Genetic Polymorphisms as a Risk Factor for Anorexia Nervosa

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Abstract: Anorexia nervosa (AN) is an eating disorder affecting mostly young people which could lead to serious complications and consequences. There are ethnical and gender differences in the incidence and prevalence of AN, but the influence of urbanization has not yet been proved. The relationship of genetic background to the risk of AN is still being investigated. In this review we summarize current knowledge about the relationship between AN and polymorphism of substances known to be regulating eating behaviour or metabolic pathways e.g. serotonin, ghrelin, catechol-O-methyl transferase, neuropeptide Y, brain-derived neurotrophic factor and adipokines.

Introduction
Anorexia nervosa (AN) is a psychiatric eating disorder with the most common onset during adolescence with bimodal distribution between age of 13–14 years and 17–18 years, respectively [1]. AN is characterized by inappropriate perception of body image and the fear from obesity that leads to dieting, often accompanied by compulsive exercise, and, in a subgroup of patients, purging behaviour with or without binge eating. Long term presence of AN usually results in persistently low body weight due to markedly reduced body fat content [2].

AN can result in numerous metabolic complications and has also serious social consequences, as it affects mostly young people. Although there has been huge progress over the last decade in our understanding of this disease its exact ethiopathogenesis still remains elusive. The most common cause of death in AN is suicide and complications of alcoholism [5, 6]. The influence of the environment has been demonstrated [7], and the genetic background of the disease is now being intensively investigated. Several genes with an essential role in the regulation of eating behaviour and body weight are considered candidates involved in the aetiology of eating disorders such as AN. The aim of this article is to give an outline of current knowledge about AN with special focus on the role of the genetic background of this disease.

History and current status of anorexia nervosa, its incidence and prevalence
Richard Morton is generally credited for the first medical description of anorexia nervosa in 1689 [8] as a disease with psychiatric origin [9]. A few years later French neuropsychiatrist Ernest Charles Lasègue described the condition as “hysterical anorexia” in a translation of his French article, which was published in British Medical Journal in 1873 [10, 11].

Interestingly, anorexia nervosa had not attracted much attention in the 19th century, when especially in German-speaking countries physicians considered this disease as “a nervous dyspepsia” rather than anorexia nervosa as a nosological unit [12].
During the last century the neuropsychiatric, endocrine and social aspects of this disease were investigated more carefully. The most discussed social aspects are the relationships between the mother, and/or family environment and the child. It is suggested that family dysfunction can lead to maladaptive search for own autonomy by “anorectic” control of body appearance [9].

The incidence and prevalence of AN was increasing from the 1960s [9], but seems to remain relatively stable over the last five years reaching 4.7–8.1 cases per 100,000 population per year [13, 14, 15, 16]. The lifetime prevalence is between 0.4%–1% [17, 18] and it is ten times higher in females than in males [19]. There are also ethnical differences as described in a study from the USA. This study found no anorexia nervosa in black women in contrast to the lifetime prevalence of 1.5% among young white women [20].

In general, the close link between the degree of urbanisation and the prevalence of some of mental disorders has been accepted. For example, the incidence of bulimia nervosa is five times higher in cities than in rural areas. On the contrary, the relation between anorexia nervosa and urbanization has not been proved [21].

**Diagnostic criteria and risk factors of anorexia nervosa**

To be diagnosed as having anorexia nervosa the patient has to fulfil all diagnostic criteria according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). These criteria are depicted in the Table 1. [22].

As mentioned above, the risk factors related to AN are multifactorial and can be of both external and internal [inherited] origin. Some of external factors may be modified, which is very important for prevention and treatment of this disorder. Modifiable factors include social attributes such as peer, familial and cultural pressures including the combination of food abundance and emphasis on the female attractiveness that is equated with thinness.

Internal [inherited] factors include genetic influences, particularly personality traits of perfectionism and compulsiveness; anxiety disorders; family history of depression and obesity. Unfavourable combinations of these factors contribute to the overvaluation of slimness, distorted perceptions of body weight, and phobic avoidance of food [3, 6, 9, 20].

**Single nucleotide polymorphisms and anorexia nervosa (SNP)**

*Brain-derived neurotrophic factor (BDNF)*

Brain-derived neurotrophic factor (BDNF) has been implicated in the regulation of food intake and body weight in rodents. The Met66 variant of BDNF is strongly associated with all subtypes of eating disorders (AN, restricting subtype – AN, binge-eating/purging AN and bulimia nervosa). On the other hand the –270C/T BDNF polymorphism – has an effect on BN and late age at onset of weight loss. This association with the pathophysiology of eating disorders in different
populations supports a role for BDNF in the susceptibility to aberrant eating behaviours [23].

On the contrary Rybakowski et al. genotyped BDNF Met66 and −270C/T polymorphisms in 149 patients with AN and 100 healthy control females and observed no significant differences between patients with anorexia nervosa and controls in frequency of genotypes and alleles [24].

**Serotonin**
Serotonin (5-hydroxytryptamine; 5-HT) is a key mediator in the control of food intake possibly involved in the aetiology of AN [25]. Within the brain, the medial hypothalamus is believed to be a critical location in the mediation of serotonin’s action. The most frequently studied gene with regards to the regulation of food intake is the 5-HT(2A) gene, with positive or negative results [26].

Rybakowski et al. studied connection between polymorphism of serotonin receptor gene and personality dimensions in adolescent with AN [27]. In this study

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<th>Table 1 – The diagnostic criteria of anorexia nervosa according to the <em>Diagnostic and Statistical Manual of Mental Disorders</em>, fourth edition (DSM-IV) [3]</th>
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<td><strong>Criterion</strong></td>
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<td>Body Image Issues</td>
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the –1438 A/G polymorphism in the 5-HT2A receptor gene and serotonin transporter linked-polymorphic region (5-HTTLPR) were genotyped. Personality dimensions in AN patients were assessed using the Temperament and Character Inventory. There was no significant difference in the 5-HTTLPR frequency between AN patients and controls; however, there was a statistical trend towards a higher frequency of the A allele of the –1438 A/G polymorphism in patients than in controls. There was also a significant association between the A allele of this polymorphism and two temperamental traits. Patients homozygous for the A allele showed lower reward dependence than G/G homozygotes, and A/A homozygotes showed lower harm avoidance than heterozygotes. Low reward dependence and harm avoidance were more characteristic of the restrictive-type AN than of other subtypes of the disorder. No association of 5-HTTLPR with personality dimensions in AN patients was observed. These results may suggest that the A allele of the –1438 A/G polymorphism confers some genetic risk for adolescent AN patients, especially in those with personality traits, which are typical for the restrictive-type AN [25, 27].

On the contrary Ando et al. presented the negative results on the Japanese population. Their case-control study revealed no significant association between the 5-HT2A promoter polymorphism and AN. Thus, at least for Japanese subjects, the A-allele of the –1438G/A polymorphism in the promoter region of the 5-HT2A receptor gene does not contribute to a predisposition to AN [28]. Similar negative results were found in the Polish population [29].

The possibility of treatment intervention by SSRI in patients with eating disorders (Selective Serotonin Reuptake Inhibitor) stimulated interventional studies with citalopram and fluoxetine [30, 31, 32, 33]. The results of these studies are very controversial. Citalopram was found to be effective in a subgroup of anorectic patients in one study [30], while fluoxetine failed to demonstrate any benefit in randomized double-blind, placebo – controlled trial [33]. Based on the current results of clinical studies SSRI are not generally recommended for the treatment of anorexia nervosa [34, 35].

Ghrelin
Ghrelin, identified as an endogenous ligand for the growth hormone secretagogue receptor (GHSR), serves as a somatotrophic and orexigenic signal from the stomach. The secretion of ghrelin increases under conditions of negative energy-balance, such as starvation, cachexia, and anorexia nervosa, whereas it decreases under conditions of positive energy-balance such as feeding, hyperglycemia, and obesity [36].

Measurement of the total plasma levels of ghrelin in AN during cognitive-behavioural treatment were performed. The mean ghrelin levels in AN (BMI 15.1 kg/m²) were 6.56 ng/ml in comparison to the control healthy group (BMI 21.4 kg/m²) with mean ghrelin level 4.86 ng/ml (p < 0.05). After 24 weeks of
treatment the mean BMI increased to 17.5 kg/m², ghrelin level decreased to the value of 3.92 ng/ml [37].

Furthermore, a link between Arg51Gln and/or Leu72Met polymorphisms of the human ghrelin gene and anorexia nervosa was studied. There were no significant differences found in the frequencies of the Arg51Gln and the Leu72Met ghrelin gene variants among patients with AN and healthy controls. These results suggest that the Arg51Gln and the Leu72Met polymorphisms of the human ghrelin gene do not contribute to the genetic susceptibility to AN [38].

Miyasaka et al. studied 171T/C polymorphism of the ghrelin receptor (growth hormone secretagogue receptor, GHSR) gene in patients diagnosed with eating disorders. They found that the CC type of GHSR gene polymorphism (171T/C) is a risk factor for BN, but not for AN [39].

Catechol-O-methyl transferase (COMT)
Catechol-O-methyl transferase is an enzyme involved in the breakdown of the catecholamine neurotransmitters dopamine, epinephrine and norepinephrine. This enzyme introduces a methyl group donated by S-adenosyl methionine (SAM) to the catecholamine [40].

Mikolajczyk et al. studied an association of eating disorders with catechol-O-methyltransferase gene functional polymorphism. They analysed COMT for polymorphism in exon 4 (codon 158 Val/Met). Both the low-activity allele and the high-activity allele were determined. In the anorexia group, the H allele frequency was higher than in the control group. Their findings suggest an association between high-activity allele of COMT and the risk of anorexia nervosa [41].

The same polymorphism of the COMT gene was studied in another study by Frisch et al. (2001). The authors found that individuals homozygous for the high activity allele (HH) had a two-fold increased risk for AN development [42].

Neuropeptide Y (NPY)
Neuropeptide Y (NPY) plays a critical role in the regulation of appetite and energy expenditure through NPY Y1 and Y5 receptor subtypes. Moreover, the NPY Y1 receptor is highly expressed in human adipocytes, where it inhibits lipolysis [43].

The polymorphism of the NPY Y5 receptor was investigated in obese and AN adolescents by Rozenkranz et al. (1998) with no significant differences between the patients and the controls [44].

Adipokines
Adipokines are bioactive mediators released from the adipose tissue produced by both adipocytes and other cells present within the fat. Typical adipokines like leptin or adiponectin have been initially recognized through their role in the regulation of

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energy storage and homeostasis. To date, more than 100 adipokines have been described to be produced and released by adipose tissue, but the function and clinical significance of most secretory products is completely unknown. [45, 46].

Leptin and its receptor are known to be important factors in the control and regulation of body weight. Leptin levels are reduced in underweight anorexic patients and these levels correlate with the decreased body mass index (BMI). [47]. Single nucleotide polymorphisms (SNPs) in the leptin receptor are associated with measures of body weight. Quintan et al. analysed SNPs in the coding region of the leptin receptor their possible association with anorexia nervosa. This analyse came out with no significant difference in allele or genotype frequency, for any SNP, between the normal controls and the cohort of anorexia subjects. [48].

Adiponectin is a protein hormone produced predominantly by adipose tissue. Its role may lie in the regulation of insulin sensitivity and inflammation. Insulin sensitizing and antiinflammatory properties of adiponectin have been shown in numerous experimental studies including those on adiponectin knock-out mice [49]. There is an inverse relationship between the amount of adipose tissue and adiponectin levels in both clinical and experimental studies. AN patients have hyperadiponectinaemia, while in obese patients there are lower levels of adiponectin [50, 51].

Resistin is another adipose tissue-derived hormone that was identified in 2001 [52]. The connection between its levels and obesity is still being discussed. Antibodies against resistin increase insulin sensitivity [52]. Resistin knock-out mice have lower fasting glycaemia [53]. The results of human studies focused on the interconnection between resistin levels and insulin sensitivity are controversial. Some of the studies found increased resistin levels in patients with obesity and insulin resistance while others failed to do so [54].

Our group studied the frequency of single nucleotide polymorphisms 45T>G and 276G>T of the adiponectin gene and 62G>A and –180C>G of the resistin gene in patients with obesity, AN and in lean women and the influence of particular genotypes on serum concentrations of these hormones. Adiponectin levels were lowest in obese women and highest in AN patients. Resistin concentrations were lowest in AN and highest in obese patients. [55, 56, 57].

We did not find any minor allele A in 62 position of the resistin gene in our group of AN patients. AN patients with minor allele G in –180 position of the resistin gene had higher BMI than AN patients homozygous for allele G (16.12±1.54 vs. 14.53±1.67, p=0.036). AN patients with minor allele T in position 276 of the adiponectin gene had higher cholesterol levels than AN patients homozygous for allele G (5.85±0.67 vs. 4.56±0.59, p=0.006). In other monitored parameters, including adiponectin, resistin, insulin, TNF-α, cholesterol, glycaemia, glycated haemoglobin and Homa index, there were no differences in AN patients based on their single nucleotide polymorphism of mentioned adipocytal hormones [55, 57].
Summary
Anorexia nervosa is serious disease affecting mostly young people with chronic course and uncertain prognosis. The aetiology is multifactorial, and includes modifiable and unmodifiable risk factors. The genetic background has recently been investigated and the study of gene polymorphisms could explain increased susceptibility of some patients to this disease. Further simultaneous analysis of genetic variants of the biological determinants of energy metabolism and feeding behaviour in very larger populations are needed to contribute to the better understanding of the heritability of eating disorders.

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