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ORIGINAL ARTICLE

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Association of *PTPN22* polymorphism and its correlation with Graves' disease susceptibility in Polish adult population—A preliminary study

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Abstract

Background: Susceptibility to Graves' disease (GD) is determined by various genetic factors; the gene encoding protein tyrosine phosphatase (*PTPN22*) may be one of those associated with higher risk of GD. The aim was to estimate the association of the *PTPN22* gene polymorphism rs2476601:c.C>T (c.1858C>T) with the predisposition to GD within the adult north-eastern Polish population.

Methods: *PTPN22* gene polymorphism was analyzed in individuals with clinical GD history ($n = 166$) and healthy subjects ($n = 154$). The presence of different variants of the investigated gene polymorphism was estimated using the DNA Sanger sequencing method.

Results: Patients with GD had a more frequent occurrence of the T gene allele of *PTPN22* gene compared to the control group, however, it was not significant ($p = 0.257$). Analysis of genotype distribution showed significantly more frequent occurrence of TT homozygote in GD patients compared to control individuals ($p = 0.016$, OR = 9.28). Patients with ophthalmopathy had a less frequent occurrence of the T gene allele of *PTPN22* gene compared to patients without ophthalmopathy, however, it was not significant ($p = 0.12$). Occurrence of the T gene allele of *PTPN22* gene in GD manifestation in those under 40-year old was more frequent compared to individuals over 40, but the obtained difference was also not significant ($p = 0.75$).

Conclusions: Our preliminary study suggest that *PTPN22*:c.1858C>T gene polymorphism may be associated with a predisposition to GD within the adult north-eastern Polish population. The studied polymorphism of the *PTPN22* gene did not significantly affect the risk of ophthalmopathy developing and disease manifestation before the age of 40.

KEYWORDS
gene polymorphism, Graves' disease, *PTPN22* gene

1 | INTRODUCTION

Graves' disease (GD) is one of the most common autoimmune diseases of all endocrinopathies. The pathogenetic factors affecting the manifestation of clinical symptoms are antibodies directed against the thyroid-stimulating hormone (TSH) receptor. According to previous research, genetic factors play the dominant role in initiating the development of the disease (Collins & Gough, 2002; Tomer, 2010). Predisposition to GD is conditioned by different genes and is characterized by a multifactorial model of inheritance, and the alleles composition of many different genes determines an increased predisposition to the disease (Tomer & Huber, 2009; Vaidya, Kendall-Taylor, & Pearce, 2002). Of the many "candidate genes" researched so far, only two loci show an unambiguous relationship to the pathogenesis of GD: antigen 4 cytotoxic lymphocytes (*CTLA-4;*OMIM:123890) and major histocompatibility complex (*HLA*) (Lee, Li, Hammerstad, Stefan, & Tomer, 2015; Tomer & Menconi, 2009). There is a number of reports in the available literature concerning the relationship of specific candidate genes with GD, whose role in the disease's pathogenesis is potentially justified by the importance of the proteins encoded by them. Within these genes, there are genes encoding the CD40 molecule, the thyroglobulin, the TSH receptor, deiodinase I, and also many cytokines and adhesion molecules involved in immune regulation (Chistiakov, Savost'anov, & Turakulov, 2004; Collins & Gough, 2002; Tomer & Menconi, 2009; Vaidya et al., 2002).

It has been shown that the key gene conditioning predisposition to GD, but also to other autoimmune diseases, is the gene coding a specific type of protein tyrosine phosphatase, nonreceptor-type, 22 (*PTPN22* gene; also known as *LYP* – lymphoid-specific phosphatase; OMIM:600716; HGNC:9652) located on the surface of lymphocytes (Smyth et al., 2004; Velaga et al., 2004). It has been shown that LYP on the T-cell surface plays a key role in the prevention of spontaneous T-cell activation and reduces the response to antigen by dephosphorylation and inactivation of kinases (and their substrates) associated with the TCR receptor.

Recent studies indicated that the conversion of arginine to tryptophan at position 620 of the amino acid chain (NP_057051.3:p.Arg620Tr, R(Arg) > W(Trp)) due to polymorphism rs2476601:C>T in the DNA chain, blocks the binding of LYP to Csk. As a result, hyper-responsive T cells show an increased predisposition toward a destructive cellular response to their own autoantigens that may temporarily occur as a result of a viral infection or other inducer of "immune stress." The above functional studies are confirmed in many populations by clinical observations on autoimmune diseases: GD, type 1 diabetes, rheumatoid arthritis, and visceral lupus in different population (El Fotoh, El Razek Midan, & El Shalakany, 2018; Orozco et al., 2005; Stanford & Bottini, 2014; Zheng & She, 2005).

Therefore, the aim of the study was to evaluate the relationship between polymorphism of the *PTPN22*:c.1858C>T gene and the predisposition to GD within the Polish population. We also analyzed the influence of polymorphic variations of the examined gene depending on the presence of ophthalmopathy as well as the age of the disease manifestation.

2 | METHODS

2.1 | Ethical compliance

The study was carried out in agreement with the Helsinki-II-declaration and was approved by the local Bioethics Human Research Committee. All subjects included in the study gave their informed written consent.

2.2 | Study population

The study group included 166 GD patients from the region of Podlasie (eastern Poland) (139 females, 27 males, mean age 42 ± 14 years), who were previously treated in the Endocrine Outpatient Clinic (minimum 24 months after the diagnosis). GD was diagnosed on the basis of clinical observations (size of goiter), biochemical parameters of hyperthyroidism: TSH, free triiodothyronine (fT3), and/or free thyroxine (fT4) were analyzed on Cobas e 411 biochemical analyzer (Roche Diagnostics) by means of electrochemiluminescence "ECLIA" method. GD was confirmed with positive antibodies against receptor for TSH (TRAb) > 1.5 (U/L) measured by RIA using the TRAK kit (BRAHMS, Berlin, Germany).

The control group was composed of 154 healthy volunteers without a family history of GD and other autoimmune diseases. They were age and gender matched to the group of patients with GD.

Fasting blood was collected from all of the subjects included in the study: 10 ml into an EDTA-K3 tube to obtain whole blood (genetic tests) and 5 ml into a tube without anticoagulant to obtain serum.

2.3 | Genetic tests

DNA for genetic tests was isolated from the whole blood lymphocytes by the classic "salting out" method. Fragments of the *PTPN22* gene (the reference sequence: NC_000001.11) were amplified using predesigned allelospecific primers (using the GenBank database version CM000674 and the BLAST program): ascending [5′-TCACCAGCTTCCTC AACCACA-3′] and descending [5′GATAATGTTGCTTCAACGGAATTT-3′]. Reactions were performed in a PTC-200 thermal cycler (MJ Research, Cambridge, MA) as follows: 2 min at 96°C; 6 cycles of 30 s at 96°C, 45 s at 69°C, and 45 s at 72°C; 21 cycles of 30 s at

TABLE 1 Distribution of *PTPN22* alleles and genotypes among patients with Graves' disease and in the control group

Allele/genotype tested	Graves' disease ($n = 166$)	Control group ($n = 154$)	p-Value/OR
Alleles[a]			
1858C	272/332 (81.9%)	217/308 (85.4%)	—
1858T	60/332 (18.1%)	37/308 (14.6%)	0.257/1.29
Genotypes[a]			
1858CC	117 (70.5%)	112 (74.2%)	—
1858CT	38 (22.9%)	38 (25.1%)	—
1858TT[b]	11 (6.6%)	1 (0.7%)	**0.016/9.28**

Note. OR, odds ratio; 95% CI, 95% confidence interval. Bold indicates the statistically significant of p-Value < 0.05.
[a]NC_000001.11. [b]Due to the number of observed cases, the Fisher correction was used.

TABLE 2 Distribution of *PTPN22* alleles and genotypes among patients with Graves' disease depending on the prevalence of ophthalmopathy

	Graves' disease ($n = 166$)		
Allele/genotype tested	With ophthalmopathy ($n = 67$)	Without ophthalmopathy ($n = 99$)	p-Value
Alleles[ab]			
1858C	115/134 (85.8%)	157/198 (79.3%)	0.12
1858T	19/134 (14.2%)	41/198 (20.7%)	
Genotypes[ab]			
1858CC	51 (76.1%)	66 (66.7%)	0.41
1858CT	13 (19.4%)	25 (25.3%)	
1858TT[bc]	3 (4.5%)	8 (8.1%)	

Note. [a]NC_000001.11. [b]due to the number of observed cases, the Fisher correction was used.[c]due to the number of observed cases, the Fisher correction was used.

94°C, 45 s at 65°C, and 45 s at 72°C; and 5 cycles of 30 s at 96°C, 60 s at 55 °C, and 120 s at 72°C. Products of amplification were identified (MJ Research 200 thermal cycler) by electrophoresis in a 2% agarose gel using ethidium bromide staining and visualization using an UV transilluminator. The rs2476601:C>T polymorphism of the *PTPN22* gene was evaluated by direct sequencing using the ABI Prism 310 sequencer (Applied Biosystems).

2.4 | Statistical analysis

The obtained results were statistically analyzed with the use of the STATISTICA 12.0 PL software (StatSoft Inc., Tulsa, Oklahoma) and STATA 12.1 (StataCorp LP). A χ^2 test with the Fisher correction was used for statistical analysis of allele incidence. Differences were considered statistically significant for $p < 0.05$.

3 | RESULTS

No significant gender differences were observed between the groups. GD patients revealed high fT3, fT4, mean: 14.13 ± 2.55 pg/dl and 1.89 ± 1.54 ng/dl, respectively. The mean level of anti-TSHR antibodies equaled 7.64 ± 0.7 U/L.

The results of our research showed a more frequent occurrence of the T gene allele of the *PTPN22* gene in the group of patients with GD in comparison to the control group, however, this difference was not statistically significant ($p = 0.257$) (Table 1). Genotype distribution analysis showed significantly more frequent occurrence of TT homozygote in the study group of patients with GD compared to control individuals ($p = 0.016$; OR = 9.28) (Table 1). In the group of patients with GD, the distribution of alleles and genotypes of the *PTPN22* gene was also assessed with regard to the presence of ophthalmopathy (Table 2) and the age of onset. Interestingly, patients with ophthalmopathy had less frequent occurrence of the T gene allele of the *PTPN22* gene compared to patients without ophthalmopathy, however, this difference was not significant ($p = 0.12$). Occurrence of the T gene allele of the *PTPN22* gene in GD manifestation in under 40 years ($n = 91$) was more frequent (34/182; 18.7%) compared to individuals over 40-year old ($n = 75$) (26/150; 17.3%), but the obtained difference was also not significant ($p = 0.75$). Analysis of the distribution of genotype frequencies in the control group and among patients with GD was consistent with the Hardy–Weinberg equation.

4 | DISCUSSION

Our preliminary studies concerning rs2476601:c.1858C>T polymorphism in the *PTPN22* gene showed a higher prevalence of the T allele and TT homozygotes in the adult GD patients group compared to subjects in the control group, which may suggest an important role for this polymorphism in the pathogenesis of GD within the north-eastern Polish population.

The *PTPN22* gene is located on the short arm of chromosome 1 at position p13.2 and consists of 22 exons. The product of the gene is a protein, which is a negative regulator of T lymphocyte activity (Hendriks & Pulido, 2013). The analyzed variant is a functional polymorphism rs2476601:c.1858C>T leading to inhibition of binding of the *PTPN22* gene product to Csk kinase, which results in general over-activity of T lymphocytes (Bottini et al., 2004).

The relationship between type 1 diabetes and GD and the polymorphism of the *PTPN22/LYP* gene (NP_057051.3:p. Arg620Tr, R(Arg) > W(Trp)) was demonstrated for the first time in case–control studies by Smyth et al. carried out on the British population. The authors stated that the Trp^{620} variant may be an important determinant not only of type 1 diabetes but also of GD and other autoimmune diseases (Smyth et al., 2004). Velaga et al., (2004) and Heward et al., (2007) also showed an association of the T allele of rs2476601:c.1858C>T polymorphism with GD. In addition, meta-analyzes confirmed the close association of T allele on the *PTPN22*:c.1858C>T gene variant in the Caucasian population with GD as well as rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes (Lee et al., 2007; Zheng, Ibrahim, Petersen, & Yu, 2012). In the same type of analysis other authors also found that *PTPN22*:c.1858T allele was significantly associated with latent autoimmune diabetes in adults (LADA), rheumatoid arthritis, and type 1 diabetes in Caucasians (Dong et al., 2014; Nabi et al., 2016; Xuan et al., 2013). Interestingly, despite so much data on the role of the NM_015967.6:c.1858C>T variant in the pathogenesis of GD, there are also reports in the literature that did not show an association between gene polymorphism and GD. The studies conducted by Ikari et al. and Ban et al., carried out on the Japanese population, did not present a relationship between the *PTPN22* gene polymorphism and GD disease, which may indicate a significant ethnic difference in the distribution of the *PTPN22* gene polymorphism (Ban, Tozaki, Taniyama, Tomita, & Ban, 2005; Ikari et al., 2006). Therefore, further research is required in order to prove whether the rs2476601 polymorphism is only a variant of the gene associated with the GD or whether there is a genetic conjugation.

The results of our research are a partial confirmation of the results obtained by Skórka, Bednarczuk, Bar-Andziak, Nauman, and Ploski, (2005), a study, which was also carried out on the Polish population. Similar to the results of our research, the authors demonstrated the association of *PTPN22*:c.1858C>T polymorphism with the development of GD; in addition, they also demonstrated the dependence of this gene polymorphism on the age of the disease's manifestation (Skórka et al., 2005). However, the studies carried out by us did not confirm the influence of rs2476601:c.1858C>T polymorphism on the age of the disease's manifestation. The reason for this may be a smaller group of patients with GD and inadequate stratification of this group. We also did not observe a relationship between the *PTPN22* genotype and the occurrence of ophthalmopathy. These results are in line with the studies of Skórka et al., (2005) and Ichimura et al., (2008). Recent study performed by Rydzewska et al., (2018) found the relationship between GD, Hashimoto's thyroiditis, and *PTPN22*:c.1858T gene variant. This study was conducted on 142 children with GD (mean age 16.5 ± 2 years) from the same region as in our study. Following the results of Rydzewska et al. study, we wanted to test the trend in the occurrence of this *PTPN22*:c.1858C>T polymorphism in adults from the same region of Poland.

In conclusion, our results suggest that the genetic polymorphism rs2476601 in the *PTPN22* gene influences an increased susceptibility to GD within the north-eastern (Podlasie region) adult Polish population. The study group and the control group were small ($n = 166$ and $n = 154$, respectively), but this is only a preliminary study. However, it is valuable in the context of further meta-analysis, as the GD patients' group was age and gender matched to the control group. It should be also noted that the described gene is one of many genetic factors and its variants, which significantly increases the risk of developing autoimmune diseases along with the modulating environmental factors. Future research and functional analysis are necessary to explain the true role of these factors in the development of GD and their impact on the autoimmunity process.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLOSURE

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AUTHORS CONTRIBUTIONS

NWK: the concept and design of the study, acquisition of data, analysis and interpretation of data; drafting of the article; final approval of the version to be published. **OMK-L:** analysis and interpretation of data; drafting of the article and revising article for it content; final approval of the version to be published. **JG:** analysis and interpretation of data; final approval of the version to be published. **JM:** revising article for it content; final approval of the version to be published. **AJK:** revising article for it content; final approval of the version to be published

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