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Association Study of Interferon Gamma (IFN-γ) +874T/A Gene Polymorphism in Patients with Paranoid Schizophrenia

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Abstract Schizophrenia is a multifactorial disease with changes affecting the immune system. Dysregulation of the cytokine network in schizophrenia has been well documented. Such changes may occur due to disturbances in cytokine levels that are linked to polymorphisms of cytokine genes. However, research in the role of cytokine gene polymorphisms in schizophrenia has been surprisingly scanty. The aim of this study was to identify, in a case control study, whether polymorphism of *IFN-γ* gene is a risk factor for the development of paranoid schizophrenia. To the best of our knowledge, this is the first study that examines the association between the *IFN-γ* gene polymorphism and psychopathological symptoms in patients with paranoid schizophrenia. Polymorphism of *IFN-γ* (+874T/A, rs 62559044) in schizophrenic patients (n=179), as well as healthy individuals (n=196), both Polish residents, was genotyped using AS-PCR method. Of note, when analyzing the results, we took into consideration the gender of studied individuals. Surprisingly, a single-nucleotide polymorphism in the first intron of the *IFN-γ* gene was found to be associated with paranoid schizophrenia in males, but not in females. The presence of allele A at position +874 in the *IFN-γ* gene correlates with 1.66-fold higher risk of paranoid schizophrenia development in males. Differences in the genotypes may have an important role in determining the level of I gene transcription. Because other polymorphisms have been demonstrated to influence *IFN-γ* transcription, further analysis is necessary to clarify the role of this gene in the pathogenesis of paranoid schizophrenia.

Keywords Polymorphism · IFN-γ · Paranoid schizophrenia

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Introduction

There have been several hypotheses explaining the etiopathogenesis of schizophrenia: neurodevelopmental, genetic, linked to neurotransmitters such as dopamine, serotonin, glutamic acid, and gamma-amino butyric acid. Considering the immune system changes observed in patients suffering from schizophrenia, some authors also distinguish a neuroimmunological hypothesis (Leonard 2005).

Among genes that predispose to schizophrenia development are genes encoding cytokines which are closely associated with the central nervous system (O'Donovan et al. 2003; Craddock et al. 2005). The communication between peripheral cytokines and brain cells during pathological conditions is possible by passive transport, secondary messengers, active transport, and afferent nerve terminals (Kronfol and Remick 2000; Banks 2005). As cytokine regulation is affected by stress, these proteins may possibly play a relevant role in major psychiatric disorders (Kronfol and Remick 2000).

Interferon γ (IFN-γ) stimulates Th1 and inhibits Th2 clonal expansion. This cytokine is secreted by native T and

Th1 cells, CD1d-restricted natural killer T cells, and by microglia. It is hypothesized that demyelination may be connected with direct deleterious effects on oligodendrocytes or may be due to activation of macrophages and microglia, determined by IFN-γ expression. Dendritic reaction and inhibition of synapse formation are also determined by IFN-γ (Kim et al. 2002). IFN-γ also plays a pivotal role in macrophage activation in defense against viruses and intracellular pathogens and is involved in the induction of immune-mediated inflammatory response (Billiau et al. 1998). Moreover, IFN-γ induces class I major histocompatibility complex (MHC) antigen expression on both neuronal and glial cells and also induces MHC class II expression on microglia, some population of astrocytes, and endothelial cells (Male and Pryce 1988). Finally, IFN-γ may play an important role in the induction of various central nervous system pathologies since it enhances the function of microglia by increasing the production of some cytokines, e.g., TNF-α, nitric oxide, as well as of free radicals (Yong et al. 1991).

There has been evidence that polymorphism +874T/A in the first intron of the gene encoding IFN-γ is associated with production of this molecule. The presence of genotype A/A is linked with low cytokine production, whereas genotype A/T is linked to medium cytokine production, and genotype T/T to high cytokine production, respectively (Pravica et al. 2000).

Studies examining the relationship between promoter polymorphism in *IFN-γ* -encoding gene and paranoid schizophrenia development have been scarce. Considering the potential role of IFN-γ in paranoid schizophrenia, the linkage studies pointing to the chromosomal region containing the *IFN-γ* gene and the proposed Th1/Th2 imbalance in schizophrenia, the present study focused on examining the association between *IFN-γ* gene polymorphism at position +874T/A and the occurrence of paranoid schizophrenia among Polish residents.

Methods

Patients and Controls

Schizophrenia patient groups consisted of 179 individuals (45.2% female and 54.8% male) of mean age 42.8±12.4 (median, 44.0; range, 20–70 years) recruited from among the inpatients treated at the Department and Clinic of Psychiatry, Medical University of Silesia in Katowice as well as from Psychiatric Hospital in Lubliniec. There was a statistically significant difference in age between males and females (39.6±11.8 vs. 46.6±11.8; $p<0.0001$). All patients met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) criteria for paranoid type of schizophrenia (APA). The diagnoses were assigned based on a Structured Clinical Interview for DSM-IV Axis I Disorders, Clinical Version (First et al. 1997) by two independent experienced psychiatrists. Other available resources such as clinical course, medical records, and family history information were also used. Only the cases meeting diagnostic consensus were included in the study. Exclusion criteria involved other Axis I and Axis II diagnosis, as well as neurological illness, endocrine disorders, and autoimmune disease. We defined the age of schizophrenia onset as the first appearance of positive psychotic symptoms. Psychopathology at the time of admittance was monitored using the structured interview of the positive and negative symptom scale (PANSS; Kay et al. 1987). PANSS was administered by trained clinical raters. Patients were assessed for being capable of understanding the study goal before a written consent was obtained. The study was carried out in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and approved by the Bioethics Committee of the Medical University of Silesia.

The healthy control group involved 196 healthy unrelated individuals (38.8% females and 61.2% males, mean age 46.6±8.4; median, 43.0; range, 20–61 years) recruited from among volunteer blood donors at the Department of Blood Donation of the Medical University of Silesia. Before sampling, it was verified if they had current psychiatric problems or family history of schizophrenia and, by direct interview, any other neurological disorders.

IFN-γ Genotyping

DNA was isolated from whole peripheral blood using phenol–chloroform method. DNA extracts were qualitatively evaluated by electrophoresis in 1.5% agarose gel and quantitated spectrophotometrically (Gene Quant II by LKB Pharmacia Biotech).

Polymorphism of the *IFN-γ* gene (+874T/A) was determined by allele-specific PCR method. For each allele, PCR reaction was carried out on a DNA template with a pair of specific primers (reverse: TCA ACA AAG CTG ATA CTC CA; forward +874T: TTC TTA CAA CAC AAA ATC AAA TCT or forward +874A: TTC TTA CAA CAC AAA ATC AAA TCA; amplimer length, 262 bp), 25 μl total volume reaction mix (provided by the manufacturer), and Tth polymerase (Epicentre Biotechnologies, Madison, WI, USA). Amplification was performed using G-Storm GS1 thermal cycler (Gene Technologies LTD, Essex, UK). PCR was performed using a touchdown method. PCR cycling conditions were as follows: 95°C for 1 min, followed by 10 cycles at 95°C for 15 s, 52°C for 50 s and 72°C for 40 s, and 20 cycles at 95°C for 20 s, 49°C for 50 s and at 72°C for 50 s; elongation was performed at 72°C for 3 min. The genotypes were determined by analyzing electrophoresed 2% agarose gel slabs stained with ethidium bromide.

Statistical Analysis

Differences in the frequencies of IFN-γ alleles, in both study and control groups, were analyzed either by the χ^2 test or with the maximum likelihood χ^2 test. The odds ratio (OR) was used as a measure of the strength of association between allele and genotype frequencies and paranoid schizophrenia. The distribution of the variable was evaluated by the Shapiro–Wilk test. Homogeneity of variance was assessed by Levene's test. Descriptive variables are presented as mean±standard deviation. For PANSS and time of occurrence of the first episode, a two-way ANOVA was used. Associations between sex and genotype distribution in the control group and among patients with paranoid schizophrenia were assessed with the log-linear analysis. Kaplan–Meier estimates and IFN-γ proportional hazard models were used to describe the effect of genotype on schizophrenia risk.

All calculations were performed with STATISTICA v. 8.0 (StatSoft Inc., [www.statsoft.com]), R software [cran.r-project.org/], and SNPStats [bioinfo.iconcologia.net]. All p values were two-tailed, and $p<0.05$ was established as statistically significant.

Results

Control Group

There were no statistically significant differences in age between males and females (42.4±8.3 vs. 42.8±8.8; $p=0.7344$) and between different genotypes (A/A, 39.7±10.4; A/T, 42.9±8.6; and T/T, 42.0±6.7; $p=0.4667$). There were also no differences between males and females in the distribution of genotypes ($\chi^2=4.25$; $p=0.1192$) and alleles ($\chi^2=0.75$; $p=0.3865$; see Table 1). The control group was, therefore, uniform in terms of age and the incidence of various genotypes and alleles.

Paranoid Schizophrenia

There was a statistically significant difference in age between males and females (39.6±11.8 vs. 46.6±11.8; $p<0.0001$). There were no statistically significant differences in age between different genotypes (A/A, 43.4±13.5; A/T, 42.8±12.8; and T/T, 42.0±10.1; $p=0.8688$). However, there were statistically significant differences between males and females in the distribution of genotypes ($\chi^2=6.36$; $p<0.05$) and a tendency towards statistical significance in the distribution of alleles ($\chi^2=3.50$; $p=0.0614$; see Table 1).

The Comparison of Genotypes and Allele Distributions Between Control and Paranoid Schizophrenia Groups

We compared the distribution of alleles and genotypes of *IFN-γ* +874T/A polymorphism among females and males in the controls and schizophrenic patients. There was no statistically significant difference in the incidence of *IFN-γ* genotypes between schizophrenic and healthy females, while such a statistically significant difference was found between schizophrenic and healthy males (see Table 1). It was observed that in males with schizophrenia, the genotype A/A is more often present than in healthy ones (see Table 1). Statistically significant differences in allele distributions between those groups were also observed. Male patients with allele A are more predisposed to schizophrenia development (OR=1.66; 95% CI, 1.14–2.44; $p<0.01$).

Co-dominant, dominant, recessive, and inheritance models were tested and the results are presented in Table 2. *Co-dominant model* is the most general model and it allows every genotype to give a different and non-additive risk. This

Table 1 *IFN-γ* (rs 62559044) SNP genotypes and allele distributions in patient and control groups

Group	*n*	Genotype distribution					Allele frequency			
		A/A	T/A	T/T	χ^2	*p*	A	T	χ^2	*p*
Paranoid schizophrenia	179	42	99	38			183	175		
		23.46%	55.31%	21.23%			51.12%	48.88%		
Control	196	10	155	31	32.04	<0.0001	175	217	3.14	0.0764
		5.10%	79.08%	15.82%			44.64%	55.36%		
Paranoid schizophrenia males	98	30	49	19			109	87		
	54.75%	30.61%	50.00%	19.39%			55.61%	44.39%		
Control males	120	3	97	20	36.04	<0.0001	103	137	6.96	<0.01
	61.22%	2.50%	80.83%	16.67%			42.92%	57.08%		
Paranoid schizophrenia females	81	12	50	19			74	88		
	45.25%	14.81%	61.73%	23.46%			45.68%	54.32%		
Control females	76	7	58	11	3.89	0.1430	72	80	0.09	0.7642
	38.78%	9.21%	76.32%	14.47%			47.37%	52.63%		

Table 2 Odds ratio (OR) calculated assuming different models of inheritance of *IFN-γ* (rs 62559044) SNP

Genotype	Controls	Patients	OR[a] (95% CI)
Co-dominant sex-adjusted			
T/T	31 (15.8%)	38 (21.2%)	1.00
T/A*	155 (79.1%)	99 (55.3%)	0.52 (0.30–0.89)
A/A*	10 (5.1%)	42 (23.5%)	3.53 (1.52–8.18)
Females			
T/T	11 (14.5%)	19 (23.5%)	1.00
T/A	58 (76.3%)	50 (61.7%)	0.50 (0.22–1.15)
A/A	7 (9.2%)	12 (14.8%)	0.99 (0.30–3.27)
Males			
T/T	20 (16.7%)	19 (19.4%)	1.00
T/A	97 (80.8%)	49 (50.0%)	0.53 (0.26–1.09)
A/A*	3 (2.5%)	30 (30.6%)	10.53 (2.75–40.30)
Dominant			
T/T	31 (15.8%)	38 (21.2%)	1.00
T/A–A/A	165 (84.2%)	141 (78.8%)	0.70 (0.41–1.18)
Recessive			
T/T–T/A	186 (94.9%)	137 (76.5%)	1.00
A/A*	10 (5.1%)	42 (23.5%)	5.88 (2.84–12.17)
Overdominant			
T/T–A/A	41 (20.9%)	80 (44.7%)	1.00
T/A*	155 (79.1%)	99 (55.3%)	0.32 (0.21–0.51)

* $p<0.05$

[a] Odds ratios of genotypes

model compares heterozygous A/T (He) and homozygous for the variant T/T (Va) to the homozygous for the most frequent A/A genotype. It was shown that the co-dominant and recessive inheritance models are statistically significant. In the co-dominant model, the patients with genotype T/A have lower risk of development of paranoid schizophrenia in comparison with A/A-genotype patients. In the recessive model, the patients with A/A genotype have higher risk of development of paranoid schizophrenia in comparison with T/T and T/A genotypes (Table 2).

Log-linear analysis was performed. Association between genotype distributions and sex was found between schizophrenia and controls (G2=45.82; $p<0.0001$), as well as between genotypes and schizophrenia/control group (G2=33.58; $p<0.0001$).

Kaplan–Meier estimates and IFN-γ proportional hazard models were used to describe the effect of genotype on schizophrenia risk. Hazard models were adjusted for age of the occurrence of first episode and sex (see Fig. 1, left and right panels). Twenty five percent (I quartile) of patients underwent first episode of the disease before age 25 and half of them before age 42. There were also statistically significant differences between curves depending on genotypes ($\chi^2=23.8$; $p<0.0001$). The genotype A/A is connected with younger age of the first episode of disease (see Fig. 1, right panel).

There were statistically significant differences between the curves for males, depending on genotype ($\chi^2=28.5$; $p<0.0001$); however, not for females ($\chi^2=1.8$; $p=0.4133$). Kaplan–Meier analysis showed that schizophrenic males with the A/A genotype had the first episode of the disease earlier than male patients with other genotypes (see Fig. 2, right panel).

There was a statistically significant difference between males and females with paranoid schizophrenia in time occurrence of the first episode. As can be seen, the time of the occurrence of the first episode is significantly lower in males with A/A or T/A genotypes. We have not found a statistical significance in P (positive), N (negative) and G (general) scale values (PANSS scale) between the analyzed groups (see Table 3).

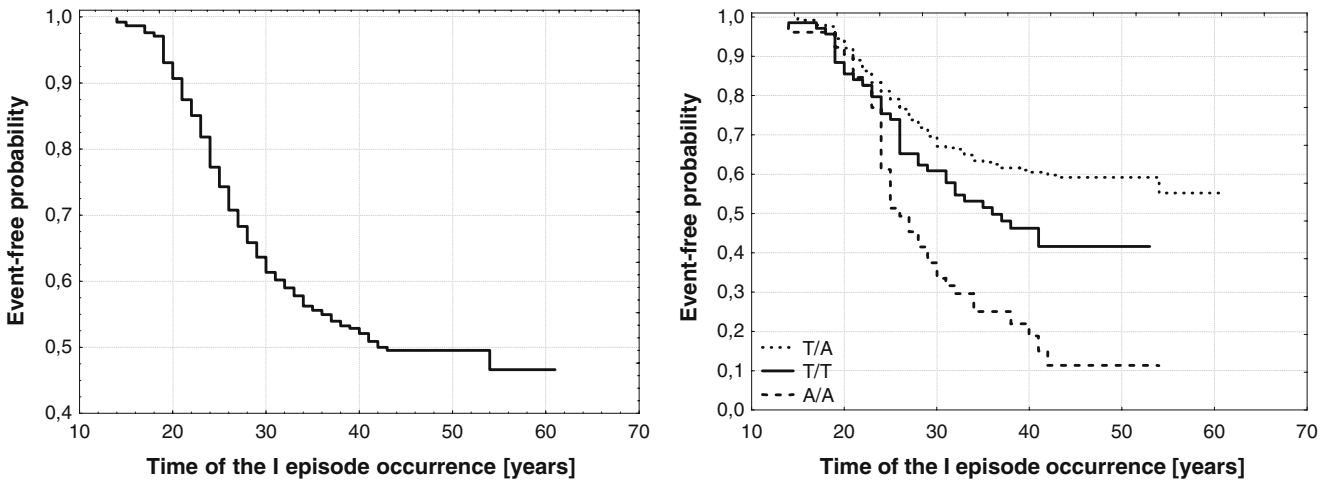

Fig. 1 Kaplan–Meier estimates of the percentage of individuals remaining free of the first episode of paranoid schizophrenia in total population studied (*left*) and according to genotype (*right*)

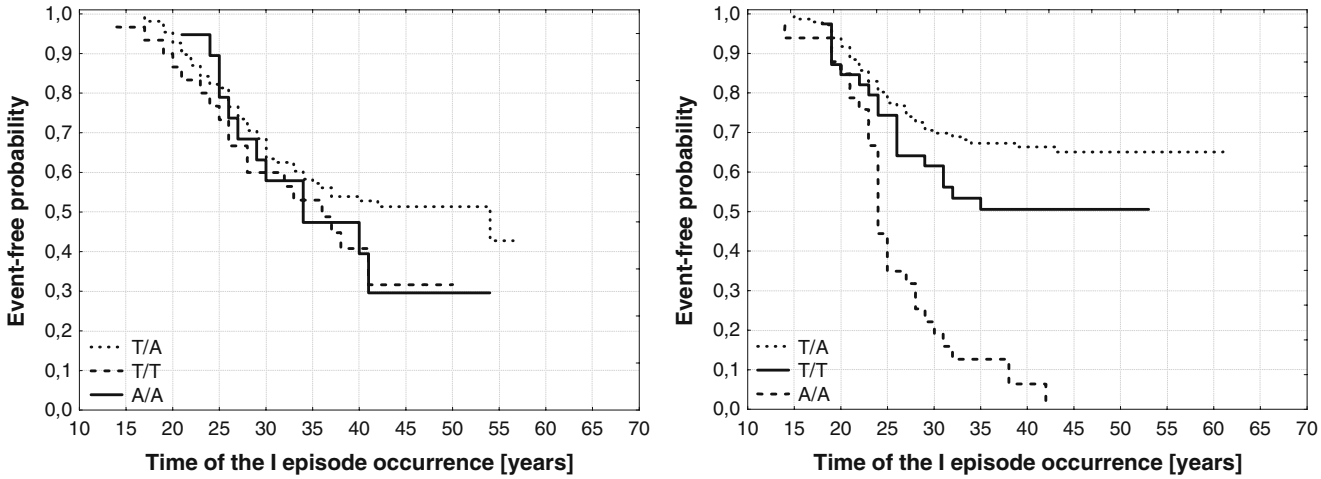

Fig. 2 Kaplan–Meier estimates of the percentage of individuals remaining free of paranoid schizophrenia, among women (*left*) and men (*right*), according to genotype distribution

Discussion

Possible role of the immune response system in the pathogenesis of schizophrenia was indicated by several authors (e. g., Plata-Salaman and Turrin 1999; Nawa et al. 2000). Cytokines are closely associated with the works of the central nervous system and are known to be involved in the pathophysiology of different types of schizophrenia. Cytokines could interact with neurons, influencing neurotransmission and neurodevelopment (Jarskog et al. 1997). Additionally, by binding to specific receptors at the neurons' surface, the cytokines may modulate the secretory activity of these cells in relation to catecholamines or neuropeptides (Plata-Salaman and Turrin 1999). The effect exerted by cytokines on the release of various neurotransmitters, particularly on monoaminergic system, may play a key role in the development of mental disorders (Dunn 2006).

Many genes were selected as being related to the development of schizophrenia. The potential role for susceptibility to schizophrenia development was forwarded, for example, for TNF-alpha or IL-1 gene complex (Kowalski et al. 2001) as well as for IL-6 and IL-10 cytokines (Paul-Samojedny et al. 2010). The SchizophreniaGene database includes 1,650 works presenting association analysis of 8,466 different variants of 965 genes (state as of 4 August 2010) [http://www.schizophreniaforum.org/res/sczgene/default.asp.]. *IFN-γ* gene is not included in the database.

Table 3 Results of two-way ANOVA (genotypes distribution and sex) for PANSS scale and time of the first occurrence of episode

Effect	*p*		
	Sex	Genotype	Sex × Genotype
PANSS positive	0.1277	0.9882	0.2986
PANSS negative	0.7600	0.1483	0.2379
PANSS general	0.1477	0.3826	0.5381
PANSS total	0.1966	0.4283	0.2914
Time of the first episode	<0.01	0.4900	0.7194

There is evidence that IFN-γ may play a role in immune changes occurring in schizophrenia. Arolt et al. (1997) indicated that reduced IFN-γ production is associated with acute exacerbation of schizophrenia. Inglot et al. (1994) showed a decreased production of IFN-γ in psychotic patients (including schizophrenia and depression). On the other hand, Preble and Torrey (1985) reported higher serum level of IFN-γ in schizophrenic patients. The level of gene expression may be linked to SNPs in introns of genes encoding cytokines (Smith and Humphries 2009).

In this study, we attempted to establish an association between polymorphism in the first intron (at position +874) of the *IFN-γ* gene and the occurrence of paranoid schizophrenia among Polish residents (Caucasian origin).

Polymorphism at position +874 in *IFN-γ* gene is connected with the production of this cytokine. The T allele provides a binding site for the transcription factor nuclear factor-B, which is able to upregulate IFN-γ expression (Pravica et al. 2000). To our knowledge, there have been no published data pointing to the relationship between IFN-γ +874T/A polymorphism and risk of paranoid schizophrenia development. The present report is also the first that examines the association between *IFN-γ* gene polymorphism and paranoid schizophrenia and taking into account the gender of individuals examined.

In here, a relationship between sex and IFN-γ +874T/A polymorphism was observed. We found a frequent occurrence of genotype A/A and allele A in schizophrenic males in comparison to healthy ones. This may indicate a

decreased serum level of IFN-γ in male patients. There is evidence that many genes, or rather genetic variants, may act differentially in females and males. The functioning of genes depending on gender may be due to the impact of sex hormones on gene expression or regulation by factors (other than genetic) correlated with sex (Shalev et al. 2009). The inclusion of gender in these considerations seems to be very important as the interaction between gender and genotypes may be the cause of individual differences in vulnerability to stress in females and males. The interaction between sex and IFN-γ genotypes was also observed in multiple sclerosis (Kantarci et al. 2008).

Similarly, gender differences associated with schizophrenia have been known for age of onset, better premorbid functioning, better treatment response, more affective and paranoid symptoms, and fewer negative symptoms (Häfner 2003). In schizophrenia, sex differences may be affected by structural brain differences (Lewine et al. 1996). A neuroprotective effect of estrogens is hypothesized. Estrogens regulate neurotransmitter activity within diverse neuronal population (Członkowska et al. 2005). It has been known that estrogens inhibit postsynaptic dopamine transmission and have antipsychotic properties (Rao and Kölsch 2003; Akhondzadeh et al. 2003). It is also well documented that estrogens increase IFN-γ promoter activity by ERE sequence, which was mapped to the 5′ flanking sequence of IFN-γ (Sarvetnick and Fox 1990). There is also evidence for differential IFN-γ responses between males and females. It is postulated that sex differences in IFN-γ secretion may be a downstream consequence of IL-12 expression differences between females and males (Członkowska et al. 2005).

Gender differences are also observed in the clinical presentation (age of the first episode and P and N scale values) and psychosocial functioning in patients with schizophrenia. According to some references, males develop a relatively severe first episode at younger age than females (e. g., Willhite et al. 2008). We also observed younger age of first episode of paranoid schizophrenia in males (age, 24.5±5.5) than in females (age, 27.8±7.2). Most published reports indicate a greater frequency of positive and affective symptoms for females and greater frequency of negative symptoms for males (Choi et al. 2009). This is in contradiction to our observations about negative and positive symptoms in females and males. We found (however, not statistically significant) a slightly higher P scale value in males (24.0±6.0) than in females (22.0±5.5). However, there are also some reports showing a greater frequency of typical hallucinations and delusions in schizophrenic males, as compared to affected females (e. g., Salem and Kring 1998; Leung and Chue 2000).

Summarizing the results of the presented study, it should be emphasized that polymorphism +874T/A in the *IFN-γ* gene is associated with paranoid schizophrenia in males, but not in females. The presence of allele A at position +874 correlates with 1.66-fold higher risk of paranoid schizophrenia development in Polish male residents. Moreover, the differences in genotype of IFN-γ +874T/A polymorphism may have an important role in determining the level of transcription of the *IFN-γ* gene.

Because other polymorphisms have been demonstrated to influence IFN-γ transcription, further analysis is necessary to clarify the role of this gene in the pathogenesis of paranoid schizophrenia.

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