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# **ROLE OF 5-HYDROXYTRYPTAMINE RECEPTOR 2A GENE IN EATING DISORDERS** YEME BOZUKLUKLARINDA 5-HIDROKSITRIPTAMIN

**RESEPTÖR 2A GENININ ROLÜ** 

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# Öz

Bu derlememizde beslenme bozuklukları altında yatan biyolojik nedenleri ve bu bozuklukların genetik altyapısını özetlemeyi amaçladık. Anoreksia Nervosa (AN) ve Blumia Nervosa (BN) karmaşık yapıları olan beslenme bozukluklarıdır. Genetik bağı olduğu konusunda güçlü bulgular olan bu bozukluklara çoğu zaman kaygı bozukluğu, duygudurum bozukluğu, obsesif kompülsif bozukluk ve mükemmeliyetçilik eşlik eder. Son dönem çalışmaları bu bozuklukların ailesel kalıtım yolu ile aktarılmasını araştırmak yerine biyolojik kökenlerini araştırmaktadır. Yeme bozuklukları ve kilo kaybı bozuklukları birbiri ile benzer özellikler göstermektedir. Ailelerle ve ikizlerle yapılan çalışmalarda 5-Hidroksittriptamin (5-HT2A) Reseptör 2A'nın AN ve BN patogenezindeki önemi belirtilmiştir. Gelecekte bu alanda yapılacak çalışmalar, serotonerjik sistemin ve bu sistemde rol alan biyolojik belirteçlerin, bu beslenme bozuklarının tedavisindeki önemini belirtecektir. Daha büyük hasta grupları ile yapılacak yatkınlık ve famakogenetik çalışmalar ile genin yeme bozukluklarındaki önemi daha sağlam kanıtlarla belirlenebilecek ve tedaviye yaklaşım açısından hekimlere önemli bilgiler sunacaktır.

Anahtar Kelimeler: gen, 5-hidroksitriptamin, reseptör, 2a, yeme bozuklukları

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# Abstract

Aneroxia Nervosa (AN) and Blumia Nervosa (BN) are eating disorders with complex structures. These disorders, which have strong evidence of genetic linkage, are often accompanied by anxiety disorder, mood disorder, obsessive compulsive disorder and perfectionism. Recent studies investigate the biological origins of these disorders, rather than the familial inheritance. Eating disorders and anxiety disorders have several characteristics in common. Family and twin studies indicate the important role of 5-Hydroxytryptamine (5-HT2A) Receptor 2A in AN and BN pathogenesis. Future studies in this field will indicate the importance of the serotonergic system and its biological markers in the treatment of these nutritional disorders. Predisposition and farmacogenetic studies with larger sample groups will produce more information about the receptor gene in nutritional disorders with more reliable arguments and will provide important information to physicians in terms of treatment approach.

Keywords: gene, 5-hydroxytryptamine, receptor, 2a, eating disorders

### 1. Introduction

Anorexia nervosa (AN), Bulimia nervosa (BN), binge eating disorder or other specified feeding or eating disorder (OSFED) are considered to be mental disorders according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10). These are known to have familial components for a long time, which is a strong evidence for genetic basis. They usually present themselves with a comorbidity with anxiety or mood disorders, and also with perfectionism and obsessive-compulsive behaviour. Recent studies head towards from familial risk studies to molecular and genetic studies, searching for special roles of the related genes (Yao et al, 2019). Datas obtained from recent molecular genetic studies, which consist of animal models, linkage studies and quantitative genetic researches, are still being evaluated in the terms of predisposition to certain conditions (Maussion et al, 2019).

AN and BN are complex disorders. Individuals suffering from these disorders mostly have complain about their own body shapes and body weights. This is believed to be the most important underlying reason for psychiatric conditions of eating disorders.

When compared to anxiety disorders, eating disorders are reported to be more rare. Anxiety disorders are common psychiatric disorders that have been observed in Western populations for more than a hundred years. Obsessive-compulsive disorder (OCD), which is also usually observed in individuals with eating disorders, is considered to be a disorder of anxiety, according to ICD-10. The lifetime prevalence of anxiety disorders range from 10% to 25% (Kessler et al., 1994), while their sixmonth prevalence range from 6% to 15% (Myers et al., 1984). AN has been known for more than 300 years in scientific literature since with Morton's records (Pearce, 2004) and firstly defined in 1874 (Walsh & Devlin, 1998). While AN's prevalence through life is less than 1%, BN's is about 2% (Wade et al., 1996). The incidence of Bulimia and anorexia nervosa cases varies considerably by gender.

Eating disorders and anxiety disorders have several characteristics in common like increased fear or concern about feeding and weight gain. The most frequently observed symptoms of patients with AN are: maintaining a body weight that's below normal levels, having an intense fear of feeding or weight gain, or being obese. Usually, BN emerges after a dieting period and main symptoms consist of uncontrollable binge eating, selfinduced vomiting, excessive exercise and low self-esteem related to body shape (Bulik et al., 1997). AN and BN have much in common, about 25 to 30% of patients with BN appear to have a history of AN (Strober et al., 1997).

### 2. Family Studies

Family studies have led us to have information about the genetic components of eating disorders, by along with some explanations for the molecular mechanisms of AN and BN. Studies to date have shown that the prevalence of AN and BN increases 7 to 12 times in relatives with eating disorder probands (Strober et al., 2000). AN and BN patients generally have an obsessive-compulsive disorder comorbidity. 18% of AN patients and 33% of BN patients are considered to be diagnosed with OCD (Matsunaga et al., 1999). Patients diagnosed with OCD also had the eating disorders at a rate of 11 to 13% (Rubin et al., 1992).

#### 3. Twin Studies

Most studies to date reported the high incidance of AN in monozygotic twins when compared to dizygotic twins. This difference implies the importance of genetic factors, and may explain why AN is more common (Kipman et al., 1999). Studies having reliable statistical results showed that genetic factors appeared to be more prominent than environment factors (Bulik et al., 2000). In the Virginia twin study, genetic predisposition's associated with BN and depression was reported (Walters et al., 1992).

#### 5-Hydroxytryptamine Receptor 2A Gene

5-Hydroxytryptamine Receptor 2A gene (HTR2A, ID: 3356) encodes one of the receptors for serotonin, a neurotransmitter highly produced by serotonergic neurons (Brunoni et all, 2019). It is a G-protein coupled receptor, and mainly located in the neocortex, caudate nucleus, nucleus accumbens and hippocampus. HTR2A receptors play a role in appetite control. Ligand binding causes a conformation change that starts the signaling process via guanine nucleotide-binding protein (G protein) and modulates the activity of down-stream effectors. One of the most important down-stream pathway is the activation of phospholipase C and a phosphatidylinositol-calcium, a second messenger signalling system that modulates the activity of phosphatidylinositol 3-kinase and promotes the release of Ca(2+) ions from intracellular stores.

It is widely accepted that there is an altered serotonin neurotransmission existence in AN and many studies tried to explain which serotonin receptor subtype is involved in the aetiology of this condition. As metachlorophenylpiperazine (m-CPP) binds to the HTR2A receptor and also has an agonist effect for the HTR2A receptor, dynamic studies including m-CPP or other serotonergic agents showed that 5-hydroxytryptamine receptor 2C (HTR2C, ID: 3358) and HTR2A receptors could be more specifically relevant (Brewerton & Jimerson, 1996). Although nutritional status and body weight could act as confusing factors, it has been suggested that synaptic serotonergic susceptibility including these receptors is reduced in patients with AN (Wolfe et al., 1997). The probable model of platelet HTR2A receptor in AN has also been used (Elliott & Kent, 1989). Platelet HTR2A receptor-coupled intracellular signal transduction and HTR2A receptor-mediated platelet aggregation were found to be higher in AN patients with eating disorders (Okamoto et al., 1995). In a study with 10 patients with AN, the increase in Kd, and Bmax values for [3H]LSD (lysergic acid diethylamide) binding to HTR2A receptors were reported (Spigset et al., 1999).

Elucidate the impact of genetic basis of AN and BN in the terms of serotonergic pathway, HTR2A gene and its promoter has been widely analysed. rs6311 polymorphism (A/G transtion) within the promoter region was found to be associated with AN and BN. Also mutations causing Thr25Asn and His452Tyr amino acid alterations within the gene have been also reported (Kouzmenko et al., 1999). The effect of rs6311 polymorphism in AN patients have been identified by some studies (Nacmias et al., 1999; Collier et al., 1997; Sorbi et al., 1998; Enoch et al., 1998), but these results could not be confirmed by other independent studies (Ziegler et al., 1999; Campbell et al., 1998; Hinney et al., 1997; Nishiguchi et al., 2001; Kipman et al., 2002). Therefore, rs6311 polymorphism of HTR2A gene may act as a genetic biomarker for AN. Controversial results can be explained by sample size, genetic origin of the samples, genetic heterogeneity and methods of the studies (Ioannidis et al., 2001).

In order to determine rs6311 polymorphism effect and heritage patterns in patients with AN, researchers analyzed 316 patients from six European centres, and they utilised a family-based transmission disequilibrium (TDT) approach to understand the HTR2A-1438 G/A polymorphism function. In this study they detected no statistically significant difference in the transmission of the polymorphism by using transmission disequilibrium test (TDT) (Gorwood et al., 2002). One hypothesis suggests that the positive case-control association studies were biased by patients or/and controls ethnic origins since the TDT approach is protected from the stratification bias.

## 4. Conclusion

None of the estimations of heritability of AN, which are based on various studies, are completely protected from the potentially involved biases. Various twin studies, population-based or family aggregation, reported the consistency of the results of these heritage studies, all converge on a 70% heritability. Even so, AN and other disorders that exist comorbidly such as mood disorders, other specified feeding or eating disorders or OCD, the phenotypical relation is assessed poorly at the genetic level.

According to the current meta-analysis of case-control studies, HTR2A rs6311 polymorphism is significantly associated with AN. But in triplet examined with TdT, similar results can not be replicated. To explain the exact mechanism of the rs6311 polymorphism on understanding of the psychopathology of eating disorders, studies with larger samples are needed.

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