The current state of research on psychiatric genetics in Poland and the world: A report covering recent years*

Stan badań dotyczących genetyki psychiatrycznej w Polsce i na świecie – raport z ostatnich lat

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Summary

The aim of this article was to review the results of research carried out in recent years in relation to genetic studies in psychiatry. The authors’ focus is on the selected disorders, with particular emphasis on the reports from Poland. For this purpose, the most often mentioned studies describing genes and biomarkers involved in psychiatry were selected. Genetic polymorphisms were described in relation to schizophrenia, alcoholism, addiction to psychoactive substances, autistic spectrum, unipolar depression and bipolar disorder, eating disorders and other psychiatric disorders. Characterizing the impact of inheritance factors on the processes in the central nervous system, it can be observed that some biological mechanisms forms associations with tested genetic variants and this combination is linked with the risk of mental disorders. To understand the role of psychiatric genetics, surveys which join genotype and phenotype associations (endophenotype) are essential. It seems important to study and search for associations of genes polymorphisms and biomarkers with mental and psychiatric disorders in order to better understanding the biological basis of the disease and more effective treatment of patients. In many cases, the variability analysis of selected genes sheds new light on understanding the etiology of diseases and mental disorders. Genetics is a powerful technique which allows us to study the impact of the inherited variance on changes in mental state, even without having prior knowledge about biological changes.

Keywords: mental disorders • psychiatric disorders • genetics • polymorphism

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**GENETICS OF SCHIZOPHRENIA**

The biggest part of studies on the genetics of schizophrenia includes case-control studies in which researchers seek associations. Occasionally, they analyze nuclear family trios. In some analyses comparisons are made in the subgroups and haplotypes are also analyzed.

Tylec et al. 2013 [92] performed a study on 100 patients with schizophrenia, including 50 males, as well 50 sane controls, including 20 males. The group under study and the control group were matched appropriately with respect to age, gender and ethnicity. The researchers identified an association between the COMT Val158Met (Catechol-O-Methyltransferase) polymorphism variant and cognitive deficits in patients with schizophrenia. The presence of the Met allele was in connection with better cognitive performance and less acute progression of the disorder process. However, the 4/4 VNTR (Variable Number Tandem Repeat) genotype of the MAO-A (Monoamine Oxidase A) polymorphism was related to better cognitive performance. There were no statistically significant differences found between schizophrenia and the COMT Val158Met polymorphisms and the VNTR MAO-A in the promoter region. The frequency of the presence of particular allelic variants of the COMT Val158Met and MAO-A VNTR polymorphisms in the promoter region was not significantly different between the groups on which the study was performed. Interestingly, significant cognitive deficits were displayed by patients with the Val/Val homozygotic variant of the COMT Val158Met polymorphism. Genetic diversity of the COMT Val158Met and MAO-A polymorphism in the promoter region seems to have an influence on cognitive functions in the group of sane people. The study confirms the hypothesis that the COMT Val158Met polymorphism has an influence on cognitive performance in both groups covered by the study. The Met/Met genotype was significantly much more present in patients who were well educated and whose cooperation in the treatment process was better. Their hospitalization was less frequent and the development of the disease was less acute. On the other hand, the Val/Val genotype was significantly much more present in young patients with more severe negative and depressive symptoms, who were poorly educated and whose cooperation in the treatment process was worse. The schizophrenic process was more acute and they were hospitalized more often. In the control group, the Met/Met genotype was much more frequent in people with higher education and the Val/Val genotype was more often a distinctive quality of people with more severe depressive symptoms [92].

Groszewska et al. [28] performed a study into the – 1562C>T MMP-9 (matrix metalloproteinase 9) polymorphism which is a functional polymorphism influencing the level of gene transcription. SNPs (single nucleotide polymorphism) in the MMP-9 promoter consist in C>T substitution and have influence on the reduction of bindings of nuclear proteins in this region, which results in increased transcriptional activity. The promoter activity is changed depending on the presence of genotypes: C/C – reduced activity compared to C/T or T/T (the highest level of transcription) [104]. It is assumed that the MMP-9 may play a role in transmitting signals in synapses [40]. The researchers performed an analysis of 147 unrelated people with schizophrenia, including 74 females and 73 males, as well as their sane parents (both) from a Polish population in Greater Poland. No significantly statistical association was found between the functional – 1562C>T MMP-9 polymorphism and the development of schizophrenia. They also found no statistically significant differences in the transmission of particular alleles. The C allele was transmitted more frequently – transmitted in 16 cases, not transmitted in 10 cases. However, the level of statistical significance (p) was 0.241.

The study performed by Tybura et al. [91] covered 104 patients (51 males, 53 females) with paranoid schizophrenia and 234 controls (120 females and 114 males) with mental disorders excluded. The researchers analyzed numerous candidate genes which can be potentially related to susceptibility to schizophrenia (DRD2 – Dopamine Receptor D2, DAT – Dopamine Transporter, GRIK3 – Glutamate Ionotropic Receptor Kainate Type Subunit 3, SERT – Serotonin Transporter, 5HT2A-5-Hydroxytryptamine Receptor 2A, MAO-A and COMT) and the effect of antipsychotic treatment. No associations were found between the genotypes of polymorphisms of the analyzed genes and an increased susceptibility to the disease. No relationship of the analyzed polymorphisms with paranoid schizophrenia was found. The frequency of presence of particular genotypes was not significantly different in the studied groups. Additionally, the analyzed polymorphisms had no influence on the therapeutic response in patients with paranoid schizophrenia who took antipsychotics. Due to the small number of persons in the group under study these results ought to be regarded as preliminary.

However, Kapelski et al. [44] conducted a family-based association study into polymorphisms of the following genes: DRD1, DRD2, DRD3, DRD4, DAT and COMT in schizophrenia. The study covered 116 unrelated families including 70 mentally ill males, 46 females and both parents from a Polish population in Greater Poland. No mental disorders were found in the parents. In the case of the – 48 A/G polymorphism of the DRD1 gene a trend towards more frequent transmission of the A allele of the DRD1 gene by parents to their children with schizophrenia (p=0.091) was found. The A allele was transmitted in 59 cases and not transmitted in 42 cases. However, no relationship between the remaining polymorphisms and schizophrenia was found (no statistically significant preference towards transmission of any allele of the studied polymorphisms was found).

Tylec et al. [93] also studied the relationship between functional gene polymorphisms of the enzymes, which are inactive of catecholamines and deficits in emotio-
nal processes in paranoid schizophrenia. One hundred patients with schizophrenia including 43 females and 57 males, and 50 mentally stable, age and gender-matched controls with no mental were included in the study. No association between the genotypic distribution of the COMT Val158Met and MAO-A VNTR polymorphism in the promoter region and schizophrenia was found. The allele frequency spectrum of the COMT and MAO-A VNTR polymorphism in the promoter region showed no differences between the studied group and the control group. Patients with the Val/Val genotype of the COMT Val158Met polymorphism displayed bigger emotional deficits. Patients with the 4/4 genotype of the MAO-A VNTR polymorphism in the promoter region displayed bigger deficits in processing facial expressions.

Apart from the disorders of dopaminergic conductivity (hyperactivity) the key role in pathogenesis of schizophrenia is recognized in the serotonergic transmission. It is believed that, apart from dopamine, other neurotransmitter systems, including the serotonin system (system hyperactivity), play their particular role in producing negative symptoms. Kapelski et al. [43] undertook a study on polymorphisms of the serotonergic system genes. In family-based studies they identified no association between schizophrenia and the insertion-deletion polymorphism of the promoter section of the SLC6A4 (5-HTTLPR) serotonin transporter gene and the T102C polymorphism of the gene coding the 5HT2A receptor. 116 families, including patients and both of their parents, were covered by the study. They found no statistically significant preference in transferring any of the alleles in both polymorphisms. In the case of the T102C polymorphism of the 5HT2A allele, the T allele was more often transmitted by parents to their mentally ill children (transmitted in 52 cases, not transmitted in 40 cases, p=0.211). However, in the case of the 5-HTTLPR polymorphism, it was the s allele that was transmitted more frequently (transmitted in 55 cases and not transmitted in 47 cases; p=0.428). In both analyses the level of statistical significance was not reached.

The deficient subtype of schizophrenia is a supposedly pathophysiological separate subgroup of patients with schizophrenia who suffer from permanent, idiopathic negative symptoms and various neuropsychological deficits. Matrix metalloproteinases (MMP) are extracellularly active endopeptidases, whose substrates are matrix molecules and adhesive molecules. It has been revealed recently that MMP-9’s take part in various forms of synaptic plasticity, learning and memory consolidation. Bienkowski et al. [8] undertook a study which aimed at assessing an association between the –1562C/T polymorphism of the gene functional polymorphism and a deficient and non-deficient subtype of schizophrenia. The study was performed between 2009 and 2012. The deficit syndrome in schizophrenia was identified by means of SDS (Schedule for Deficit Syndrome). The sample included 468 Caucasian patients of Polish ancestry with schizophrenia identified by means of ICD-10 (International Classification of Diseases). A total of 189 persons, including males (51%), were included in the subgroup without the deficit syndrome; 279 patients, including males (53%), were included in the subgroup with the deficit syndrome. The control group included 532 Caucasian patients of Polish ancestry including males (51%). The frequency of presence of genotypes and alleles did not differ in patients with schizophrenia and in the control group. Patients with the deficit and without the deficit were no different with respect to the frequency of genotypes and alleles. No differences were found in the frequency of genotypes and alleles between patients with the deficit and control and patients without the deficit and control. No evidence was found for an association between the –1562C/T MMP-9 gene functional polymorphism and the deficient and non-deficient subtypes of schizophrenia.

Kapelski et al. [45] performed a family-based study into polymorphisms of the TGFBI (Transforming Growth Factor Beta1) gene in schizophrenia. The transforming growth factor beta (TGFβ) represents a family of cytokines with closely related isoforms coded by three different genes. TGFBI, TGFβ2 and TGFβ3 display an expression in various CNS (Central Nervous System) cells, including neurons, astrocytes and microglia [15,24] and are effective survival factors for intracerebral dopaminergic neurons [95]. TGFβ1 is a multifunctional cytokine and a key controller of growth, cell differentiation, immunological modulation, wound healing and embryogenesis [81]. TGFβ1 plays an important role in the survival of nerve cells and their return to normal functioning in the progression of CNS diseases [105] and may be a decisive controller in the development of CNS [89]. What is more, TGFβ1 has a trophic effect on dopaminergic neurons [50].

The signal pathway initiated by TGFβ in the Genome Wide Association Study (GWAS) demonstrates a strong association with schizophrenia. These results are confirmed by two studies performed by Jia et al. using advanced statistical methods including Gene Set Enrichment Analysis (GSEA), hypergeometric test and the generalized additive model for GWAS analysis (gamGWAS) [38,39]. This pathway is involved in numerous cellular processes, such as protecting the neurons from apoptosis and excitotoxicity [96]. The signal pathway of TGFβ is involved in numerous processes [54] and neurogenesis in adults [2,14]. It controls numerous cellular processes, including differentiation, apoptosis, proliferation and cell definition [1,4]. The canonical signal pathway of TGFβ is critical in modulating synaptic conductivity of the GABA A receptor (type-A γ-aminobutyric acid receptor) and dendritic homeostasis. What is more, an imbalance in hampering and stimulating pathways in the hippocampus region may result in behavioral changes, which are typical of mental diseases [84]. It was found that the components of the signal pathway of TGFβ in the hippocampus are changed in people with mental diseases including schizophrenia [6].
Kapelski et al. [45] performed a study on a group of 147 trios (patients with diagnosed schizophrenia and their sane parents). The group of patients included 66 males at the age of 24.3 (average), SD 6.7 and 81 females at the age of 26.9 (average), SD 6.8. The average age of the onset of the disorder was 22.9. The group included 21 patients with schizophrenia in their families and 42 patients had other mental disorders confirmed in the family history. The rs1800470 and rs1800469 polymorphisms in the TGFBI gene were studied. No associations of the rs1800470 polymorphism (p = 0.7216; OR = 0.948; CI 0.6617–1.331) and rs1800469 polymorphism (p = 0.7184; OR = 0.9531; CI 0.6912–1.354) of the TGFBI gene with the risk of developing schizophrenia were identified. The power used for detecting genetic associations was 6.6% and 5.9%, respectively. The results of the studies did not confirm the theory that the rs1800470 and rs1800469 polymorphisms of the TGFBI gene are related to the pathogenesis of schizophrenia.

BDNF (Brain-Derived Neurotrophic Factor) is an important biomarker in the progression and treatment of schizophrenia. Our knowledge on the BDNF gene, its products and processes in which they are involved, is still limited. It seems that we have fairly recently started to notice the complexity of the phenomena related to this neurotrophin [52].

**GENETICS OF ALCOHOLISM**

Alcohol dependence is a complex and multifactorial disease. Social, psychological and biological factors which influence alcohol dependence syndrome are being intensely studied all over the world. It is believed that the most essential risk factors in alcohol dependence are genetic (40-50%) as well as environmental (50-60%) [13,27,58]. Alcohol dependence syndrome is a complex and multigenic disease. Neurobiological, pathogenetic hypotheses of alcohol dependence syndrome include the dopaminergic, serotonergic and glutamatergic concepts as well as the protective role of aldehyde dehydrogenase (ADH) [27].

Waszkiewicz et al. [98] described the biomarkers of alcoholism. Apart from the markers for alcohol abuse and its recent consumption (the so called state markers), trait markers (susceptibility markers for the development of dependence or liver cirrhosis) are helpful in diagnosing alcohol dependence, which, along with the family history of dependence, may suggest a diagnosis [51]. The presence of the A1 allele of the D2 receptor, reduced activity of plate monoamine oxidase (MAO) and adenylyl cyclase, reduced level of GABA and beta endorphins, alcohol dehydrogenase alleles (ADH3*1, ADH2*2) as well as aldehyde dehydrogenase (ALDH2*2) may facilitate the development of alcohol dependence [23,51]. The development of liver cirrhosis may be facilitated by HLA (human leukocyte antigen) antigens (B8, BW40, B13, A2, DR2, DR3), the collagen alpha(1) gene polymorphism and ADH3*1 or ALDH2*2 alleles [51].

Samochowiec A. et al. [79] studied the influence of personality traits and DRD4 and 5HTT gene polymorphisms in parents on their sons’ predisposition to alcohol dependence. The study aimed to answer the question how differences between the aspects of temperament as well as character and gene polymorphisms influence the dopaminergic and serotonergic transmission in the alcohol dependent patient and his parents, which may indicate the occurrence of specific relations between the alcohol dependent proband and his parents. No preferential transmission of any of the alleles, i.e. no polymorphism of the 5HTT and DRD4 genes, was found. 213 people, including 71 trios of Polish ancestry, were cove-

Gene polymorphisms interact with personality traits and are influenced by the environment. Candidate genes are those which determine serotonergic and dopaminergic neurotransmission [29,78].

By taking into account the phenotypic preference for sweet taste, Jasięwiec et al. [37] performed a study into polymorphic variants of the DAT1 dopamine transporter gene and the 5-HTTLPR serotonin transporter gene in patients with alcohol dependence syndrome. The study covered 100 alcohol dependent males who fulfilled the ICD-10 dependence criteria. No association was found between the presence of particular alleles of the DAT1 and 5-HTT gene polymorphisms and preference for sucrose in probands (patients with diagnosed alcohol dependence syndrome). The statistically significant relationship was found between the presence of the 9/10 genotype polymorphism of the DAT1 dopamine transporter gene and preference for sucrose in probands (p = 0.0370). The presence of DAT 9/10 VNTR in the studied group increased the “sweet liking” trait threefold (p = 0.015, odds ratio=3.00). The frequent presence of the 10/10 (68.18% vs 47.92%) and 9/9 (6.82% vs 2.08%) genotype in SWL (sweet liking) probands was also found. There was over a twofold reduction in the chance of SWL+ presence (p = 0.051, odds ratio=0.43) due to the presence of DAT1 10/10 VNTR in the probands. The relationship between the “sweet liking” phenotype with the DAT1 dopamine transporter genotype was confirmed.

Grochans et al. [27] performed an association study into selected DRD2, 5HTT, GRIK3, ADH4 polymorphisms in patients with alcohol dependence syndrome. The study covered a group of 100 hospitalized patients with alcohol dependence syndrome, including 13 females and 87 males. The control group included 100 unrelated people who were somatically healthy, without mental disorders and had no addictions excluding nicotine dependence. No statistical dependence (p = 0.005) excluding two genotypic analyses (ADH4, rs1800769, p = 0.047 and ANKK1-Ankyrin Repeat And Kinase Domain Containing 1; rs1800497, p = 0.004) was found. Both the A/A genotype and the A allele were more frequent in people with alco-
hol dependence syndrome (ADH4 gene). The ANKK1 and ADH4 polymorphisms may play a big role in the pathogenesis of alcohol dependence.

Enzymes which metabolize alcohol and have an influence on the acetaldehyde accumulation, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) were identified in the genetic study on ethanol dependence. The presence of alleles of gene enzymes ALDH2 and ADH2 leads to the accumulation of acetaldehyde, which results in side effects including facial flushing, temperature rise, headaches and vertigo, anxiety, nausea, vomiting, reduced blood pressure and tachycardia. People with these alleles tend to avoid excessive drinking [16,27,56]. Evidence was found that genetically conditioned differences in activities of these enzymes are only to a limited extent related to the risk of alcoholism [27,76].

The dopaminergic concept is related to the reward system. The studies performed by Volkow et al. [97] provided evidence that alcohol-dependent people have a smaller concentration of dopaminergic receptors and the signals transmitting dopamine to the cells are weaker. Therefore, they have a reduced perception of joy and satisfaction [27]. As a result of the dopaminergic transmission involvement, the genes coding dopaminergic receptors were also among the genes standing for the role of markers [10,11,27]. It was established that the serotonergic system disorders have their influence on the pathogenesis of alcoholism by way of triggering impulsive and aggressive behaviors, mood disturbances and the originally high resistance to ethanol [82]. This is mainly in relation to the SHTT serotonin transporter coded by a single gene located on chromosome 17q12. What is characteristic of this gene is that in its polymorphism insertion or deletion of the 44 bp fragment takes place and that it is related to the differentiated transcriptional activity of the gene. Compared to the allele with 44 bp insertion (allele long), the transcriptional activity in the allele with 44 bp deletion (allele short) is three times less intense. The frequent presence of the s “allele short” of the serotonin promoter gene was found in patients with alcohol dependence syndrome [22,27].

The glutaminergic system plays a significant role in the pathogenesis of alcohol dependence.

Its receptors are mainly postsynaptic and may be connected with N-Methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid (KA). If these receptors are stimulated, permanent plasticity and adaptive changes take place in synapses, which is essential for the processes of memorization and learning as well as key in the development of addictions. Alcohol has a dual influence on the functioning of the glutamate receptor ion channels. If it is severely abused, it blocks the flow of ions through the channel-receptor complexes. If it is chronically abused, it facilitates the flow of ions. It was established that increased glutaminergic neurotransmission (GRK3), which results from intoxication, can result in hyperactivity after drinking is stopped, which can lead to delirium tremens and convulsions [27,78].

Kalwa A. described the issue of impulsivity and decision-making in alcohol-dependent people [42]. According to the author, the current studies are also focused on the genetic background of impulsivity in addictions. Attention is paid to the genes connected with the dopaminergic system, including the gene coding of the D4, D2 dopaminergic receptor, the dopamine transporter DAT gene and the catechol-O-methyltransferase (COMT) gene [35]. The serotonergic system also plays an important role with regard to the impulsivity of alcohol-dependent people. However, a smaller serotonin concentration is related to a higher level of impulsivity severity. What is stressed as of significant importance in this mechanism is the C/C genotype in the T102C HTR2A (5-Hydroxytryptamine Receptor 2A) polymorphism [36]. The authors also refer to the results of other studies which indicate that the described effect may be increased by the influence of the serotonergic system on the dopaminergic and glutaminergic system and GABAergic neurotransmission.

Wroński et al. [102] studied the intensity and perceived pleasantness derived from the sucrose taste in male alcoholics. The study aimed at assessing a possible relationship between reactions/responses to the taste of sweet solutions and alcoholism. Forty-five alcohol-dependent males and 33 male controls with no alcohol dependence were covered by the study. The assessed intensity (but not pleasantness) of the taste of water (0% sucrose) was higher in alcoholics. Both groups enrolled in the study were no different with regard to the assessed intensity and pleasantness derived from the taste of concentrated sucrose solutions (1-30%). The proportion of those who preferred the sweet taste (e.g. patients who viewed the 30% sucrose solution as the most pleasant) was similar in both groups (controls: 57.6%, alcoholics: 62.2%). The subgroup of alcoholics with the family history of alcoholism (n=22) viewed the highest concentration of sucrose (30%) as more pleasant compared to the perception of this taste in alcoholics without a family history of alcoholism. The proportion of alcoholics among those with a family history of alcoholism (77.3%) who preferred the sweet taste was much higher compared to the people without a family history of alcoholism (47.8%). The results suggest that alcohol dependence is unrelated to bigger changes in the response to/preference for concentrated sucrose solutions. The preference for sweet taste is a phenotypical marker of male alcoholics with a family history of alcoholism.

Samochowiec et al. [77] performed an association study on the Taq1A gene ANKK1 polymorphism in patients with alcohol dependence syndrome according to the Lesch alcoholism typology. Three hundred three alcohol-dependent people and 169 healthy people of Polish
ancestry were included in the study. No association was found between alcohol dependence and the Taq1A gene ANKK1 polymorphism. According to the authors, the Lesch tylophagy is a clinical result of the disease manifestation and its phenotypical description is too complex for simple genetic analyses.

While considering and analyzing the genetic aspect of alcoholism, attention must be paid to the important factor in the development and maintenance of alcohol dependence which is craving for alcohol. There has been no agreement on its precise definition and what uniform model of its origin should be applied. If this aspect is extended with genetic studies, it may result in developing a strategy for dedicated treatment in which clinical and pharmacological data are taken into account [34].

**Genetics of Addictions to Psychoactive Substances**

Szukalski described genetic variants, which determine the susceptibility to various groups of narcotics abuse and dependencies, some of which are primarily related to the genes coding active enzymatic, receptor and transport proteins:

- enzymes metabolizing narcotics (CYP2A6 – Cytochrome P450 Family 2 Subfamily A Member 6);
- enzymes metabolizing neurotransmitters (dopamine beta hydroxylase DBH, monoamine oxidase MAO);
- neurotransmitter receptors (dopamine receptor D2);
- receptors by means of which narcotics have an influence on the organism (cannabinoid CB1 and CB2, opioid OPRM, gamma-Aminobutyric acid and benzodiazepine GABA A, nicotine-acetylcholine nACh);
- neurotransmitter transporters (serotonin SHIT, dopamine DAT1) [86].

Biskupska et al. [9] performed a study on the relationship between the DRD2 Taq1A polymorphism and the risk of addiction to psychoactive substances. One hundred patients (88M, 12F), aged 18-52, were included in the study. The control group included 114 neonates (95 males and 19 females). The groups of addicted patients and controls were not significantly different in terms of genotypic and allelic distribution. No association was found between the DRD2 Taq1A polymorphism and an increased risk of addiction to the psychoactive substances, i.e. amphetamine, THC and opiates, which were the subject of the study.

**Genetics of Autistic Spectrum**

Szczaluba [85] described the diagnostics of genetic reasons for the autism spectrum disorders from the perspective of a clinical genetics specialist. According to the author, autism spectrum disorders belong to neuropsychiatric disorders with a significant involvement of genetic factors in their pathogenesis. This is, for example, confirmed by an approximately 20-fold increase in the risk of the disorder development in the nearest relatives (siblings, children) and a high rate of concordance rate in monozygotic twins, expressed by a probability degree of up to 80% for the development of the disorder in both siblings [5]. So far, over 100 genes, in which genetic defects (mutations) lead to the development of a disorder, have been identified, plus 40 loci on chromosomes, where genes which are casually related to autism and related disorders, including intellectual disability, epilepsy and schizophrenia [7]. The results of the multisite studies performed on big groups of people with ASD (Autism Spectrum Disorders) over the last ten years suggest that in most cases numerous changes (the so-called variants) in various genes, and not a single mutation, are responsible for the manifestation of the disease [30].

The diagnostics of mutations consists in DNA analysis of the examined person (molecular diagnostics) and is most often connected with the necessity of establishing a clinical diagnosis for a particular, genetically determined disorder, e.g. fragile X syndrome, Rett syndrome, tuberous sclerosis, disorders related to PTEN (Phosphatase And Tensin Homolog), SHANK3 (SH3 And Multiple Ankyrin Repeat Domains 3), NLGN (Neuroligin 1), NRXN (Neurexin 1), type 1 neurofibromatosis or Angelman syndrome. Some of the above genes, including FMR1 (Fragile X Mental Retardation 1), SHANK3 and genes from the NLGN and NRXN proteins play a significant role in interneuronal communication in which the NF (Neurofibromin 1) gene and a group of TSC (Tuberous sclerosis complex) genes code suppressive proteins in tumours, but the MECP2 (Methyl-CpG Binding Protein 2) gene regulates the DNA transcription process [71]. It would seem that the diagnostic efficiency with regard to the group of monogenic disorders depends, to the greatest extent, on the knowledge and skills of medical specialists, including clinical geneticists, who take care of autistic children. The knowledge of natural history of disorders such as Rett or Angelman syndrome and PTEN or SHANK3 mutation phenotype is particularly useful. However, in fragile X syndrome (FRAX) it is necessary to perform an ancestry analysis, which is also advisable in the case of other disorders.

Lisik [53] described a molecular foundation of autism spectrum disorders. ASD and other psychiatric disorders belong to the group of multigenic disorders in which numerous genes, which are inherited in a co-dominant way, interact additively or synergistically among each other [31]. After a clinical diagnosis is made, genetic tests may be used to help understand the patient’s unique aetiology. “Genetic” diagnosis may be used for several objectives including initiating contact through support groups with other families affected by the same disorder, easing guilt, determining the risk of the disorder recurrence in succeeding children in a more precise way, providing access to specific therapies [31]. What should be taken into account is that children may also have some sleep disorders [41].

Identification of mutations in several candidate genes, such as coding genes, neuroligins, neurexins and SHANK,
pointed to the synapse as the main player in the predisposition to ASD [70]. Studies on the genome using microarrays facilitated identification of submicroscopic deletions and duplications called copy number variations (CNVs) on numerous loci occurring de novo in 5–15% of people with ASD. Exome sequencing has recently allowed us to discover de novo pathogenic mutations in 3.6 – 8.8% of people with ASD. The study results reveal that autism is an aetiologically heterogeneous group of disorders including various kinds of copy number variations (CNVs) and single nucleotide polymorphisms (SNP) located on almost each chromosome distinguished by a different level of penetration. The occurrence of the same mutation was described in 1–2% cases of ASD [32]. Evidence can be found that genes coding synaptic proteins have an important role in ASD pathophysiology. This hypothesis has been supported by identified mutations (both CNVs and point mutations) in numerous genes coding proteins, which are key for formation, maturation and stabilization of synapses. Noh et al. [65] stated that a big number of genes located within CNVs are related to synaptic transmission among neurons. It is well known that proteins coded by these genes interact with each other as well as proteins coded by other genes located in the CNV regions. As a result, they create a vast, biological network. Proteins related to the function of synapses include presynaptic neuromodulators (NRXN1, NRXN2 and NRXN3) and their postsynaptic ligands (NLGN1, NLGN3, NLGN4X and NLGN4Y) as well as the family of SHANK proteins which are part of the postsynaptic density (SHANK1, SHANK2, SHANK3). At the extracellular level postsynaptic neuroglia interact with presynaptic and postsynaptic α- or β- neuromodulators and, therefore, stimulate the formation of presynaptic membranes, but at the intracellular level, neuroglia bind with postsynaptic SHANK proteins [68,70,72,101]. Functional studies related to the development of animal models have revealed that changes in the concentration of these proteins result in changes to the morphology, plasticity and function of synapses. What is important, numerous phenotypes may be reversed as a result of changes in the protein concentration [49]. Comprehensive genotyping of patients with ASD as well as their siblings, together with the results of studies on animal models, may result in personalized therapeutic options. It is also possible that autism is a phenotypically heterogeneous group of disorders which result from combinations of changes in numerous candidate genes which are different to each patient. Therefore, they need an individual therapeutic strategy [72].

The endophenotypic aspect is an issue which cannot be omitted in deliberations on psychiatric genetics. Endophenotype is defined in psychiatry as a syndrome of clinical symptoms which describe a particular disorder. However, it is assumed that this disorder is biologically (genetically) determined. What is interesting in this context is the study performed by Kasperek-Zimowska et al., in which a group of patients with Asperger syndrome and anorexia nervosa were analyzed with regard to relations between symptoms and genes [46].

GENETICS OF UNIPOLAR DEPRESSION AND BIPOLAR DISORDER

Nemec et al. [63] found no association between the glucocorticoid receptor gene rs6190 polymorphism and unipolar depression and bipolar disorder. Six hundred twenty-three people including 144 patients with unipolar depression and 479 patients with bipolar disorder were included in the study. The ethnically uniform group of patients was from the region of Greater Poland. The control group included 595 healthy patients.

Stress plays a significant role in the development of unipolar depression and bipolar disorder. Negative life experiences may be responsible for the occurrence of the first periods of depression [48,57]. A significant influence of stress on the occurrence of new periods of mood disorders was found in patients with bipolar disorder [21,75].

From the biological point of view, if a factor triggering stress in the organism is activated, the hypothalamus secretes two neurohormones, including the corticotropin-releasing hormone (CRH) and vasopressin (AVP). On the other hand, they stimulate secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland. ACTH is responsible for secretion of adrenal cortex hormones, including glucocorticoids and mineralocorticoids. Adrenal cortex hormones have numerous functions in the organism, such as carbohydrate and sodium-potassium regulation, and act through glucocorticoid (GR) and mineralocorticoid (MR) receptors respectively. Secretion of adrenal cortex hormones caused by ACTH results in blocked secretion of CRH, AVP and ACTH in the nervous system by way of negative feedback [33]. Therefore, glucocorticoids regulate the activity of the hypothalamic–pituitary–thyroid axis (HPT), but disturbances in the HPT axis regulation lead to an increased level of cortisol in the blood. The HPT axis disturbances are observed in the progression of various mental disorders, including bipolar disorder and unipolar depression. For example, an elevated level of cortisol was found in the urine of patients with severe depressive disorders [25,74] and an increased CRH concentration in the cerebrospinal fluid in patients with unipolar disorder [64]. Schmider et al. revealed an elevated level of cortisol in patients experiencing periods of depression, as well as in its remission in the dexamethasone suppression test combined with CRH (test Dex/CRH) [80]. Wichowicz, on the other hand, in his study, which included cortisol concentration measurement in people suffering from depression in the afternoon hours, found no significant differences compared to healthy people [99]. Dashauer et al., however, found that in remission the cortisol concentration does not change in relation to the control group of healthy people, which, as a result, points to the fact that hypercortisolism is caused by stress and periods of depression [18]. The HPT axis regulation is related to the proper functioning of the glucocorticoid receptor. A reduction in the influence of glucocorticoids on the immune system and metabolic functions in the peripheral tissues
was found in patients suffering from depression, which points to the reduced sensitivities of the GR receptor [67]. However, clinical studies showed that applying the GR receptor antagonists, such as mifepristone, resulted in mood improvement in patients with unipolar depression and bipolar disorder [103]. Several clinically significant polymorphisms of the GR receptor have been described to date. They include BclI (rs41423247), ER22/23EK (rs6189 and rs6190), N363S (rs33389), A3669G (rs6198) and NR1C1-1 (rs10482605). In patients from Swedish and Belgian populations an association of the GR receptor polymorphisms with depression was found [62]. Two out of the above polymorphisms (ER22/23EK and N363S) lead to changes in the amino acid sequence of the GR receptor. A relationship between polymorphism ER22/23EK and the risk developing unipolar depression and bipolar disorder was studied in this research study. The results revealed that there is no association between polymorphism ER22/23EK and unipolar depression and bipolar disorder.

Other biomarkers, e.g. magnesium concentration in serum, should be kept in mind in the course of genetic analyses. On the basis of the obtained results, Styceżni et al. [83] have drawn a conclusion that the concentration of magnesium in serum shows certain qualities of the state biomarker. However, in order to confirm this hypothesis clinical studies performed on considerably larger groups of patients are required [83]. Another aspect is that the current division into unipolarity and bipolarity and hidden bipolarity in numerous patients is dubious. If in doubt, clinicians have to rely on their own diagnostic assessment on the basis of bipolarity ratings including the family history of mania or bipolar disorder, their early onset, high rate of recurrence, presence of psychotic symptoms, mixed states, quick onset and remission, complete remission between the periods of the disorder, temperament (hyperthymic, cyclothymic) and responsiveness. Both DSM-5 (296.80) (Diagnostic and Statistical Manual of Mental Disorders) and ICD (F31.9) provide room for this approach [83]. In genetic studies, particularly in the context of the division into homogeneous subgroups, the clinician’s information seems to be of key importance.

OTHER

Dragan et al. [19] performed a family-based association study into polymorphisms in the dopaminergic system genes and EAS (Emotional Availability Scales) temperament traits. Significant associations were found between variabilities in two genes of the dopaminergic system, i.e. DAT1 and SNAP-25 (Synaptosomal-associated protein 25), and the level of shyness recognized as a child’s temperament trait. It seems that the obtained results may contribute significantly to our understanding of the biological foundations of temperament.

According to Buss and Plomin [12] temperament is defined as a set of an individual’s personality traits which are revealed in the early stages of an individual’s life. In their genetic theory of temperament they distinguished three separate dimensions including emotionality, activity and sociability – EAS.

The idea that polymorphisms in the dopaminergic system genes may be related to some personality traits measured in children and adults is now being advocated. Polymorphism VNTR in the DRD4 gene exon III was linked to novelty seeking [20] as well as the intensity of reactions measured in 3-year-old infants using Creche Children Temperament Rating Scale [17]. Polymorphism VNTR in the DAT1 gene in some studies was linked to novelty seeking [94]. What should also be kept in mind is that a relationship of variability in this gene with sensory sensitivity [66] and cooperativeness [69] was found quite recently. Polymorphism TaqIA in the ANKK1 gene was linked to alcohol dependence [27] as well as neuroticism and novelty seeking in males [47]. And as for the last quality, interaction of the polymorphism in the ANKK1 gene with – 141C Ins/Del polymorphism in the gene coding the type 2 dopamine receptor was found recently [90]. Novelty seeking was also linked to variability in the DRD3 gene [88]. However, polymorphism in the gene coding of the SNAP-25 protein was linked to the level of intelligence in children [26].

A study conducted by Dragan et al. [19] made an attempt to determine potential relationships among polymorphisms of the genes which belong to the dopaminergic system and EAS temperament traits. A family-based association analysis was used. The study covered 283 adults (149 females and 134 males) aged 26–55 (M = 34.92; SD = 5.18) and 154 children (76 girls and 78 boys) aged 3 to 12 (M = 6.83; SD = 1.9) who came from 149 families with one or two children from the conurbation of Warsaw.

Analyses were made using the DAT1 gene haplotype made up of polymorphism rs27072 and rs463379 as well as VNTR in 3’UTR, and a haplotype made up of polymorphism rs363039, rs363043 and rs363050 in the SNAP-25 gene. Haplotype C10 in the DAT1 gene was positively linked to shyness – with the assumed additive and dominant model. On the other hand, with the assumed additive and recessive model, haplotype ACG in the SNAP-25 gene turned out to be “protective” with regard to shyness. With the assumed dominant model including the “risk” of shyness haplotype GCA turned out to be bound. All the above associations were also statistically significant after the correction for multiple testing had been applied. The study revealed that variability in the SNAP-25 and DAT1 genes is in connection with intensification of shyness. The first one (SNAP-25) codifies the protein which is a component of the mechanism docking and connecting synaptic membranes. The second one (DAT1) produces a dopamine transporter which is involved in reuptake of this neurotransmitter. The obtained results may be interpreted within the bounds of the above proposition provided by Johnson. It seems that haplo-
Genetics of eating disorders

Modern brain imaging has revealed that the neurotransmitter regulation in patients with eating disorders is radically different from the control group. These disorders are related to the serotonergic and dopaminergic systems, and may be inherited and genetically determined.

However, before we refer to the genetic studies in this respect, attention should be paid to the particular correlations of excess weight and obesity ratings with cognitive parameters, which was studied by Lopuszańska et al. [55], who found that excessive fat tissue is related to a reduction in efficiency in abstract thinking as well as immediate and delayed memory. However, there are differences in this respect in relation to women and men [55].

The most frequent studies related to analyses of eating disorders in the context of genetic studies are association studies. For example, the study performed by Mikołajczyk et al. [60] aimed at analyzing the association between eating disorders, such as anorexia and bulimia, and two polymorphisms of the COMT gene. The study also aimed at analyzing correlations between selected personal and psychological women’s qualities and genetic variations. 103 adult females (average age = 22.45 ± 3.8) suffering from serious eating disorders, which lasted at least 12 months, were covered by the study. According to the ICD-10 criteria, 61 females were diagnosed with anorexia, whereas 42 patients experienced bulimia. The control group included 108 females without mental disorders, selected in terms of ethnicity and age. The studied groups filled in the Eating Disorders Inventory (EDI) and Temperament and Character Inventory. The genotypes of two catechol O-methyltransferase polymorphisms including rs4633 (his102his) and rs4680 (val158met) were determined. According to Mikołajczyk E. et al. [60] the GGCT genotype increased the risk of eating disorders more than fivefold and the risk of bulimia was increased more than sevenfold. The presence of haplotype CT was also found to be three times more frequent in women with eating disorders than in the control group. Apart from the homozygotic genotypes, AACC and GGCC considerably decreased the relative risk of eating disorders. Patients with a low activity of the COMT genotype had higher values on the EDI scale with regard to ineffectiveness as well as attempts made to achieve slimness and perfectionism. The high activity of the genotype was related to undeveloped character traits labeled as poor cooperativeness and poor self-directedness. These relationships between genotypes and character traits were even more emphasized (expressed) in the group of patients with bulimia.

Eating disorders – this is a complex and multidimensional issue. Racicka et al. [73] drew a conclusion from their studies that adolescents with diabetes belong to the group of people with an increased risk of eating disorders. It is very often difficult to recognize these disorders in this population and interdisciplinary involvement of a team including an endocrinologist, diabetologist, psychologist and psychiatrist is required. Early diagnosis is critical from the perspective of prognosis and development of complications [73].

There is not too much information in the literature in relation to the dental needs of patients with eating disorders. However, the study performed by Szupiany et al. [87] is interesting in this respect as their results suggest that dental consultation as a supplementary examination ought to be had in the course of treatment provided to these patients [87].

Non-specific eating disorders described by Michalska et al. [59] should also be taken into account. The non-specific eating disorders presented by the authors have some shared characteristics, but they also differ. Pica, rumination syndrome, avoidance of/restrictions on food intake and BED (Binge Eating Disorder) are classified in DSM-5 as a separate category. NES (Night Eating Syndrome), however, is defined as “another eating disorder”. SRED (Sleep-Related Eating Disorder), orthorexia and bigorexia are completely excluded in DSM-5 [59]. These new classifications ought to be taken into account in the successive studies including genetic studies.

References


[106] The authors have no potential conflicts of interest to declare.