

Gene-sex interaction in Hypercompetitive Attitude suggests beneficial effect of the DRD4 7-repeat allele in adaptation

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Twin studies provide evidence for the heritability of social attitudes, e.g. competitiveness, however, there are no psychogenetic association results linking competitive attitudes to genetic polymorphisms. Candidate gene studies report association with competitiveness-related phenotypes, risk taking for example was linked with the 7-repeat allele of the dopamine D4 receptor gene. This polymorphism has been studied extensively with novelty seeking and certain psychiatric disorders, as it plays a crucial role in molecular genetic mechanisms driving behavioral responses to the environment, especially modulating behavior through the reward circuitry. In the present study, we examined association of the DRD4 48-bp VNTR and competitiveness using self-report data from 399 non-related Caucasians. We found an interesting gene-sex interaction: 7-carrier males were more hypercompetitive as compared to non-carriers, while 7-carrier females were less hypercompetitive as compared to non-carriers. This finding remained significant after Bonferroni correction for multiple testing. Interestingly, among females we observed a significant positive correlation between hypercompetitiveness and mood characteristic variables, however, no such relationship could be detected in males. In 7-carrier females the association of hypercompetitiveness and anxiety or depression was more robust as compared to non-carrier females. These results highlight the importance of cultural influences in interpreting gene-sex interaction effects. Our results underlies interaction between genes and the environment; suggesting that the 7-repeat allele plays an important role in adaptivity, enabling sex-specific behavior to social expectations.

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INTRODUCTION

Heritability of competitiveness

Several twin studies provide evidence for heritability of social attitudes necessary in achieving one's goals (e.g.; Waller et al., 1990; Olson et al., 2001). According to a large-scale twin study (Krapohl et al., 2014), heritability of educational achievement originates not only from intelligence but also from several geneti-

cally influenced factors (e.g. personality). According to a Swedish twin study, financial decision making is partly genetically determined (Barnea et al., 2010). In another twin research (Cesarini et al., 2010) it was found that genetic differences are responsible for about 25% of the individual differences in financial risk taking. Interestingly, according to our best knowledge the construct of competitiveness has not been studied yet in candidate gene studies. The present study is the first attempt to link competitive at-

titudes to a candidate genetic polymorphism. Here we studied the role of the 7-repeat allele of the dopamine D4-receptor gene (DRD4) in relation to human traits related to competitiveness.

The DRD4 7-repeat allele and its associations with personality and other human traits

The D4 receptor is one of the five dopamine receptors. The DRD4 gene contains a repeat polymorphism in the exon 3 region of the gene, where a 48 base-pair sequence can be repeated between 2 and 11 (Van Tol et al. 1992). The most frequent allele types involve either 4 or 7 repeats in the Caucasian population (Ding et al., 2002). According to the description of Ding and colleagues the 'allele age' of the 7-repeat form is 5–10-fold younger, as compared to the ancient 4-repeat form. They suggest that this allele emerged from one or more rare mutational events. They also claim that the widespread frequency of this allele world-wide (see Chang et al., 1996) is the result of positive selection. According to a current analysis of population-specific biogeographic indicators, the natural selection hypothesis of the DRD4 7-repeat allele has been supported (Gören, 2016).

The 7-repeat form (also called as the 'adventure-gene variant' in the earliest candidate gene studies) was previously associated with novelty seeking (e.g. Ebstein et al., 1996), attention deficit and hyperactivity disorder (e.g. Swanson et al., 1998; Grady et al., 2003; Faraone et al., 2005), and substance abuse (e.g. Kotler et al., 1997). Meta-analyses did not confirm association of the DRD4 7-repeat allele with novelty seeking (Paterson et al., 1999; Ebstein, 2006; Munafò et al., 2008) or addiction (McGeary, 2009). In the field of attention deficit hyperactivity disorder (ADHD), association with the DRD4 7-repeat allele was verified by two meta-analyses (Li et al., 2006; Gizer et al., 2009), but according to the most recent meta-analysis results run in opposite direction (Bonvicini et al., 2016). Due to controversial results of dopaminergic candidate genetic studies and biological overlaps among psychiatric disorders it would be more fruitful to focus rather on intermediate phenotypes (e.g. personality) and neurocognitive endophenotypes than on diagnostic categories (Varga et al., 2011; Kotyuk et al., 2014). According to previous results of our laboratory, lower persistence (Szekely et al., 2004) and lower trait impulsivity (Varga et al., 2012) was found in the presence of the DRD4 7-repeat form. Result also showed that 7-carriers also made more errors in the Stroop task (Katonai et al., 2011) suggesting that there are dif-

ferences in executive function mechanisms between carriers and non-carriers.

In a recent study by Grady and colleagues (2013) frequency of the 7-repeat allele was reported to be higher among the oldest old (90–109 years old) group as compared to an ancestry matched younger (7–45 years old) sample. Accumulation of the 7-repeat allele in older population was confirmed by our research group as well (Szekely et al., 2016) in a large, healthy Hungarian sample. These results suggest that this allele may play an important role in longevity. Results from experiments with mice reared in different environmental conditions (Grady et al., 2013) fit well with these results. The DRD4 knock-out mice lived shorter and showed less spontaneous locomotor activity as compared to the wild type mice. On the other hand, knock-out mice were more susceptible to locomotor stimulation effect of cocaine and methamphetamine. Wild type mice lived longer, when reared in a rich environment (cages with many explorative options) as compared to mice reared in a poor environment. However, this beneficial effect of the environment on the lifespan was not observed in the DRD4 knock-out mice. Authors conclude that this gene seems to shape behavioral responses to fit to the environmental challenges through molecular mechanisms in mice and presumably in humans as well.

DRD4 7-repeat allele and competitiveness-related constructs

During the last decades a large number of association studies was published between dopaminergic gene polymorphisms and various psychological and psychiatric traits. The genetic background of hypercompetitiveness, however, has not been investigated yet according to our best knowledge, although several hypercompetitiveness-related behavioral constructs, such as financial success or risk taking were shown to be related to the genetic variants of the dopaminergic system.

Sapra and colleagues (2012) examined the genetic background of financial success on Wall Street in a group of traders (N=60) compared to a control group of university students (N=54). Although there were no differences in the frequency of DRD4 7-repeat allele, only in the polymorphism of that gene: traders were more likely homozygous for the long (L) allele of DRD4 promoter region and less likely carriers of the short (S) allele as compared to the controls. Traders also showed higher frequency of A/A alleles of COMT Val158Met polymorphisms as compared

to controls. An interaction effect of COMT x DRD4 emerged, but no association was found with candidate genes of other neurotransmitter systems (e.g. MAOA or SERT polymorphisms).

Among 94 young males, Dreber et al. (2009) found that 7-repeat carriers risk more money than non-carriers in financial decisions making test (the average difference was 39 USD). Later they examined 237 professional bridge players, but there were no differences in risk taking behavior of 7-repeat carriers and non-carriers (Dreber et al., 2011). In the study of Garcia and colleagues (2010) 181 young adults participated: results showed that the frequency of sexually promiscuous and/or unfaithful behaviors were higher among 7-repeat carriers as compared to non-carriers. This result is in line with the results of Grady and colleagues, and provide further evidences for the role of the 7-repeat allele in adaptivity to environmental factors.

Measures of different types of competitiveness

The earliest definition of hypercompetitiveness by Horney (1937) implies a very strong need to compete and win (regardless the means and costs) in order to maintain or enhance feelings of self-worth. Aggression, exploitation, manipulation and denigration of others often emerge in such competitive situations. Several tools were developed to measure this concept (e.g. Lakie, 1964; Martin & Larsen, 1976).

Ryckman et al. (1990) created the Hypercompetitiveness Attitude scale, which is the most widely used self-report tool on this construct to date. Similarly to Horney (1937), Ryckman et al. (1990) viewed hypercompetitiveness as a maladaptive form of competitiveness emphasizing that hypercompetitive subjects are more neurotic and show lower self-esteem and psychological health and higher dogmatism and mistrust. Ryckman et al. (1992) also created the concept of 'personal development competition orientation' (or self-development competitive attitudes) which refers to the positive form of competitiveness, focusing rather on the task and on enjoyment, mastery and self-development than on the outcome of the task (e.g. winning).

According to Thornton et al. (2011) the two types of competitiveness showed association with two different types of Type A behavior: hypercompetitiveness correlated positively with Impatience-Irritability while personal development competitiveness correlated positively with Achievement Strivings. Furthermore, hypercompetitiveness is positively cor-

related with reported health problems while self-development competitiveness is negatively correlated with them.

Sex differences in competitiveness and related traits

Competitive attitudes are linked to certain personality characteristics. Sex differences are also well established. Hypercompetitive males are more likely to show insulting sexual attitudes towards women, behave in a derogatory manner with them and to use violence under certain conditions (Ryckman et al., 1990). Ryckman et al. (1994) found that hypercompetitive subjects showed stronger narcissism, Type E behavior and different forms of sensation seeking. Since they found no differences in the strength of correlations between females and males, they did not analyze them separately. Scheer et al. (2012) examined adolescents and found that hypercompetitiveness showed inverse relationship with emotional intelligence. They also showed that girls had higher emotional intelligence and were less competitive than boys. Gneezy et al. (2003) found that the performance of students in solving mazegames is different in males and females according to the competitiveness of the environment. Males were more effective when their performance was measured to that of others, as compared to when only their own performance was measured. Later, Gneezy et al. (2009) found that sex differences in competing depends on whether the society is maternalistic or paternalistic. Based on a review of related research, they concluded that the reason for sex-differences in competitiveness is rather due to overconfidence and competitive attitudes in males, than to risk aversion of females (Niederle & Vesterlund, 2011). Others disagree, and emphasize the advantage of males in handling competitive pressure, their stronger desire to win and their stronger enjoyment of competition (Cotton et al., 2015).

Kayhan (2003) found that the so-called superiority competition, which is a construct highly similar to hypercompetitiveness, was associated with higher levels of depression among females, but not in man. Hibbard and Buhrmester (2010) also found that competing to win, a construct also similar to hypercompetitiveness, was related to higher level of depression among adolescent girls, but not among adolescent boys. It seems that high level of hypercompetitiveness among females is related to negative adjustment. One explanation for the lower level of competitiveness

among females found in the literature is that the traditional gender socialization that advocates females not to be competitive and not to be competitive in an open and explicit way like hypercompetitive people do (Hughes, 1988) and it may influence psychological well-being (Kayhan, 2003).

The aim of the present study was to examine the association between the DRD4 7-repeat allele and competitive attitudes, including analyses of possible sex differences. We also considered that gender differences may be associated with anxiety and depression in competition.

MATERIALS AND METHODS

Sample

Subjects were recruited on a voluntary basis at the Eötvös Loránd University, Hungary in the framework of a project exploring association with various human traits and cognitive behavior. Participants were asked to fill out questionnaires, provide non-invasive buccal DNA samples and perform computerized behavioral tasks. The study protocols were designed in accordance with guidelines of the Declaration of Helsinki, and were approved by the Scientific and Research Ethics Committee of the Medical Research Council (ETT TUKEB). Participants included in the present study filled out the Hypercompetitive Attitude (HCA) and/or the Personal- Development Competitive Attitude (PDCA) questionnaires.

Selection criteria for the sample to be analyzed included no past or present psychiatric history (based on self-report), age range from 18 to 35 and valid questionnaire data for at least one of the studied scales. We used a sample of 399 healthy, non-related Caucasian (Hungarian) subjects for candidate gene analyses of the DRD4 repeat polymorphism. Mean age of the sample was 21.68 (\pm 2.62) years, 40.4% of the sample was male, and 59.6% was female. Due to data collection in multiple waves, 399 subjects had PDCA scores, and 214 subjects had both PDCA and HCA scores.

Phenotype measures

Competitive attitudes were measured by two questionnaires: the Hypercompetitive Attitude (HCA) scale consisting of 26 items (Ryckman et al., 1990), and the Personal- Development Competitive Attitude (PDCA) scale consisting of 15 items (Ryckman et al., 1996). The questionnaires were translated to Hungarian from the original scales using the protocol of Beaton et al. (2000). Studies have found that both of these questionnaires have appropriate internal consistency and construct validity (Ryckman et al., 1990, 1996). The PDCA scores showed no relationship with HCA scores, the discriminant validity of these scales were satisfactory (Ryckman et al., 1996). In both scales, subjects scored statements on a 5-point Likert scale (1-5), scales were calculated as the sum of the item scores. Thus, the raw score for the HCA scale ranged between 26 and 130, and the raw score for the PDCA scale varied between 15 and 75.

Anxiety and depression was measured by the Hospital Anxiety and Depression Scale (HADS), developed by Zigmond and Snaith (1983) for a clinical, non-psychiatric population. In the present study we applied the Hungarian version (Muszbek et al., 2006). The 14 items of HADS includes 7 to assess anxiety and 7 for depression. Each item can be scored between 0 and 3, thus, the total score for both scales varied between 0 and 21.

DNA isolation and genotyping

Non-invasive samples were collected from buccal cells, and genomic DNA was isolated as described earlier (Kotyuk et al., 2013a). Here we genotyped the repeat polymorphism in the 3rd exon of the DRD4 gene, also labelled as DRD4 VNTR (variable number of tandem repeats). It is important to note that our previously elaborated genotyping method (Ronai et al., 2000) avoids unbalanced amplification of the longer and shorter PCR products in heterozygotes. Observed genotype frequencies of the DRD4 repeat polymorphism were: 2/4=42 (10.5%), 2/7=16 (4.0%), 3/4=18 (4.5%), 3/7=4 (1.0%), 4/4=175 (43.9%), 4/7=98 (24.6%), 7/7=9 (2.3%). The 4-repeat allele was the most frequent (66.0%), followed by the 7-repeat allele (17.5%). Frequencies of the other alleles were below 11%. No significant deviation was found ($P=0.56$) from the Hardy-Weinberg equilibrium (Hardy, 1908) based on the analysis of the three most common genotypes (44, 47 and 77). In accordance with other published studies the 7-repeat present vs. 7-repeat absent genotype groups were used in our association analyses.

Statistical Analysis

SPSS 20 was used for statistical analyses. Pearson correlation was used to test the possible relationship between the tested scales and age. Sex differences on

Table 1. Sex differences in HCA, PDC, and HADS scores

	Males	Females	
HCA	73.16 (± 13.64) (N=69)	69.58 (± 14.79) (N=145)	p=0.091
PDCA	53.60 (± 10.27) (N=161)	49.52 (± 2.35) (N=238)	p=0.001
HADS Anxiety	6.39 (± 3.56) (N=160)	6.73 (± 3.49) (N=235)	n.s.
HADS Depression	3.38 (± 2.70) (N=160)	2.94 (± 2.54) (N=235)	p=0.097

HCA: Hypercompetitive Attitudes; PDCA: Personal Development Competitive Attitudes; HADS: Hospital Anxiety and Depression Scale;
n.s.: non-significant

self-report scales were analyzed by one-way ANOVA. The distribution of 7-repeat allele in males vs. females was tested by chi-square test. One-way analyses of variance with covariates (ANCOVA) was used to test the association of competitiveness and the 7-repeat allele of DRD4 gene. Two-way ANOVA was used to test the interaction effect of the 7-repeat allele and sex on the two scales of competitiveness. False positive associations were ruled out by Bonferroni correction for multiple testing (Bonferroni, 1936; Miller, 1981).

RESULTS

Reliability of the self-report scales

Both competitive attitude scales showed good internal consistency. Cronbach-alpha values for the HCA were 0.907 for the total sample, 0.89 for males and 0.91 for females. Cronbach-alpha values for the PDCA were 0.842 for the total sample, 0.83 for males, and 0.85 for females. In the present sample, the mean scores were $70.73 (\pm 14.50)$ for the HCA, and 51.17 ± 11.71 for the PDCA. Correlation analysis was carried out between the two scales, but no significant correlation was observed, which is in line with the findings of Ryckman et al. (1996).

Reliability analysis was also carried out to both HADS scales. For anxiety scale, Cronbach-alpha values were 0.76 for the total sample, 0.77 for males, and 0.75 for females. For depression scale, Cronbach-alpha values were the followings: 0.68 for the total sample, 0.68 for males, and 0.69 for females. In the present sample, the mean score was 6.60 ± 3.52 for anxiety, and 3.11 ± 2.61 for depression. Anxiety and depression scales showed significant positive correlation with each other ($r=0.51$, $p < 0.001$).

Age and sex as possible confounds

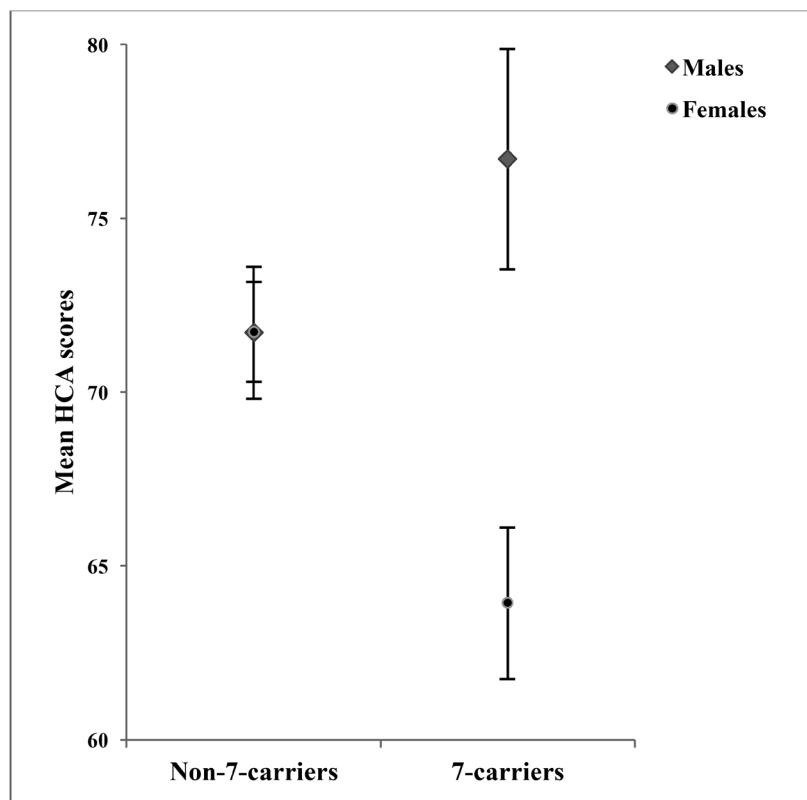
As a next step, we examined age and sex as possible confounds. There were no significant correlations between age and HCA or PDCA scores. However, males and females tendentially differed in their HCA scores ($F(1,212)=2.875$, $p=0.091$, $ES=0.013$, power=0.393), males showed higher mean HCA scores than females, see Table 1. Males also scored significantly higher on the PDCA scale ($F(1,397)=11.938$, $p=0.001$, $ES=0.029$, power=0.931). Thus, we used sex as a covariate in further analyses.

160 males and 235 females had HADS anxiety and depression data. There was no significant difference in HADS anxiety scores between males ($M=6.39 \pm 3.56$) and females ($M=6.73 \pm 3.49$), and the difference in HADS depression scores only reached the level of tendency ($F(1,393)=2.774$, $p=0.097$, $ES=0.007$, power=0.383) between males ($M=3.38 \pm 2.70$) and females ($M=2.94 \pm 2.54$).

There was no difference between males and females in the distribution of 7-repeat allele ($\chi^2=0.595$, $p=0.44$)

Single marker association analysis between the phenotypic measures (HCA, PDCA) and the DRD4 repeat polymorphism

We analyzed the effects on DRD4 repeat polymorphism on HCA and PDCA scores using one way analyses of variance with sex as a covariant. The results of the ANCOVA showed no significant differences between non-carriers and 7-carriers in HCA scores. The covariant effect of sex reached the level of tendency ($F(1,211)=2.979$, $p=0.086$, $ES=0.014$, power=0.405). On the other hand, we observed a tendency between the 7-repeat allele and the mean PDCA

Figure 1. Effect of DRD4 7-repeat allele on male and female HCA scores

Mean HCA scores in 7-repeat allele carrier and non-carrier males and females. Error bars represent \pm standard errors of the mean.
HCA: Hypercompetitive Attitudes

scores ($F(1,396)=2.788$, $p=0.096$, $ES=0.007$, power=0.384); non-carriers showed a higher mean score ($M=51.78\pm11.52$) than 7-carriers ($M=49.89\pm12.04$). We also observed a significant association between the covariant sex and PDCA ($F(1, 396)=12.424$, $p<0.001$, $ES=0.030$, power=0.940).

Interaction analysis of sex and DRD4 repeat polymorphism on HCA and PDCA

Since sex showed significant associations with competitiveness, we analyzed the possible genotype x sex interaction effect on HCA and PDCA scores with two-way ANOVAs (see Figure 1). With regards to the HCA scores, we found a significant sex main effect ($F(1,210)=7.742$, $p=0.006$, $ES=0.036$, power=0.791). Men scored higher ($M=73.16\pm13.64$) than women ($M=69.58\pm14.50$). The main effect of the 7-repeat allele was not significant, however, a significant interaction effect of genotypes and sex emerged ($F(1,210)=7.791$, $p=0.006$, $ES=0.036$, power=0.793). 7-carrier males

showed the highest mean score ($M=76.70\pm14.16$) while 7-carrier females the lowest ($M=63.93\pm13.84$). On the other hand, non-carrier males and females showed very similar mean scores ($M=71.71\pm13.29$ and $M=71.73\pm14.64$, respectively).

On PDCA scores, the main effect of sex was significant ($F(1,395)=11.159$, $p=0.001$, $ES=0.027$, power=0.915). Men scored higher ($M=53.60 \pm 10.27$) than women ($M=49.52\pm12.35$), but neither the main effect of genotypes nor the interaction effect of sex and genotypes were significant.

Bonferroni correction for multiple testing was also carried out (Bonferroni, 1936; Miller, 1981). The nominal p value (0.05) was divided by the number of analyses (4) for the main hypothesis, resulting a corrected level of significance of 0.0125. The nominally significant ($p=0.006$) finding regarding association of the Hypercompetitive Attitude Scale with the DRD4 repeat polymorphism remained significant after Bonferroni correction for multiple testing. Other nominally significant results did not survive correction for multiple testing.

Table 2. Relationship between competitiveness and mood separately by sex and 7-repeat allele

		Females		Males	
		7-carriers	Non-carriers	7-carriers	Non-carriers
HCA	HADS Anxiety	r=0.45 p=0.002 (N=40)	r=0.27 p=0.005 (N=105)	n.s.	n.s.
	HADS Depression	r=0.53 p=0.0004 (N=40)	r=0.17 p=0.09 (N=105)	n.s.	n.s.
PDCA	HADS Anxiety	n.s.	r=-0.27 p=0.001 (N=161)	r=-0.30 p=0.024 (N=56)	n.s.
	HADS Depression	n.s.	r=-0.29 p<0.001 (N=161)	r=-0.41 p=0.002 (N=56)	n.s.

HCA: Hypercompetitive Attitudes; PDCA: Personal Development Competitive Attitudes; HADS: Hospital Anxiety and Depression Scale; n.s.: non-significant

Relationship between competitive attitudes and depression or anxiety – post hoc analyses

Hypercompetitiveness and mood

We hypothesized that hypercompetitiveness in females show association with anxiety and depression based on the available literature (Kayhan, 2003; Hibbard & Buhrmester, 2010). Thus, we performed correlation analyses to see if there is relationship between hypercompetitive attitudes and anxiety and depression in females and males separately. For results, see Table 2. We found significant positive relationship between HCA hypercompetitiveness and HADS anxiety scores in females ($r=0.34$, $p=0.00002$, $N=145$), but not in males where the correlation was close to zero ($r=-0.01$, $p=0.97$, $N=69$). HADS depression scores also correlated with HCA scores in females ($r=0.28$, $p=0.001$, $N=145$), but not in males ($r=0.001$, $p=0.94$, $N=69$).

Next, we explored whether the correlation of HCA and mood variables was stronger in 7-repeat carriers as compared to non-carriers in females. Interestingly, significant positive association of HCA and anxiety was far more robust in 7-repeat carrier females ($r=0.45$, $p=0.002$, $N=40$) as compared to non-carrier females ($r=0.27$, $p=0.005$, $N=105$). The difference of these correlation values for carriers and non-carriers was significant using the Fisher r-to-z transformation ($Z=3.97$, $p=0.0001$).

Relationship of hypercompetitiveness and depression in females was also stronger in 7-carriers ($r=0.53$, $p=0.0004$, $N=40$) as compared to non-carriers ($r=0.17$,

$p=0.09$, $N=105$), and the difference between correlation coefficients was significant ($Z=2.18$, $p=0.0146$). In non-carrier or 7-carrier males, the relationship between hypercompetitiveness and anxiety or depression was not significant.

Personal Development Competitive Attitudes and mood

We also explored if there is association between PDCA self-development competitiveness and HADS anxiety and depression scores, see Table 2. Personal development competitive attitude is a more positive way of competing (Ryckman et al., 1992) than hypercompetitiveness. In our sample males' PDCA scores negatively correlated with anxiety ($r=-0.20$, $p=0.011$, $N=160$), and with depression ($r=-0.28$, $p<0.001$, $N=160$). Females also showed significant negative correlation between PDCA score and anxiety ($r=-0.17$, $p=0.01$, $N=235$), and PDCA score and depression ($r=-0.21$, $p=0.001$, $N=235$).

In the next step, based on the results above, we carried out correlation analyses in both males and females, regarding to the presence/absence of the 7-repeat allele. As results showed, in males there was no significant correlation among non-carrier males between PDCA score and anxiety ($r=-0.11$, $p=0.265$, $N=104$), and between PDCA and depression ($r=-0.16$, $p=0.111$, $N=104$). In 7-carriers, significant negative association was observed between PDCA score and anxiety ($r=-0.30$, $p=0.024$, $N=56$), and PDCA and depression ($r=-0.41$, $p=0.002$, $N=56$). In females, results were the opposite: in non-carriers, there was

a significant negative association between PDCA scores and anxiety ($r=-0.27$, $p=0.001$, $N=161$), and PDCA and depression scores ($r=-0.29$, $p<0.001$, $N=161$), while in 7-carriers we found no significant relationship between PDCA and anxiety ($r=0.002$, $p=0.986$, $N=74$) or PDCA and depression scores ($r=-0.04$, $p=0.737$, $N=74$).

DISCUSSION

Our most important results highlight the importance of societal factors in interpreting gene x sex interaction effects in psychogenetic findings. Recent research suggests that phenotypes, such as educational achievement and financial decision making are partly inherited (e.g. Barnea et al., 2010; Cesarini et al., 2010; Krapohl et al., 2014). On the other hand, heritability of competitive attitudes have not yet been established. Moreover, there are no studies to date investigating association of DRD4 gene polymorphisms and competitiveness. Some studies found association between the 7-repeat allele and different types of risk-taking behavior (e.g. Dreber et al., 2009; Garcia et al., 2010), but the others have not (e.g. Dreber et al., 2011; Sapra et al., 2012). Earlier results about the relationship between the 7-repeat allele and other risk-related personality phenotypes are inconsistent (e.g. novelty seeking: Ebstein, 2006; Munafò et al., 2008, addictions: McGahey, 2009).

DRD4 repeat polymorphism, as a possible modulator of adaptive behavior

When testing the difference of hypercompetitive attitudes in those with different DRD4 alleles, we found no significant differences using the full sample, however sex was a significant covariant. We assumed that sex could be an important factor in shaping the DRD4 effect on competitiveness, similarly to the results of Grady et al. (2013) who found association between the 7-repeat allele and longevity only in females. Our group also reported similar female-specific longevity effect of the DRD4 7-repeat allele (Szekely et al., 2016). Our findings presented here show a significant interaction of genotype and sex on hypercompetitiveness ($p=0.006$): 7-repeat carrier males showed higher hypercompetitiveness as compared to non-carriers, while 7-repeat carrier females showed less hypercompetitiveness than non-carrier females or males.

Our results also support earlier results about the DRD4 gene - environment interaction effect in mice behavior (Grady et al., 2013). The beneficial effect of

social and environmental stimuli on lifespan was present only in wild type mice but not in DRD4 knockout mice. Consistent with their findings, in our study the sex differences in hypercompetitiveness (which is most probably a gender role effect) was more robust in 7-carriers but was missing in non-carriers. These results suggest that DRD4 7-repeat allele could have an important modulating role in shaping behavioral responses to environmental cues. These results support findings of Ding et al. (2002), who explained the widespread dissemination of the 7-repeat allele by positive selection mechanisms.

Exact molecular-functional differences as a consequence of the DRD4 repeat polymorphism are not fully understood to date. It is important to note that the studied DRD4 repeat polymorphism is in the exonic area, therefore the coded receptor proteins have also variable length. According to Asghari et al. (2002) the length of the intracellular loop of the receptor might have an importance as a connecting area of various proteins playing a role in signal transduction.. There is no linear connection, however, between number of repeats and signaling effectiveness. We fully agree with the notion of a recent review (Pappa et al., 2015) that results to date are very inconsistent and functionality of the DRD4 repeat polymorphism needs to be explored further.

Sex differences in competitiveness

Previous studies (Kayhan, 2003; Hibbard & Buhrmester, 2010) found that in females strongly competitive attitudes show relationship with higher levels of depression. Our findings also highlight a positive correlation in females between hypercompetitiveness and mood variables such as anxiety ($r=0.34$) and depression ($r=0.28$). These results suggest that hypercompetitive females (who are not in line with the traditional gender role expectations of the society that rewards a less competitive attitude for female) display poorer psychological well-being. Van de Vliert and Janssen (2002) found that competitive societies are happier if women are less competitive than men. It was also found that a society is the most unhappy if both men and women are highly and equally competitive. The deviation from the stereotype that women are less competitive (Williams & Best, 1990; Fülöp & Berkics, 2015) costs subjective well-being. In males, however, we did not observe a positive relationship between hypercompetitiveness and mood variables. Societies reward dominance strivings more in case of men than women (Cashdan, 1998) and females find

competitive men more attractive (Riskind & Wilson, 1982).

Interaction between DRD4 repeat polymorphism, competitiveness and mood characteristics

We also showed that the DRD4 repeat variants may serve as an important moderator of the relationship between hypercompetitiveness and mood variables. Among 7-repeat carrier females the correlation between hypercompetitiveness and mood variables was more pronounced (in anxiety $r=0.45$, in depression $r=0.53$) as compared to non-carrier females (in anxiety $r=-0.27$, in depression $r=0.17$). These findings highlight a genetic effect on how men and women adapt to culturally distinct expectations of society. Jiang et al. (2015) also confirmed the modulating role of DRD4 gene on altruistic behavior: they found that in the 4/4 homozygous group Christian males were more altruistic as compared to non-Christian males.

Results related to self-development competitive attitudes were different: we found no significant interaction of genotype and sex on this type of competitiveness. When seeking relationship with this type of competitiveness and mood variables we observed negative correlation between personal development attitudes and mood variables, contrary to our earlier results between hypercompetitiveness and mood. Although consistently with our present results, PDCA and HCA do not correlate according to previous literature (Ryckman et al., 1996), studies examining relations of these two competition types with personality (e.g. Thornton et al., 2011) suggest that they function quite differently. As previous studies showed association between mood variables and other candidate genes, e.g. glial cell line-derived neurotrophic factor – GDNF (Kotyuk et al., 2013b), it worth to examine its relations with competitiveness and mood.

Evaluation of the present results

Strength of the study presented here is that here we examined first time the dopaminergic relations of competitiveness. Our results show the modulating role of the DRD4 7-repeat allele on sex differences in competitiveness. Limitation of the present study is the relatively low number of subjects ($N=399$), mainly from the same (young) age group.

We believe that large cross-cultural studies are needed including various age-groups and both sexes to reinforce the presented result and explore further genetic effects and gene x environment interactions.

CONCLUSIONS

The gene-sex interaction in Hypercompetitive Attitude presented here suggests beneficial effect of the DRD4 7-repeat allele in adaptation. We report that males carrying the DRD4 7-repeat allele were more hypercompetitive as compared to non-carriers. Females, however show an opposite direction: 7-carrier females were less hypercompetitive as compared to non-carriers. We assume that this gene-sex interaction is the result of social influences: gender socialization dictates females to be less competitive than males (Hughes, 1988). We also found relationship between hypercompetitiveness and mood variables, specific for females only. Moreover, this relationship was more pronounced in 7-carrier females, as compared to non-carrier females. Thus, social influences are crucial to explore in interpreting gene x sex interaction effects. We conclude that the 7-repeat allele plays an important role in adaptivity through sex-specific behavior to social expectations. These findings fit well with prior findings suggesting that the 7-repeat allele is indeed a “success” allele (Chang, 1996; Ding et al., 2002; Gören, 2016). It may also function as a longevity enabling gene (Perls & Terry 2003) by modulating phenotypes which may play role in longer lifetime. Future directions may be to reveal possible mediators in the association of the DRD4 7-repeat allele and longevity.

LIST OF ABBREVIATIONS

MDRD4 VNTR:	Dopamine Receptor D4 gene, variable number tandem repeat polymorphism
COMT:	Catechol-o-methyltransferase
GDNF:	Glial cell-derived neurotrophic factor
HCA:	Hypercompetitive Attitudes
PDCA:	Personal Development Competitive Attitudes
HADS:	Hospital Anxiety and Depression Scale
ANOVA:	Analysis of Variance
ANCOVA:	Analysis of Covariance

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A gén és a nem interakciója hiperversengésben: a DRD4 7-es allél adaptív szerepe

Ikertanulmányok eredményei szerint az olyan társas attitűdök, mint például a versengés, tartalmaznak öröklődő komponenseket. Ennek ellenére nem ismert a szakirodalomban olyan munka, amely a versengő magatartást genetikai polimorfizmusokkal kapcsolná össze. A versengéshez kapcsolható fenotípusokra fókuszáló genetikai asszociációs vizsgálatok olyan eredményekről számolnak be, mint pl. a kockázatvállalás és a DRD4 7-es alléljának kapcsolata. Ezt a polimorfizmust korábban széleskörűen tanulmányozták az újdonságkeresés és egyes pszichiátriai rendellenességekkel kapcsolatban. Felmerült az is, hogy ez a genetikai variáns szerepet játszik a környezetre adott viselkedéses válaszok irányításában, feltehetően a jutalmazó mechanizmusokon keresztül. A jelen tanulmányban a DRD4 7-es allél és a versengés kapcsolatát 399 egymással rokonságban nem álló, kaukázusi résztvevő önbeszámolója alapján vizsgáltuk. Eredményeink szerint érdekes gén-nem interakció mutatható ki: a 7-es allélt hordozó férfiak hiperversengőbbnek mutatkoztak mint a nem-hordozók, míg a 7-es allélt hordozó nők kevésbé voltak hiperversengők a nem-hordozókhöz képest. Ez az eredmény a többszörös összehasonlításra történő Bonferroni korrekció után is szignifikáns maradt. Csak a nők esetében volt szignifikáns pozitív együttjárás a hiperversengés és a hangulati változók (szorongás és depresszió) között, és ez az összefüggés a 7-es allélt hordozók esetében sokkal kifejezettebb volt. Férfiak esetében nem kaptunk hasonló eredményeket. Mindez arra utal, hogy a társadalmi és kulturális tényezők is fontosak lehetnek egyes, nemekre jellemző viselkedést kialakító génhatásokban. Gén-környezet interakciót feltáró pszichogenetikai asszociáció eredményeink alapján a 7-es allél fontos szerepet játszhat abban, hogy a férfiak és nők versengési stílusa a társadalmi elvárásoknak megfeleljen.

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Kulcsszavak: DRD4 polimorfizmus, 7-es allél, versengő attitűdök, hiperversengés, önfeljlesztő versengés, gén-nem interakció, adaptivitás