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12-16-2019

## Genetic Variations in the Dopamine Reward System Influence Exercise Reinforcement and Tolerance for Exercise Intensity

Kyle D. Flack

*University of Kentucky, [kyle.flack@uky.edu](mailto:kyle.flack@uky.edu)*

Christopher Pankey

*USDA, Agricultural Research Service*

Kelsey Elise Ufholz

*USDA Agricultural Research Service*

LuAnn Johnson

*USDA, Agricultural Research Service*

James N. Roemmich

*USDA Agricultural Research Service*

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### Repository Citation

Flack, Kyle D.; Pankey, Christopher; Ufholz, Kelsey Elise; Johnson, LuAnn; and Roemmich, James N., "Genetic Variations in the Dopamine Reward System Influence Exercise Reinforcement and Tolerance for Exercise Intensity" (2019). *Dietetics and Human Nutrition Faculty Publications*. 28.

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## Genetic Variations in the Dopamine Reward System Influence Exercise Reinforcement and Tolerance for Exercise Intensity

Digital Object Identifier (DOI)

<https://doi.org/10.1016/j.bbr.2019.112148>

### Notes/Citation Information

Published in *Behavioural Brain Research*, v. 375, 112148.

© 2020 Published by Elsevier B.V.

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The document available for download is the authors' post-peer-review final draft of the article.

## Highlights:

- Exercise reinforcement, similar to other reinforcing behaviors, can be predicted by genetic variations in the central dopamine reward system.
- Having at least one copy of the G allele for the DRD2/ANKK1 polymorphism (rs1800497) predicts greater exercise reinforcement
- Tolerance for exercise intensity, which is related to exercise reinforcement, is influenced by SNP's related to pain neurotransmission.
- Greater moderate-to-vigorous physical activity was observed among those homozygous for the T allele for the CNR1 polymorphism at rs6454672.

## Abstract

**Background:** Exercise is a reinforcing behavior and finding exercise highly reinforcing is characteristic of habitual exercisers. Genotypes related to dopamine metabolism moderate the reinforcing value of behaviors, but genetic moderators of exercise reinforcement have not been established. **Purpose:** Determine whether singular nucleotide polymorphisms (SNPs) that moderate central reward pathways and pain neurotransmission are associated with exercise reinforcement, tolerance for exercise intensity, and usual physical activity. **Methods:** Adults (n=178) were measured for the reinforcing value of exercise relative to sedentary activities ( $RRV_{\text{exercise}}$ ), minutes of moderate-to-vigorous physical activity (MVPA) and completed the Preference for and Tolerance of the Intensity of Exercise Questionnaire. Genotyping of 23 SNPs known to influence central dopamine tone, pain, or physical activity was performed. ANOVA tested differences in  $RRV_{\text{exercise}}$ , tolerance, and MVPA among genotype groups. Linear regression controlling for BMI, sex, and liking of exercise was used to further predict the association of genotype on  $RRV_{\text{exercise}}$ , tolerance, and MVPA. **Results:** Having at least one copy of the G allele for the DRD2/ANKK1 polymorphism (rs1800497) conferred greater  $RRV_{\text{exercise}}$ . Greater tolerance for exercise intensity was observed among those homozygous for the T allele for the CNR1 polymorphism (rs6454672), had at least one copy of the G allele for the GABRG3 polymorphism (rs8036270), or had at least one copy of the T allele for the LPR polymorphism (rs12405556). Homozygous individuals for the T allele at rs6454672 exhibited greater MVPA. **Conclusion:** Similar to other reinforcing behaviors, there is a genetic contribution to exercise reinforcement, tolerance for exercise intensity, and MVPA.

**Key words:** Dopamine, Exercise, SNPs, Physical Activity, Tolerance for Exercise Intensity

1 Genetic Variations in the Dopamine Reward System Influence Exercise Reinforcement and  
2 Tolerance for Exercise Intensity

3 Kyle Flack, PhD, RD.<sup>1,2\*</sup> Christopher Pankey, PhD<sup>2,3</sup>, Kelsey Ufholz, PhD<sup>2</sup>; LuAnn Johnson<sup>2</sup>  
4 James N. Roemmich, PhD<sup>2</sup>

5 <sup>1</sup>Department of Dietetics and Human Nutrition, University of Kentucky, Lexington, KY.

6 <sup>2</sup>USDA, Agricultural Research Service, Grand Forks Human Nutrition Research Center, 2420 2<sup>nd</sup>  
7 Ave N., Grand Forks, ND

8 <sup>3</sup>Department of Biomedical Sciences, West Virginia School of Osteopathic Medicine,  
9 Lewisburg, WV

10

11 \*Corresponding author:

12 Kyle Flack, PhD, RD.

13 University of Kentucky

14 206E Funkhouser Building

15 Lexington, KY 40506-0054

16 Phone: 859-257-4351

17 Fax: 859-257-3707

18 email: [Kyle.Flack@uky.edu](mailto:Kyle.Flack@uky.edu)

19        **1. Introduction**

20        Physical activity (PA) and the exercise subcomponent of PA are well-established as effective  
21 strategies to improve the health of nearly every organ system in the body, increase energy  
22 expenditure, and promote maintenance of a healthy body weight (1). Despite the long-term public  
23 health emphasis by the US government regarding the importance of PA for the health of  
24 Americans, more than 90% of US adults fail to meet PA recommendations when objectively  
25 assessed by accelerometry, and just 1 in 4 Americans report engaging in any leisure time physical  
26 activity (2, 3). Producing sustained increases in exercise and PA is an intractable problem;  
27 interventions designed to increase long-term PA have not yet demonstrated adherence in efficacy  
28 trials, let alone effectiveness trials (4).

29        Understanding individual-level factors associated with exercise participation may help to  
30 solve the problem of low adherence to the physical activity guidelines. One such factor is the  
31 reinforcing value of exercise relative to a competing alternative behavior (relative reinforcing  
32 value of exercise,  $RRV_{\text{exercise}}$ ). The alternative behavior is often a desired sedentary activity such  
33 as screen time or reading that is often chosen in favor of physical activity/exercise. Exercise  
34 reinforcement is a measure of how much an individual is willing to work to gain access to (i.e.,  
35 consume) exercise. Individuals who find a behavior highly reinforcing will perform more work  
36 to obtain access relative to a less reinforcing behavior (5). Indeed, the  $RRV_{\text{exercise}}$  is associated  
37 with engaging in physical activity at a frequency, duration, and intensity sufficient to meet  
38 physical activity guidelines (6), the choice to be physically active among children (7), and  
39 predictive of habitual vigorous PA among adults (8).

40           The dopamine hypothesis of reward explains that behavioral reinforcement and the  
41 appetitive drive to consume a reward are predominately a function of the meso-accumbal  
42 dopamine system (9, 10). At the core of this system, specific genotypes explain some of the  
43 individual variability in the reinforcing nature of, and participation in behaviors such as drug  
44 abuse, alcohol consumption, nicotine use, gambling, and eating (5, 11-13). For example, SNP's  
45 influencing protein expression for the DRD2 or DRD3 dopamine receptors are associated with  
46 opioid addiction, alcoholism, cocaine abuse, and smoking (14-16). Also, SNPs affecting central  
47 dopamine tone such as the dopamine transporter gene (SLC6A3), DRD2 receptor, monoamine  
48 oxidase A (MAOA-LPR), and serotonin receptor genes are associated with food reinforcement  
49 and energy intake (17), while SNPs of the fat mass and obesity associated (FTO) gene moderate  
50 the relationship between food reinforcement and energy intake (18).

51           Exercise can be realized as a reinforcing behavior as exercise dependency has been  
52 demonstrated in both humans (19, 20) and rodents (21-23). The wide individual differences in  
53 successful adherence to regular PA and exercise (2) suggest that genetic variability in central  
54 mechanisms of reinforcement may be associated with individual differences in  $RRV_{\text{exercise}}$ ,  
55 although this has not yet been studied. Identifying such variations in the central dopaminergic  
56 reward system would provide initial evidence that some SNPs may moderate exercise  
57 reinforcement, thus influencing individual differences in physical activity behaviors (9, 24) and  
58 adherence to physical activity guidelines (6). Prior work suggests that SNPs involved in control  
59 of the central dopaminergic reward system may associate with PA behavior (25, 26). SNPs  
60 associated with pain neurotransmission could additionally impact exercise reinforcement (27, 28)  
61 because exercise reinforcement is positively associated with the ability to tolerate the discomfort  
62 of increasing exercise intensity (6). Thus, the current study was performed to test the hypothesis

63 that SNPs associated with central dopamine physiology that moderate the reinforcing value of  
64 other behaviors (17, 29, 30), activity of central nervous system reward pathways (9, 14, 16, 31,  
65 32), or those associated with pain neurotransmission (27, 28) would be associated with exercise  
66 reinforcement, tolerance for exercise intensity discomfort, and usual (habitual) physical activity.

67

## 68 2. Materials and Methods

### 69 2.1 Participants and Study Design

70 The study sample was a combined data set from two studies on exercise reinforcement.  
71 One study was a cross-sectional study to determine predictors and correlates of exercise  
72 reinforcement (clinical trials.gov identifier: NCT02416882) while the other was a longitudinal  
73 study on changes in exercise reinforcement (clinical trials.gov identifier: NCT02444247). The  
74 baseline assessment of exercise reinforcement from the longitudinal study was used for the  
75 present analysis. A total of 178 participants (127 female) age 18 to 49 years were included.  
76 Baseline participant characteristics are presented in Table 1. Participants were a sample who  
77 responded to recruitment media including printed brochures, fliers, and online advertisements  
78 placed on the Grand Forks Human Nutrition Research Center website. Entry criteria were very  
79 similar for both studies. All participants were non-smokers and healthy enough to participate in  
80 an exercise program assessed by a physical activity readiness questionnaire, not taking any drugs  
81 that affect energy expenditure (e.g., thyroid, glucose-lowering drugs), could not have gained or  
82 lost more than 5% of body weight over the past 6 months or 10 pounds over the past 3 months,  
83 could not use tobacco, and could not be pregnant or lactating or plan to become pregnant in the  
84 next 6 months. Both studies were approved by the University of North Dakota Institutional



85 Review Board and registered with ClinicalTrials.gov, numbers NCT02444247 and  
86 NCT02416882.

87 For both studies, after having the study explained and providing written informed  
88 consent, participants provided a blood sample for genetic assessment and were given an  
89 ActiGraph accelerometer (Pensacola, FL) to measure usual PA. Participants wore the  
90 accelerometer for seven days before performing additional assessments. During subsequent  
91 visits, participants completed assessments of anthropometrics (height and weight), exercise  
92 reinforcement, and tolerance for discomfort during intense exercise.

93

## 94 *2.2 Assessments*

95 *2.2.1 Height and weight:* Height was measured in triplicate to the nearest 0.1 cm using a  
96 stadiometer (Seca; Chino, CA). Body weight was measured using a calibrated digital scale  
97 (Fairbanks Scales- Model SCB-R9000-HS; MO) to the nearest 0.1 kg. Measures were completed  
98 with participants wearing either provided lab scrubs or light casual clothes (t-shirt, shorts) and  
99 not wearing shoes.

100

101 *2.2.2 Physical activity:* Habitual, free-living PA was measured using an ActiGraph  
102 accelerometer (GT3X+ model; Pensacola, Florida). Each participant wore the device for seven  
103 days prior to performing other assessments. Participants were instructed to wear the monitor at  
104 the right hip using the provided belt during all hours awake except when bathing or swimming.  
105 Data were cleaned of non-wear time, defined as consecutive strings of zeros greater than 20  
106 minutes. An epoch of 10 seconds was used for data collection as a shorter epoch is more suitable

107 to reflect bout duration under free-living conditions where many bouts of sporadic PA last 30  
108 seconds or less (33, 34). These data were used to determine participants' usual PA, defined as  
109 weekly minutes of MVPA using the Crouter et al. algorithm (35) and Freedson cut-points (36).

110

111 *2.2.3 Liking:* Participants' liking (hedonic value) of the exercise options (treadmill, elliptical,  
112 stationary bike) and sedentary alternatives (TV, video games, reading magazines,  
113 puzzles/Sudoku) was assessed using a 10-point scale (1 = "do not like at all" and 10 = "like very  
114 much"). The most liked sedentary activity and exercise option was used as the sedentary and  
115 exercise alternative for the  $RRV_{exercise}$  testing session, respectively.

116

117 *2.2.4  $RRV_{exercise}$ :* Participants'  $RRV_{exercise}$  (specifically, aerobic-type exercise) was assessed  
118 against a sedentary alternative chosen based upon hedonic liking scores (see "Liking" above).  
119  $RRV_{exercise}$  was assessed by evaluating the amount of operant responding (mouse button presses)  
120 a participant was willing to complete to gain access to exercise or a sedentary alternative (11,  
121 37). The testing space included two adjacent computer workstations. The participant could earn  
122 points towards their most liked exercise activity at one station, while the other station was an  
123 identical setup that could be used to earn points toward their most liked sedentary alternative.  
124 Participants could switch between stations as much as they chose. The program presented a game  
125 similar to a slot machine with a row of three shapes of various colors; a point was earned each  
126 time the shapes and colors matched. For every 5 points a schedule was completed and the  
127 participant received 5 min of access to the reinforcer that was earned (either exercise or  
128 sedentary activity). The game was performed until the participant no longer wished to work for  
129 access to either the exercise or sedentary activities, with no minimum or maximum time limit. At

130 first, points were delivered after every 4 presses (schedule of reinforcement was 4), but then the  
131 schedule of reinforcement doubled (4, 8, 16, 32, [...] 1024) each time 5 points were earned. For  
132 instance, the participant initially had to click the mouse button 4 times to earn one point for  
133 schedule 1. After the first 5 points were earned, schedule 1 was complete and the participant had  
134 earned 5 minutes for the corresponding activity. Then, 8 clicks were required to earn each of the  
135 next 5 points for schedule 2 before another 5 minutes was earned. Schedule 3 required 16 clicks  
136 to earn one point, schedule 4 required 32 clicks to earn one point, and so on (11, 37). Participants  
137 engaged in the activity for the time earned after they complete the reinforcement task, which  
138 ended when participants no longer wished to earn points (time) for exercise or the sedentary  
139 alternative. Similar button pressing tasks have been used as valid predictors of the RRV of  
140 physical versus sedentary activity (7). Participants self-selected the intensity level when  
141 performing any earned exercise time, which was typically a low to moderate steady-state  
142 intensity. These assessments took place in private laboratory space within a large exercise  
143 facility. Participants completed their earned exercise time using the exercise facilities'  
144 equipment. The last schedule completed for exercise and the sedentary alternative were assessed  
145 separately and termed Pmax of sedentary ( $P_{\max_{\text{sed}}}$ ) and Pmax of exercise ( $P_{\max_{\text{exercise}}}$ ).  
146  $RRV_{\text{exercise}}$  was calculated as  $(P_{\max_{\text{exercise}}}/(P_{\max_{\text{exercise}}} + P_{\max_{\text{sed}}}))$  (18, 37).

147  
148 *2.2.5 Preference and tolerance for exercise intensity:* Participants completed the Preference for  
149 and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q) (38). The tolerance  
150 subscale measured ability to tolerate the discomfort associated with intense exercise and was  
151 included in the current analysis as only tolerance scores have been linked to  $RRV_{\text{exercise}}$  (6).

152

153 2.2.6 *Genetic assessment*: Table 2 details the SNPs assessed. SNP genotyping was performed on  
154 3-5 ml samples of whole blood collected in EDTA-containing tubes that were immediately  
155 processed for DNA extraction and frozen for future batch analysis. Platinum® qPCR SuperMix  
156 for SNP Genotyping (Applied Biosystems' TaqMan®-based SNP genotyping products, Life  
157 Technologies) specifically formulated for discrimination of alleles by real-time qPCR followed  
158 by allelic-discrimination analysis was used for the amplification and identification of each SNP.  
159 Predesigned SNP genotyping assays for individual SNPs that included two allele-specific  
160 TaqMan® MGB probes containing distinct fluorescent dyes and a PCR primer pair to detect  
161 specific SNP targets were used. These probe and primer assays align with the genome to provide  
162 specificity for the allele of interest.

163

164 2.3 *Analytic Plan*: Sex differences in demographics,  $RRV_{\text{exercise}}$ , MVPA, liking, and tolerance  
165 for exercise discomfort were determined by unpaired T-tests. One-way analysis of variance  
166 (ANOVA) tested whether participants homozygous for minor alleles differed for  $RRV_{\text{exercise}}$ ,  
167 tolerance of exercise intensity, MVPA, and liking of exercise and sedentary activities from  
168 participants carrying one or two major alleles.  $RRV_{\text{exercise}}$  was modeled using the beta  
169 distribution due to it being a ratio score. When used as a dependent variable, MVPA was  
170 transformed by natural logarithmic transformation due to the highly skewed distribution, and  
171 back-transformed to report means and standard errors in models predicting MVPA. All other  
172 dependent variables were modeled using the normal distribution. For SNPs that showed  
173 significant differences by ANOVA, after correcting for the false discovery rate, multiple  
174 regressions were performed to test whether SNP genotype was predictive of  $RRV_{\text{exercise}}$ ,  
175 tolerance for exercise intensity, or MVPA after controlling for possible covariates. The

176 RRV<sub>exercise</sub> model included BMI, MVPA, tolerance for exercise intensity, liking of aerobic  
177 exercise, and sex as covariates. Tolerance of exercise intensity models included BMI, MVPA,  
178 RRV<sub>exercise</sub>, liking of exercise, and sex. The MVPA model included BMI, RRV<sub>exercise</sub>, liking of  
179 aerobic exercise, tolerance for exercise intensity, sex, and the interaction of tolerance and  
180 genotype.

181

### 182 3. Results

183 Men had greater ( $p < 0.05$ ) BMI, MVPA, and tolerance for exercise intensity than women.  
184 No sex differences were found for age or RRV<sub>exercise</sub>, (Table 1). Genotype prevalence was  
185 consistent with NIH databases (<https://www.ncbi.nlm.nih.gov/snp/>) as shown in Table 3.

186 Participants that were homozygous (A:A) for rs1800497 had a lower RRV<sub>exercise</sub> than  
187 participants carrying one or two G alleles when tested by ANOVA ( $p < 0.01$ ) and by regression  
188 ( $p < 0.01$ ) that modeled potential covariate effects on RRV<sub>exercise</sub> (Table 4). From ANOVA,  
189 tolerance for exercise intensity was greater ( $p < 0.05$ ) for participants that were homozygous for  
190 rs6454672 (T:T), and lower for homozygous rs8036270 (A:A) and rs12405556 (G:G) ( $p < 0.01$ ,  
191  $p < 0.05$ , respectfully). Results from the regression models demonstrated that SNP's rs6454672,  
192 rs8036270, and rs12405556 were significant ( $p < 0.03$ ) predictors of tolerance for exercise  
193 intensity. MVPA and RRV<sub>exercise</sub> were also significant ( $p < 0.01$ ) predictors of tolerance for  
194 exercise intensity in each model (Table 5). SNP rs6454672 was a significant predictor ( $p < 0.001$ )  
195 of MVPA, as homozygous carriers of the T allele exhibited lower ( $p < 0.01$ ) MVPA (Table 6.).  
196 The interaction of tolerance and genotype was tested to further examine the synergy between  
197 genotype and the ability to tolerate exercise intensity but was not significant ( $p = 0.41$ ). There  
198 were no SNP genotypes that influenced in liking of the exercise or sedentary alternatives.

199

#### 200 4. Discussion

201 This is the first investigation of the association of SNPs that moderate central dopamine  
202 physiology and pain neurotransmission with exercise reinforcement, tolerance for exercise  
203 intensity, and usual physical activity. The results support the hypothesis that a genetic  
204 contribution to  $RRV_{\text{exercise}}$  exists. Specifically, individuals carrying the polymorphism of a G  
205 allele at rs1800497 had greater  $RRV_{\text{exercise}}$ . The rs1800497 polymorphism, also known as Taq1A,  
206 affects the ankyrin repeat and kinase domain containing 1 gene (ANKK1), and is a G > A  
207 polymorphism, causing a Glutamine > Lysine missense variant. Although there is some debate  
208 (39), Taq1A is associated with decreased ligand binding at, or decreased expression of the  
209 dopamine D2 receptor (DRD2) (40-43), and is associated with other reinforcing behaviors (30)  
210 and greater risk of alcohol and drug abuse (44). Further, central dopamine signaling is necessary  
211 for development and maintenance of exercise behavior (24), supporting a role for Taq1A in  
212 exercise reinforcement. Indeed, genotype variants affecting dopamine signaling via DRD2 or  
213 ANKK1 expression are associated with differences in usual physical activity in both rodents and  
214 humans (45, 46).

215 In the current study, homozygous Taq1A carriers (A1/A1) had lower ( $p < 0.01$ )  $RRV_{\text{exercise}}$   
216 than heterozygous A1:A2 or homozygous A2/A2 carriers (Table 4.). Adults with the Taq1A  
217 allele experience a decreased response to reinforcing stimuli (30). Notably, dopamine signaling  
218 has been investigated for its role in motivation (47, 48), motor movement (49-51) and  
219 reinforcement (52). Moreover, the dopamine system is a key player in determining voluntary  
220 physical activity (see review (24)). Antagonists of DRD<sub>2</sub> receptors (53) or similar DRD<sub>2</sub>

221 polymorphisms (46) also reduce motor activity in humans. Together these data support a  
222 mechanism by which Taq1A inhibits central dopamine signaling, therefore attenuating  
223  $RRV_{\text{exercise}}$ .

224 This study is also the first to demonstrate a genotypic association with tolerance for  
225 exercise intensity. The SNP's rs6454672, rs8036270, and rs12405556 independently predicted  
226 tolerance for exercise intensity, which is defined as an individual's ability to tolerate the  
227 discomfort associated with intense exercise such as fatigue, pain, and sweatiness (38). This is in  
228 contrast to the need to increase dosage to maintain a response, as is common with pharmacologic  
229 agents. Greater tolerance for exercise intensity is associated with participating in enough exercise  
230 to meet physical activity guidelines (6) and with self-selected exercise intensity (54), suggesting  
231 that greater tolerance for exercise intensity may lead to more frequent engagement in intense  
232 physical activity.

233 Most of what is known regarding rs6454672 is in respect to cannabinoid signaling and  
234 schizophrenia, as rs6454672 is located near the cannabinoid receptor 1 gene and is noted for its  
235 contribution to genetic coding variability for the cannabinoid receptor type 1 (CB1) gene (55).  
236 Stimulation of CB1 receptors negatively regulates pain and inflammation through its inhibitory  
237 action as a Gai-coupled receptor, decreasing neurotransmission of pain (56). Carrying even a  
238 single minor (C) allele is associated with a decreased likelihood of meeting physical activity  
239 recommendations (57), which is supported by the current finding that homozygous T carriers  
240 have greater tolerance for exercise intensity, supporting previous work demonstrating individuals  
241 with greater tolerance for exercise intensity are more likely to meet PA recommendations (6).  
242 The relationship between tolerance for exercise intensity and increased likelihood of meeting PA  
243 recommendations is also supported by the current finding that participants homozygous (T:T) at

244 rs6454672 also exhibited greater MVPA. However, no other SNP's tested in this study were  
245 associated with MVPA.

246         The gamma-aminobutyric acid type A receptor gamma 3 subunit (GABRG3) encodes a  
247 gamma-aminobutyric acid (GABA) receptor and rs8036270 is an intron variant within this gene  
248 locus. GABA, as the primary inhibitory neurotransmitter in the human brain, can bind to  
249 ionotropic receptors (K<sup>+</sup> channels - hyperpolarizing) or metabotropic receptors (G $\alpha$ i) to inhibit  
250 neurotransmission of painful stimuli (58). Consistent with the present finding that carrying at  
251 least one G allele at rs8036270 predicts increased tolerance for exercise intensity, prior studies  
252 have determined that this SNP is also associated with leisure time exercise behavior and physical  
253 activity related energy expenditure (26, 59). Although further research is necessary for  
254 verification, these findings suggest that rs8036270 positively regulates inhibitory  
255 neurotransmission through GABA signaling, thus decreasing "pain" signaling pathways,  
256 increasing exercise intensity tolerance, and therefore, physical activity.

257         SNP rs12405556 is an intron variant that affects the leptin receptor and predicts physical  
258 activity (59, 60). In agreement with the current study, prior studies have also demonstrated that  
259 glutamine to arginine substitution in codon 223 of the leptin receptor predicts levels of physical  
260 activity and adiposity in humans (60). The current work revealed that having at least one copy of  
261 the minor (T) allele predicted greater tolerance for exercise intensity. Central leptin receptors,  
262 and therefore central leptin signaling, play key roles in feeding behavior [80], energy  
263 homeostasis (61), and physical activity behavior (60, 62). Therefore, these data suggest that  
264 carrying at least one copy of the minor allele for rs12405556 may be a genetic factor driving  
265 greater tolerance for exercise intensity, and physical activity.



266 **5. Conclusion**

267 In conclusion, we found that SNP rs1800497 predicted  $RRV_{\text{exercise}}$ . Additional SNP's  
268 rs6454672, rs8036270 and rs12405556 predicted greater tolerance for exercise intensity, while  
269 rs6454672 also predicted MVPA. Having greater  $RRV_{\text{exercise}}$  is an important factor in one's  
270 choice to be more physically active (6, 8, 63). Maintaining an exercise routine likely depends on  
271 an individual's ability to experience aversive aspects of exercise yet be able to tolerate those  
272 unpleasant aspects and persist engaging in exercise behavior. Therefore, having greater  
273  $RRV_{\text{exercise}}$  and tolerance for the discomfort associated with intense exercise may lead to more  
274 frequent and sustained exercise behavior. These results demonstrate that functional changes at  
275 the protein level provide pathways by which SNPs may be driving changes in physical activity-  
276 related behavior, and these SNPs may be underlying causes for differences in habitual physical  
277 activity between individuals. Further research to determine personalized exercise prescriptions  
278 based on genotype, along with strategies to increase exercise reinforcement among certain  
279 individuals is needed to potentially increase the number of Americans being physically active.

281 **Contributions**

282 Kyle D. Flack, PhD., RD: Lead author. Contributed to study design and development, led all  
283 aspects of recruitment, intervention management, and data collection. Composed an original  
284 manuscript draft.

285 Christopher Pankey: Second author. Revised all manuscript drafts and completed writing of the  
286 manuscript.

287 Kelsey Elise Ufholz, PhD.: Third author. Assisted in data collection and composition of  
288 manuscript.

289 LuAnn Johnson, MS: Fourth author. Statistician in charge of all statistical analysis.

290 James N. Roemmich, PhD.: Senior author. Led study idea development, study design, and  
291 responsible for funding. Revised all manuscript drafts and made final decisions on manuscript  
292 and data analysis.

293 All authors have approved the final version of the manuscript.

294

295

296

**Acknowledgements**

297 The authors would like to thank Doreen Rolshoven, Jackie Nelson and student interns for  
298 their assistance with implementation of the protocol, data collection and data entry.

299

300

### **Funding**

301

This study was funded by the United States Department of Agriculture, Agricultural

302

Research Service, and Project 3062-51000-051-00D. Mention of trade names, commercial

303

products, or organizations does not imply endorsement from the U.S. government. USDA is an

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### **Data Statement**

306

Raw data available upon request to the Grand Forks Human Nutrition Research Center

307

Data Sharing Committee: phone: 701-795-8272, fax: 701-795-8230

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	Male (n=51)	Female (n=127)	Total (n=178)
Age (years)	26.3 ± 6.7	27.1 ± 9.3	26.9 ± 8.6
BMI (kg/m <sup>2</sup> ) <sup>1</sup>	27.0 ± 5.1*	25.2 ± 4.4*	25.7 ± 4.7
RRV <sub>exercise</sub> <sup>2</sup>	0.72 ± 0.34	0.71 ± 0.37	0.71 ± 0.4
MVPA <sup>3</sup>	50.4 ± 27.3*	35.7 ± 22.9*	40.0 ± 25.1
Preference <sup>4</sup>	26.1 ± 5.5	26.3 ± 6.2	26.3 ± 6.0
Tolerance <sup>5</sup>	26.0 ± 5.7*	23.9 ± 5.2*	24.5 ± 5.4

494 Table 1. Demographics, MVPA, and exercise reinforcement of the study participants

495 Data are presented as mean ± SD

496 \*means differ ( $p \leq 0.05$ ) between sex

497 <sup>1</sup>BMI: body mass index

498 <sup>2</sup>RRV<sub>AT</sub>: number of sessions completed during the RRV task to gain access to aerobic exercise training  
499 (AT) when sedentary behavior was available as a behavioral alternative.

500 <sup>3</sup>MVPA: minutes of moderate to vigorous physical activity per week

501 <sup>4</sup>Preference: Preference for the Intensity of Exercise Questionnaire score (au)

502 <sup>5</sup>Tolerance: Tolerance of the Intensity of Exercise Questionnaire score (au)

Table 2. List of single nucleotide polymorphisms (SNPs) assessed in the present study

SNP ID	Gene	Polymorphism	Residue Change
rs8066276	ACE	C/T Transition Substitution (TCT[C/T]ACT)	N/A
rs11615016	TPH2	A/G transition substitution (TAC[A/G]TTC)	N/A Intron Variant
rs6454672	CNR1	C/T Transition Substitution (CTT[C/T]ACA)	N/A Intron Variant
rs6280	DRD3	C/T Transition Substitution (GGC[C/T]ACT)	C [Gly] ⇒ S [Ser]
rs8049933	FTO	C/T Transition Substitution (AAT[C/T]GGT)	N/A Intron Variant
rs9936768	FTO	C/T Transition Substitution (TAT[C/T]GTC)	N/A Intron Variant
rs12446047	FTO	C/T Transition Substitution (GAC[C/T]TCA)	N/A Intron Variant
rs11076022	FTO	A/G transition substitution (GTC[A/G]TTC)	N/A
rs7199716	FTO	C/T Transition Substitution (TTC[C/T]CTC)	N/A Intron Variant
rs6314	HTR2A	A/G transition substitution (AAT[A/G]CTG)	A [His] ⇒ G [Tyr]
rs1800497	DRD2/AN KK1	A/G transition substitution (GTC[A/G]AGG)	A [Glu] ⇒ G [Lys]
rs10887741	PAPSS2	C/T Transition Substitution (GGG[C/T]TCC)	N/A Intron Variant

rs12612420	None	A/G transition substitution (TCC[A/G]GAT)	N/A
rs8097348	None	A/G transition substitution (TA[A/G]CTAG)	N/A
rs12405556	LEPR	G/T Transversion Substitution (CAG[G/T]ATA)	N/A Intron Variant
rs8036270	GABRG3	A/G transition substitution (GAA[A/G]TGA)	N/A Intron Variant
rs6265	BDNF	C/T Transition Substitution (TCA[C/T]GTG)	C [Val] ⇒ T [Met]
rs1076560	DRD2	A/C Transversion Substitution (TC[A/C]CCC)	N/A Intron Variant
rs4680	COMT	A/G transition substitution (GGC[A/G]TGA)	G [Val] ⇒ A [Met]
rs265981	DRD1	A/G transition substitution (GGC[A/G]GCC)	N/A
rs1800955	DRD4	C/T Transition Substitution (GGG[C/T]GCG)	N/A
rs1611115	DBH	C/T Transition Substitution (TTG[C/T]GGG)	N/A
rs6275	DRD2	A/G transition substitution (ACC[A/G]TGG)	A [His] ⇒ G [His]

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506 Table 3. prevalence of genotypes with significant predictive values

507

SNP	Allele	Frequency	Percent	Genotype	Frequency	Percent
rs1800497	A:A	10	5.6	All A	10	5.6
	A:G	52	29.2	Has G	168	94.4
	G:G	116	65.2			
rs6454672	C:C	28	15.8	Has C	116	65.5
	C:T	88	49.7			
	T:T	61	34.5	All T	61	34.5
rs8036270	A:A	52	29.2	All A	52	29.2
	A:G	88	49.4	Has G	126	70.8
	G:G	38	21.4			
rs12405556	G:G	84	47.2	All G	84	47.2
	G:T	80	44.9	All T	94	52.8
	T:T	14	7.9			

508



509 Table 4. ANOVA results and regression model results predicting the relative reinforcing value of exercise  
 510 from SNP rs1800497 and covariates

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	<b>Coefficient ± SE</b>	<b>P</b>
<b>Full regression model</b>		
	R <sup>2</sup> = 0.11	
513	Intercept	-1.10 ± 1.01      0.28
514	BMI	-0.01 ± 0.02      0.55
	MVPA	0.003 ± 0.004      0.43
515	Tolerance	0.03 ± 0.02      0.14
516	Liking of exercise	0.16 ± 0.08      0.05
	Sex = Female	-0.02 ± 0.23      0.94
517	rs1800497 A:A	-1.20 ± 0.42      0.005
<b>Regression model of significant predictors</b>		
518	R <sup>2</sup> = 0.06	
519	Intercept	0.75 ± 0.11      <0.001
520	rs1800497 A:A	-1.38 ± 0.42      0.001
<b>RRV by genotype (from ANOVA)</b>		
521	Genotype	Mean ± SE
	AA	0.35 ± 0.09*
522	AG,GG	0.68 ± 0.02*

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523 \*Means ± SE differ (p<0.01)

524 Single nucleotide polymorphism (SNP), body mass index (BMI), moderate-to-vigorous physical activity  
 525 (MVPA), tolerance for exercise intensity (Tolerance), sex coded as: female = 0, male = 1

526 Table 5. ANOVA results and regression model results predicting tolerance for exercise intensity from SNP rs6454672, rs8036270 or rs12405556,  
 527 and covariates

<b>rs6454672</b>			<b>rs8036270</b>			<b>rs12405556</b>		
	Coefficient ± SE	P		Coefficient ± SE	P		Coefficient ± SE	P
<b>Full regression models</b>								
R <sup>2</sup> = 0.21			R <sup>2</sup> = 0.24			R <sup>2</sup> = 0.21		
Intercept	19.36 ± 4.31	< 0.001	Intercept	20.27 ± 4.19	< 0.001	Intercept	20.33 ± 4.31	< 0.001
BMI	0.06 ± 0.10	0.58	BMI	0.06 ± 0.10	0.57	BMI	0.04 ± 0.10	0.73
MVPA	0.05 ± 0.01	<0.001	MVPA	0.06 ± 0.02	< 0.001	MVPA	0.06 ± 0.01	< 0.001
RRV <sub>Exercise</sub>	2.95 ± 1.09	0.008	RRV <sub>Exercise</sub>	3.17 ± 1.12	0.005	RRV <sub>Exercise</sub>	2.88 ± 1.14	0.01
Liking of exercise	-0.03 ± 0.38	0.95	Liking of exercise	-0.03 ± 0.37	0.93	Liking of exercise	0.12 ± 0.37	0.75
Sex = Female	-1.40 ± 0.96	0.15	Sex = Female	-1.10 ± 0.99	0.27	Sex = Female	-1.52 ± 1.02	0.14
rs6454672 T:T	2.12 ± 0.90	0.02	rs8036270 A:A	-2.86 ± 0.89	0.002	rs12405556 G:G	-1.86 ± 0.82	0.025
<b>Regression models of significant predictors</b>								
R <sup>2</sup> = 0.19			R <sup>2</sup> = 0.21			R <sup>2</sup> = 0.19		
Intercept	19.40 ± 0.91	< 0.001	Intercept	20.67 ± 1.0	< 0.001	Intercept	20.88 ± 1.02	< 0.001
rs6454672 T:T	2.39 ± 0.88	0.007	rs8036270 A:A	-2.95 ± 0.82	< 0.001	rs12405556 G:G	-2.08 ± 0.77	0.0072
MVPA	0.06 ± 0.01	< 0.001	MVPA	0.07 ± 0.01	< 0.001	MVPA	0.063 ± 0.01	< 0.001

RRV <sub>Exercise</sub>	2.72 ± 1.03	0.009	RRV <sub>Exercise</sub>	2.86 ± 1.05	0.007	RRV <sub>Exercise</sub>	2.90 ± 1.11	0.0096
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**Tolerance by genotype (from ANOVA)**

Genotype	Mean ± SE		Mean ± SE		Mean ± SE
TT	26.04 ± 0.73*	AA	22.41 ± 0.69**	GG	23.41 ± 0.58*
CT,CC	23.65 ± 0.46*	AG,GG	25.36 ± 0.45**	GT,TT	25.49 ± 0.51*

\*means ± SE differ between genotype (p<0.05)

\*\*means ± SE differ between genotype (p<0.01)

single nucleotide polymorphism (SNP), body mass index (BMI), moderate-to-vigorous physical activity (MVPA), tolerance for exercise intensity

(Tolerance), sex coded as: female = 0, male = 1

529 Table 6. ANOVA results and regression model results predicting the natural logarithm of daily minutes of  
 530 moderate-to-vigorous physical activity from SNP rs6454672 and covariates

	<b>Coefficient ± SE</b>	<b>P</b>
<b>Full regression model</b>		
R <sup>2</sup> = 0.22		
Intercept	3.38 ± 0.55	< 0.001
BMI	-0.01 ± 0.01	0.32
RRV <sub>Exercise</sub>	0.09 ± 0.15	0.54
Liking_AT	-0.02 ± 0.04	0.71
Tolerance	0.02 ± 0.01	0.02
rs6454672 T:T	0.35 ± 0.10	< 0.001
Sex = Female	-0.37 ± 0.09	< 0.001
<b>Regression model of significant predictors</b>		
R <sup>2</sup> = 0.19		
Intercept	3.01 ± 0.23	< 0.001
Tolerance	0.02 ± 0.01	0.01
Sex = Female	-0.30 ± 0.10	0.002
rs6454672 T:T	0.32 ± 0.09	< 0.001
<b>MVPA by genotype (from ANOVA)</b>		
Genotype	Mean ± SE	
TT	42.95 ± 2.48*	
CT,CC	31.1 ± 2.1*	

\*means ± SE differ (p<0.01)

531 Single nucleotide polymorphism (SNP), body mass index (BMI), relative reinforcing value of exercise  
 532 (RRV<sub>Exercise</sub>) tolerance for exercise intensity (Tolerance), ANOVA model means and standard errors are  
 533 back-transformed from natural logarithmic function.