fetus. Legal, social and ethical factors will follow human being before, during and till the end of her/his life.

Euthanasia is a way of ceasing of human life, which is performed by the doctor as an act of mercy. A dilemma as old as medicine is to help or not the dying man. Today this dilemma is in different legislative procedures (from approval to strong disapproval). All cultures in the world have their own principles and customs about helping man in dying. Only doctor can understand is he needed to the patient any more.

Codex of medical work exists in form of Hippocratic Chapter and that is the entrance into the modern medicine. Apparently it will be simple and sufficient if it is respected. It is difficult to maintain the idea that my colleagues are my brothers (9) where man distances from the other man.

General practitioner becomes what he/she becomes by studying and finishing modern medical studies. Codex prescribes practitioner's behaviour, a family establishes a part of family superego and the society establishes a part of social superego. It is simple how one possesses something remedial inside him/herself and resists all temptations. It is difficult when passions affect your mind.

Moral principles are easy to understand and learn, but very difficult to apply in practice. (12). By analyzing ethics of youth makes it more difficult. Their universe is full of passion of the youth; it is less permeable, more passionately protected than some distant gens when a respectable thinker from modern civilization studies it. It seems that there is an important difference between the old and young-first ones cannot spend what they have, second ones will be able to spend everything if they have it.

Today in ethical understanding of fighting and existence, there are a lot of ruined ethical characteristics of this area. It must be honestly admitted that we possesses a part of our own guilt and insufficient understanding of change in social relations and situations.

However, essential maintenance of ethic in atheism, benevolent dictatorship and other social situations show collective spirit of survival. Principles and customs left a part of culturology, other part we sank by our own.

When adults play a war game like children and then get angry, the young must show them immaturity. Immaturity calls for maturity. Maturity belongs to the immature regardless the period of life. If one wants to grow, there is no point in waiting. Politics should be left to those who, apart of knowledge, have some other qualities. This shows that nobody needs politics. It would be better to cure wounds of bad politics and then create pawn for new investments in world heritage, but without avoiding ethical, spiritual and cultural in ones broad sense of understanding. This cannot be just politics (20).

Discussion

Genetics predetermines inherited characteristics of a human being. Modern science, by studying genetics, tries to change human characteristics. Genetic

researches have some regulations, but they are separately presented in certain legislations. In this way genetic researches include those, which are completely approved and those, which are at the edge of common sense and ethics.

Researches preventing diseases or changing the course of the disease and improving quality of human life are within the borders of all human benevolences. They are privilege of the rich and other parts of mankind wait for these results.

Other group of researches is a "cosmological scope with a great number of marketing studies." Huge part of these researches is not just at the edge of ethics, but at the edge of necessity as well. They are expensive genetic researches whose aim is to improve human biological environment. These improvements are done not to make people love more but to help a type of modern communication on a subculturological level. A lot of people come in Socrates position "to suffer not just from own defects but from virtues as well." This happens before one becomes perfect, because the place for a perfect man is in the museum.

Third part of researches moves towards cloning. This new creation means being the same as before with a little bit improvement than before. Here, a lot of things are unclear (Does everyone has right to be cloned? What will destiny of clones be? Does clone reach ideality without having any possibility to change human characteristics by nature? Will clones overcome those who are not clones? Where will people live when clones take over the planet?) *Homo meiducus waits for the product of homo technocraticus as homo novus.*

Conclusion

By wishing to humanize nature and to naturalize human being, one reaches the perfection and gets even further. Problems start when one moves away from human nature and loses extent in his wishes. This lost of extent creates virtual picture of superman and subnature. To show real situation we can paraphrase one literary mother's advice: "My son, don't go at the edge of the road. A tile can fell and kill you. Don' t go in the middle of the road either, something can run over you. Just go somehow like this." Today man can stay "somehow like this" not only in Bosnia, but all over the world.

Bibliography

1. Andrić, I.: Sabrana dela, "Udruženi izdavači", Beograd, 1981.
2. Aristotel: Politika, "Kultura", Beograd, 1970.
3. Božović, R.: Kultura, "Milić Rakić", Valjevo, Naučna knjiga, Beograd,1990.
4. Cerić, I. i sar: Značaj projekta Inestinisfyng Social Cohesion by strengthening community menthal health services in South East Europe za reformu službi za mentalno zdra vlje u Bosni i Hercegovini i drugim zemljama jugoistočne Evrope, XII kongres psihijatra Srbije i Crne Gore u duhu toleracije i saradnje, zbornik rad., Herceg Novi 2004.
5. Cerić I.: Karakteristuike opasne i štetne upotrebe alkohola i droga u Bosni i Hercegovini u poslijeratnom periodu, I Kongres psihijatara Bosne i Hercegovine sa međunarodnim učešćem, Sarajevo, 2003.
6. Dvomiković, V.: Karakterologija Jugoslovena, "Prosveta", Beograd, 1988.
7. Dostojevski, M. F.: Sabrana dela, Jubilarno izdanje, I.R.O."Rad",Beograd, 1981.
8. Loga, S., Fišeković,S.: Savremeni trendovi u biloškoj psihijatriji, I Kongres psihijatara Bosne i Hercegovine sa međunarodnim učešćem, Sarajevo, 2003.
9. Loga, S., Fišeković, S.: Shizofrenija, Medicinski fakultet, Sarajevo, 2002.
10. Loga, S.: Medicinska etika, XXI edukativni seminar u psihijatriji , Klinika za psihijatriju Medicinskog fakulteta u Beogradu, Beograd, 2003.
11. Loga, S.: Kontunuirana medicinska ekuacija u psihijatriji, XII kongres psihijatra Srbije i Crne gore u duhu toleracije i saradnje, zbornik radova, Herceg Novi 2004.
9. Kaličanin, P.: Psihijatrija, "Velarta", Beograd, 2003.
10. Kant, E.: Kritika praktičkog uma, II izdanje (prevod), "BIGZ", Beograd, 1990.
12. Marić, J.: Medicinska etika, XI dopunjeno i prerađ. izdanje, "Megraf", Beograd,2001.
13. Marić, J., Lukić, M: Pravna medicina, "Bareks", Beograd, 2001.
14. Marić, J.: Klinička psihijatrija, IX izdanje, "Megraf ", Beograd, 2001.
15. Moyer, K. E.: Violence and agression, APWPA Book, New York, 1987.
16. Munro, E, Rumagy, J.: Role of risk assiment in reducing homicides by people with mental illnes. The British Journal of Psychiatry, Vol 176, London, 2000.
17. Novaković, M.: Odrastanje, (Krivac, knjiga I),"Most-print", Bijeljina,
18. Novaković, M.: Stradanje, (Krivac, knjiga II),""Most-print", Bijeljina, 2003.
19. Novaković, M.: Žrtvovanje, (Krivac, knjiga III),""Most-print", Bijeljina, 2003.

20. Novaković, M.: Zanemarivanje, (Pravdovanje knjiga I), "Mix-press", Bijeljina, 2004.
21. Oruč, LL., Pojskić, N.,: Shizofrenija i bipolarni afektivni poremećaji u svjetlu molekularno genetičkih otkrića, I Kongres psihijatara Bosne i Hercegovine sa međunarodnim učešćem, Sarajevo, 2003.
23. Popović, M.: Kultura i psihijatrija, u "Psihijatrija", Kecmanović, D,. Medicinska knjiga, Beograd-Zagreb, 1989
24. Sartorijus, N.: Gender differences and suicide prevention, 8th European symposium on suicide and sucidial behaviour, Bled, Slovenia 6-9.septmber, 2000.
25. Sartr, Ž. P.: Biće i ništavilo (prevod) "Nolit", Beograd, 1980.
26. Selimović, M.: Sabrana djela, "I. P. Veselin Masleša", Sarajevo, 1977.
27. Tadić, Lj.: Nauka o politici, I. R. O. "Rad", Beograd, 1988

MODERN PSYCHOPHARMACOTHERAPY: BETWEEN GENETICS DETERMINISM AND FREEDOM OF CHOICE

Miro Jakovljević

RETROSPECTIVE OF HUMAN POPULATION GENETICS STUDIES IN B&H

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Abstract

The earliest medical records on antroposcopic and antropometric traits in B&H population date from the end of 19th century. However, first exact results of human population-genetic research were obtained in 1930's using analysis of genotype frequencies of blood group systems. Further research was significantly intensified in the period 1960 – 1980 trough comprehensive analysis of complex phenotype systems of qualitative and quantitative traits as described in numerous reports by Berberovic and his collaborators, as well as adoption of improved sampling methodology and data collection and interpretation (Hadziselimovic 1981a, 1981b; Hadziselimovic *et* Berberovic 1981; Hadziselimovic *et al.* 1981; Hadziselimovic *et al.* 1990). After the end of war aggression on Bosnia and Herzegovina (1992-1995) the survey on local human communities in respect to

their demographic structure and ethnic and cultural characteristics have been continued using methodology of molecular genetic markers (Hadziselimovic 2002; Pojskic *et al.* 2003; Marjanovic *et al.* 2003, Kapur *et al.* 2003; Marjanovic *et al.* 2004a, Pojskic *et* Hadziselimovic 2004a, Kapur *et al.* 2004, Pojskic *et al.* 2004b, Marjanovic *et al.* 2004b - *in press* and Marjanovic *et al.* 2004c - also *in press*). The main objectives of population genetic research in Bosnia and Herzegovina are determination of diversity of local human populations especially isolated populations, as well as three main ethnic groups (Bosnian Bosniacs, Bosnian Serbs and Bosnian Croats).

Obtained results had particular significance in the process of identification of human remains after war in Bosnia and Herzegovina. During the history of population-genetic study of human population in B&H various genetic markers have been employed for complex analysis: qualitative hereditary biochemical and physiological, static-morphological and dynamic-morphological traits, microsatellite markers (15 autosomal STR loci), hipervariable regions of mtDNA (HV1 and HV2), Y-STR (12 loci) and 28 Y-biallelic markers.

All mentioned results consistently showed following population structure characteristics:

- higher intra-ethnic than inter-ethnic variability;
- rather small genetic differentiation and genetic distance among different ethnic groups in Bosnia and Herzegovina;
- observed genetic diversity of human (sub)populations in Bosnia and Herzegovina is correlated with their geographic rather than ethnic parameters;
- genetic specificity of isolated human (sub) groups no matter their ethnic origin;
- the significant effects of violent (war-caused) migrations on genetic structure of local and isolated human populations in Bosnia and Herzegovina.

FAMILY BASED ASSOCIATION STUDY OF BIPOLAR DISORDER: CURRENT STATE IN BOSNIA AND HERZEGOVINA

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Abstract

Bipolar disorder, Type 1 (BP1) is a severe psychiatric disorder characterized with episodes of mania and depression, with complex genetic background. The mode of inheritance is still unknown, but most probably polygenic. Theoretically, single gene effect in complex genetic phenomena is rather small and could not be easily revealed in samples with limited size. Therefore, the large sample size is needed for primary identification of candidate genes and further confirmation testing in geographically distinct populations. Since BP1 disorder is a broad and heterogeneous phenotypic category, diagnostic methodology and sample collection need to be harmonized within the collaborative groups that will also enable genetic association analysis with specific symptom clusters. In the framework of the collaborative study with the Department of Psychiatry, University of Bonn (2001-2004) almost 80 BP1 triads have been collected in Bosnia and Herzegovina using the same standardized phenotypic instruments.

EARLY INTERVENTION IN PSYCHOSIS

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Abstract

Over the last few decades, there has been increasing interest and research in the issues surrounding the onset of psychotic illness. From an epidemiological point of view, although schizophrenia is said to afflict up to one per cent of the population at some time in their lives, the incidence seems to be affected by

various social factors, which vary in different populations; migration is an example. It has been observed that there is often major change in the psychosocial functioning of many people with psychotic illnesses within the first three years of the onset, thereafter, the deterioration tends to plateau out, so that the first three years of the illness could be described as a 'critical period' in which the future course of the illness was set. It is suggested that intervention in a psychotic illness at the earliest possible time, particularly in this 'critical period' may offer the best chance of improving the prognosis of patients.[1]

Recently the 'prodrome' or 'at risk mental state' phase of the illness has achieved significant attention and this phase is seen, arguably as one potential target for improving the outcome of psychosis [2].

With regards to specific interventions and individual case management, it is felt that the adherence of the individual to a treatment plan is facilitated if his/hers initial contact with mental health services is a positive one, thus minimizing unnecessary delay in the initiation of adequate treatment and possibly avoiding admission to a hospital[4].

References

[1] Birchwood M Early Intervention in Psychosis ;The Critical Period *The recognition and management of early psychosis* Cambridge University Press 1999 p226-264.
[2] Yung A et al . Prediction of Psychosis. *British Journal of Psychiatry;* 1998 June vol. 172 suppl. 33 p14-19.

[3] Zubin J & Spring B [1997] Vulnerability- a new view of Schizophrenia. Journal of Abnormal Psychology vol. 86,
p 103-126.

[4]IRIS Guidelines Birmingham 1999 p.11 .

UPS AND DOWNS OF ATYPICAL ANTIPSYCHOTICS

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Abstract:
The metabolic effects of treatment with antipsychotic medications have been under considerable debate. The knowledge base about metabolic effects is evolving. The two questions are: first, whether individuals with schizophrenia or bipolar disorder are at greater risk for obesity and type 2 diabetes than the general population even without taking antipsychotic medications, and secondly, to what extent antipsychotic medications increase rates of obesity and type 2 diabetes. The most important risk factor for development of diabetes in patients taking antipsychotics are still unclear. Possible risk factors include age, gender, race, BMI prior to treatment, diet, physical activity and comorbid conditions. Unfortunately, there have been few prospective studies to determine importance of these factors, and most of the retrospective studies attempt to control for these factors. Atypical antipsychotic drugs should be chosen to minimize the risk of weight gain, diabetes, and hyperlipidemia. Weight gain and metabolic disturbances associated with atypical antipsychotics should be controlled aggressively due to associated risk of coronary artery disease. Coronary artery disease is significant cause of mortality in these patients. However, because these conditions can be treated with lifestyle modifications such as diet, exercise, and medications, these adverse events should not discourage use of the atypical antipsychotics. Some patients who experience significant weight gain may benefit from switching to an agent with less potential weight gain. It is important that psychiatrists who prescribe atypical antipsychotics educate their patients about risks and warning signs of metabolic dysfunction associated with these agents and ensure follow up.
Key words: Schizophrenia, bipolar disorder, atypical antipsychotics, metabolic syndrome, obesity, diabetes, dyslipidemia.

References

1. Brown S. Excess mortality of schizophrenia: a meta-analysis. *Br J Psychiatry.* 1997;171:502-508.
2. Osby U. Correia N, Brandt L, Ekbom A, Sparen P. Time trends in schizophrenia mortality in Stockholm County, Sweden: Cohort Study. *BMJ.* 2000;321:483-484.

3. Hansen V, Jacobsen BK, Arnesen E. Cause-specific mortality in psychiatric patients after deinstitutionalization. *Br J Psychiatry.*2001;179:438-443.
4. Thonnard-Neumann E. Phenothiazines and diabetes in hospitalized women. *Am J Psychiatry.* 1968;124:978-982.
5. Dixon L, Weiden P, Delhanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Shizohpr Bull.* 2000;26:903-912.
6. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes impaired fasting glucose, and impaired glucose tolerance in US adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care.* 1998;21:518-524.
7. Markowitz JS, Brown CS, Moore TR. Atypical antipsychotics. Part I: Pharmacology, pharmacokinetics, and efficacy. *Ann Pharmacother.* 1999;33:73-85.
8. Henderson DC. Diabetes mellitus and other metabolic disturbances induced by atypical antipsychotic agents. *Curr Diab Rep.* 2002;2:135-140.
9. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004;27:596-601.
10. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC. The effects of novel antipsychotics on glucose and lipid levels. *J Clin Psychiatry.* 2002;63:856-865.
11. Harris MI. Impaired glucose tolerance in the U.S. population. *Diabetes Care.* 1989;12:464-474.
12. Garg A. Insulin resistance in the pathogenesis of dyslipidemia. *Diabetes Care.* 1996;19:387-389.
13. Lindenmayer JP, Nathan AM, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. *J Clin Psychiatry.* 2001;62:S30-S38.
14. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry.* 2003;160:290-296.
15. Osser DN, Narjarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. *J Clin Psychiatry.* 1999;60:767-770.
16. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
17. L'italien GJ. Pharmacoeconomic impact of antipsychotic-induced metabolic events..*Prev Med Manag Care* 2003;3:S38-S42

18. Ryan MC, Flanagan S, Kinsella U, Keeling F, Thakore JH. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naïve patients with schizophrenia .*Life Sci.*2004; 74: 1999-2008
19. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. *Ann Clin Psychiatry.* 2002;14:59-64
20. Dwyer DS, Bradley RJ, Freeman AM 3rd. Glucose metabolism in relation to schizophrenia and antipsychotic drug treatment. *Ann Clin Psychiatry.* 2001; 13: 103-113
21. Ardizzone TD, Bradley RJ, Freeman AM 3rd, Dwyer DS, Inhibition of glucose transport in PC12 cells by atypical antipsychotic drugs risperidone and olanzapine and structural analogs of clozapine. *Brain Res.* 2001; 923:82-90.
22. Kroeze WK, Hufeisen SJ, Popadak BA, et al. H1-histamine receptor affinity predicts short term weight gain for typical and atypical antipsychotics. *Neuropsychopharmacology.* 2003; 28:519-526.
23. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry.* 2002;59:337-345.
24. Sowell MO. Mukhopadhyay N, Cavazzoni P, et al. Hyprglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone or placebo.*J Clin Endocrinol Metab.* 2002;87:2918-2923
25. Meyer JM, A retrospective comparison of weight, lipid, and glucose changes between risperidone-and olanzapine-treated inpatients :metabolic outcomes after 1 year. *J Clin Psychiatry* 2002;63:425-433.
26. Henderson DC, Cagliero E, Gray C et al Clozapine, diabetes mellitus, wight gain, and lipid abnormalities: a five year naturalistic study. *Am J Psychiatry.* 2000;157:975-981.
27. McConville BJ, Sorter MT> Treatment challenges and safety considerations for antipsychotic use in children and adolescents with psychoses. *J Clin Psychiatry.* 2004; 65:S20-S29.
28. Etminian M, Streiner DL, Rochon PA. Exploring the association between atypical neuroleptic agents and diabetes mellitus in older adults. *Pharmacotherapy.*2003: 23:1411-1415.
29. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev.* 2002;23:201-209.

30. Caro JJ, Ward A, Levinton C, Robinson K. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. *J Clin Psychiatry.* 2002:63:1135-1139.

JACQUES MONOD: FROM GENETICS TO PHILOSOPHY

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Abstract:

Jacques Monod, together with two other French biologists received a Nobel Prize in Physiology and Medicine in 1965, for his research in the field of molecular biology. His name is perhaps more familiar to the wider audience as the author of *L' hazard et la necessite*, that is considered to be the most important work on the philosophy of nature written in the Twentieth century. Monod's horizon in this book is wide, his thought deep and its literary quality is extraordinary. Leftist in his youth, perhaps even a communist, later a member of French Resistance, he defines socialism as a 'painful dream of the nineteenth century'.

This book was accepted with harsh criticism both from the left and from the right. The Right, naturally connected with creational interpretation of the origins of the world, attacked Monod for his denial of the Divine principles, for his statement that 'our numbers have come from the gambling table in Monte Carlo'. The Left, on the other hand has projected historical causality to the world of nature, creating and defending its God – Marx. Monod's teaching ('Destiny exists only if happens, otherwise not.') is close to the philosophies of the Far East, particularly the philosophy of ancient China in the 'Book of Prophecies' (*I King*) that states that the individual should base his preparations for the future based on his knowledge of the present, and not on prophecies.

The hazard, of course does not assume disorder because …'once encoded in the structure of DNA, singular, and therefore unpredictable event, will be mechanically precisely replicated and transferred, multiplied in millions and billions of examples. Uprooted form the realm of sheer hazard, it enters the realm of necessity, the realm of undisputable safety. Because, at the macroscopic level, on the level of living organisms, natural selection is taking place. Even the most brilliant minds of today still cannot accept and understand that it is possible to derive the *son* of the whole music of the biosphere form one source of noise', says Monod. Darwin's philosophy of nature is still applicable today, only, it is based on new assumptions about the function of hazard in the evolution.