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Dopamine Receptor D2 Gene *Taq1A* (C32806T) Polymorphism Modifies the Relationship Between Birth Weight and Educational Attainment in Adulthood: 21-Year Follow-up of the Cardiovascular Risk in Young Finns Study

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ABSTRACT

OBJECTIVE. Low birth weight is suggested to be a risk factor for a wide variety of negative outcomes, including low educational attainment, but the role of cognition-related genetic influences on this association remains unclear. The objective of this study was to study whether variation in the dopamine receptor gene (dopamine receptor D2 polymorphism, rs1800497) modifies the association between birth weight and educational attainment in adulthood.

METHODS. We studied the association between birth weight (range: 1440–4980 g) and educational attainment in 659 men and 832 women aged 27 to 39. Birth weight, gestational age, and parental education were assessed at ages 6 to 18. The genotyping was performed using TaqMan 5' nuclease assay.

RESULTS. After adjustment for age, parental education, and gestational age, birth weight was associated with educational attainment in men with A1/A1 or A1/A2 ($n = 245$) genotype but not in men carrying A2/A2 ($n = 414$) genotype. In women, no moderating effect of dopamine receptor D2 polymorphism was found.

CONCLUSIONS. Dopamine receptor D2 genotype is suggested to modify the association between birth weight and adulthood educational attainment over the whole birth weight range so that carriers of A1 allele capitalize on optimal birth weight, whereas a low birth weight seems to be a risk among them. These data support the hypothesis that the effect of birth weight on educational attainment depends on genetic influences. Gender-related difference may refer to an environmental effect (ie, to a better goodness-of-fit between girls' school behaving and expectations of school) that may mask a genetic effect.

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Key Words

education, DRD2, genetic, low birth weight, psychosocial factors

Abbreviations

VLBW—very low birth weight
DRD2—dopamine receptor D2
PCR—polymerase chain reaction
OR—odds ratio
CI—confidence interval

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IN ADDITION TO a variety of cognitive, motivational, and environmental factors, birth weight has been associated with educational attainment.¹⁻⁴ Children who were born preterm or small for gestational age have been found to be at risk for reduced cognitive test scores and to have higher rates of problems in memory, attention, and neuromotor function.^{1,5,6} Very low birth weight (VLBW; <1500 g), especially, has been shown to be a risk and to predict school difficulties^{4,7,8} and low academic achievement that was apparent still in young adulthood.¹⁻⁴ However, previous studies of general populations suggested that birth weight is associated with cognition and educational attainment across the full birth weight range.³

The association between low birth weight or small for gestational age and cognitive achievement has been found to be independent of social background,^{3,9,10} although some studies suggest that a contribution of birth weight in cognitive achievement including school and educational achievement is confounded by other factors such as socioeconomic status¹¹ or childhood home and learning environment.¹⁰

In addition, there are inconsistencies that compromise the evidence on an association between low birth weight and educational achievement. Agarwal and Lim⁴ found that more than half even of the VLBW children function within the normal range of variability, and Rickards et al⁷ found that the majority of VLBW children were developing normally and were performing in most academic and social areas as well as the normal birth weight children. Moreover, the children with VLBW have been found to perform less well in most academic achievement tests, but when the comparison was restricted to children with normal intellectual capacity, the difference disappeared.¹²

Variation in fetal and postnatal influences may in part explain the conflicting findings,^{10,11} but little is known about the extent to which genetic background may modify the effect of birth weight on educational attainment. The human central dopaminergic system and dopamine receptors are implicated in cognitive function in a large number of studies,¹³⁻¹⁷ and dopamine receptor D2 (DRD2) has been shown to be related to cognitive performance,^{14,17,18} auditory tasks,¹⁹ and memory.¹⁴ According to recent studies, the Taq1A (C32806T, rs1800497) polymorphism, a C-to-T substitution located in a non-coding region of the DRD2 locus, may affect dopamine receptor D2 availability. It has also been suggested that there is an association between the A1(T) allele of this polymorphism and lower mean relative glucose metabolic rate in dopaminergic regions in the human brain.²⁰

In this study, we examined the modifying effect of DRD2 (the Taq1A polymorphism) on the relationship between birth weight and educational attainment in a population-based sample of young adults from Finland. Because studies of general populations suggest that birth

weight is associated with cognition and educational attainment across the full birth weight range,³ the whole range was used in this study (excluding those with a very high birth weight [>5000 g]). Because familial socioeconomic situation, especially parental education, explains 38% of the children's school achievement and postsecondary schooling and $>20\%$ of academic attainment in Finland,²¹ we took into account the effect of childhood socioeconomic status as an environmental risk factor for low educational attainment.

METHODS

Participants and Selection Procedure

The participants were derived from the ongoing population-based study of Cardiovascular Risk in Young Finns.²² In this prospective, epidemiologic study, a randomized sample of 3600 healthy Finnish children and adolescents in age cohorts of 3, 6, 9, 12, 15, and 18 years have been followed since 1980. During the sixth follow-up of the Cardiovascular Risk in Young Finns in 2001 (21 years after the baseline), 2229 participants were reexamined by adulthood education level, and a randomized subsample of the original sample (1760 from 3600) was genotyped for DRD2 genotype (rs1800497). In this study, we excluded the youngest cohort (baseline $n = 310$) because they may not necessarily have attained their final educational level and those with birth weight >5000 g (because of a possibility of unknown risks, including maternal diabetes; $n = 12$). The final eligible population consisted of 1512 men and women. The sample with complete data consisted of 659 men and 832 women who were aged 27 to 39 at the time education was assessed. Compared with the population at baseline, the participants in this sample were more often women (56% vs 44%; $\chi^2_1 = 22.97$; $P < .001$), and they had slightly lower mean birth weight (3484 vs 3532 g; $P = .017$). Differences in parental education (23% vs 26% academics; $P = .06$) were small and statistically nonsignificant. There were no statistically significant differences between final eligible population and the final sample in any of the measured variables.

Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit and BioRobot M48 Workstation according to the manufacturer's instructions (Qiagen, Hilden, Germany). DRD2 C32806T (rs1800497) was genotyped by using the 5' exonuclease assay and fluorogenic allele-specific TaqMan MBG probes²³ using the ABI Prism 7900HT sequence detection system (Applied Biosystems, Foster City, CA). The nucleotide sequences of primers and probes used in the polymerase chain reaction (PCR) were deduced from published sequences deposited in GenBank and synthesized in conjugation with Applied Biosystems. PCR mix-

ture consisted of genomic DNA, 1× Universal PCR Master Mix, 900 nM of each primer, and 200 nM of each probe. Amplification was performed by using the TaqMan Universal Thermal Cycling Protocol. After PCR, end-point fluorescence intensity was measured and genotype calling was conducted by the allelic discrimination-analysis module. Negative and positive controls and random duplicates were used as quality control.

Measures

All participants completed a structured questionnaire in 2001 that stratified them into 3 categories with regard to educational attainment: academic (studying at or graduated from university), secondary education but not academic (reporting high school or vocational school as the highest education), and comprehensive school (those who had not passed a secondary education). Parental educational level was requested from both parents of all participants. Parents' educational level was measured with a similar classification as for participants. Information on the parent with a higher educational level was used in the analyses. In this sample, the between correlation of parents' education is $r = 0.68$, and children's educational attainment is more strongly related to the educational level of the parent with higher education. Birth weight and gestational age were reported by the mothers of participants in 1983. Participants also were asked to bring with them the booklet from the well-infant center in which birth weights are recorded. Other study variables were gender and age, as indicated from birth year.

Statistical Analysis

Group differences in the distribution of the DRD2 polymorphism were analyzed using the analyses of variance. The interaction effects and the multivariate relationships between birth weight and the educational attainment (odds ratios [ORs] and 95% confidence intervals [CI])

were studied using ordinal logistic regression models. Statistical significance was set at $P \leq .05$. All of the analyses were done separately in men and women, and all of the regression models were adjusted for age. Additional adjustments were made for gestational age and parental education. Statistical analysis was performed by using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

The genotype distributions in men and women followed the Hardy-Weinberg equilibrium ($P > .20$ and $P > .10$, respectively). Genotype frequencies for men were 414 (A2/A2) and 245 (A1/A1+A1/A2) and for women were 548 (A2/A2) and 284 (A1/A1+A1/A2). The sample characteristics between men and women are presented in Table 1. There was no significant difference in the overall genotype distribution between men and women ($\chi^2_1 = 1.33$; $P = .223$). There were no significant differences between men and women in educational attainment ($\chi^2_2 = 1.00$; $P = .605$) or in parental education ($\chi^2_2 = 4.20$; $P = .136$). In women and men, 22% and 25% of parents had academic education, respectively. In men 132 (20%) and in women 164 (20%) had reached the highest academic level. Birth weight range was 1440 to 4980 g (those with birth weight >5000 g were excluded; $n = 12$). As expected, men had significantly higher birth weight (mean: 3534) compared with women and (mean: 3428; $P < .001$), but there were no significant differences in gestational age between men (mean: 39.5) and women (mean: 39.6; $P = .242$). There were no relationship between parental education and birth weight ($P = .717$). There was a statistically significant interaction effect between gender and birth weight on educational attainment ($\chi^2_3 = 10.68$, $P = .001$), and the additional analyses were made separately in men and women.

As shown Table 2, there was no significant main effect of DRD2 on educational attainment (OR: 1.09;

TABLE 1 Sample Characteristics

Characteristic	Men (N = 659)			Women (N = 832)			P for Difference
	N	%	Mean (SD)	N	%	Mean (SD)	
Age at baseline, y	—	—	11.6 (3.9)	—	—	11.7 (3.8)	.702
DRD2 genotype	—	—	—	—	—	—	.223
A1/A1+A1/A2	245	37	—	284	34	—	
A2/A2	414	62	—	548	66	—	
Parental education							.136
Comprehensive school	220	33	—	316	37	—	
Secondary education	276	42	—	337	41	—	
University level	163	25	—	179	22	—	
Gestational age, wk	—	—	39.5 (1.2)	—	—	39.6 (1.4)	.252
Birth weight	—	—	3534 (537)	—	—	3428 (491)	<.001
Educational attainment	—	—	—	—	—	—	.605
Comprehensive school	78	12	—	113	13	—	
Secondary education	449	68	—	555	67	—	
University level	132	20	—	164	20	—	

— indicates no data.

TABLE 2 Relationships Between DRD2, Birth Weight, and Educational Attainment in Men and Women

Parameter	Educational Attainment			
	Men (N = 659)		Women (N = 832)	
	OR	95% CI	OR	95% CI
Birth weight, tertile				
Low	1.00	Reference	1.00	
Medium	1.17	0.83–1.66	0.87	0.63–1.27
High	1.45	1.02–2.06	0.67	0.48–0.92
DRD2 genotype				
A1/A1+A1/A2	1.00	Reference	1.00	
A2/A2	1.09	0.81–1.49	0.89	0.68–1.17
Parental education				
Comprehensive school	1.00	Reference	1.00	
Secondary education	3.61	2.54–5.12	3.37	2.45–4.62
University level	4.67	3.22–6.80	5.34	3.84–7.44

95% CI: 0.81–1.49) in men, but both parental education and birth weight were significantly and positively related to educational attainment. The interaction between DRD2 genotype and birth weight on educational attainment was significant ($\chi^2_2 = 8.32$; $P = .004$). In the A1/A1+A1/A2 genotype group, birth weight was significantly and positively associated with educational attainment even after adjustment for age, parental education, and gestational age (OR: 2.47; 95% CI: 1.16–5.87; $\chi^2_2 = 6.99$; $P = .032$). In the A2/A2 genotype group, the association was much weaker and statistically insignificant (OR: 1.13; 95% CI: 0.62–1.66; $\chi^2_2 = 0.24$; $P = .883$; Table 3).

Mean levels of education in different DRD2 genotype groups in men with low, medium, and high birth weight are presented in Fig 1. There were no statistical differences between those who carried the A2/A2 genotype and others in birth weight ($t = 1.66$; $P = .096$), in parental education ($t = 0.33$; $P = .738$), or in later educational attainment ($t = 0.66$; $P = .507$). The mean

TABLE 3 Relationships Between Birth Weight and Educational Attainment in Men Carrying Different DRD2 Genotypes (n = 659)

Birth Weight, Tertile	Educational Attainment			
	A2/A2 (N = 414)		A1/A1+A1/A2 (N = 245)	
	OR	95% CI	OR	95% CI
Model 1 ^a				
Low	1.00	Reference	1.00	
Medium	1.82	0.96–3.42	0.73	0.47–1.12
High	2.82	1.35–5.91	0.66	0.42–1.02
Model 2 ^b				
Low	1.00	Reference	1.00	
Medium	1.91	1.00–3.65	1.02	0.62–1.66
High	2.47	1.16–5.27	1.13	0.68–1.87

^a Adjusted for age.

^b Adjusted for age, parental education, and gestational age.

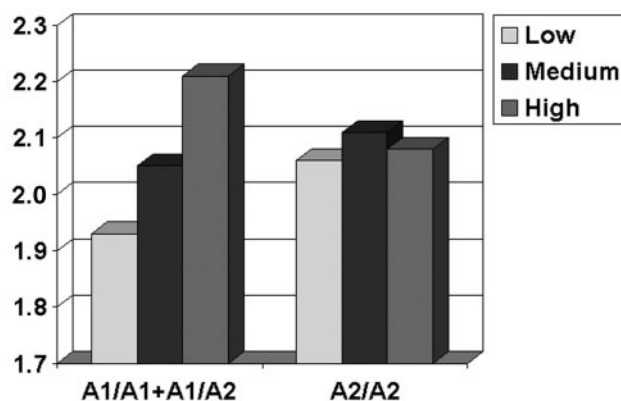


FIGURE 1

Mean levels of education in male DRD2-genotype groups according to low, medium, and high birth weight tertiles; $N = 659$. $n = 82$ in low, medium, and high birth weight groups in A1/A1+A1/A2 carriers and 138, 138, and 138 in low, medium, and high birth-weight groups, respectively, in A2/A2 carriers.

birth weight in the A2/A2 genotype group was 3610 (range: 1750–4800 g) and 3516 g in others (range: 1440–4980 g). Figure 1, however, shows that among A1/A1 and A1/A2 carriers, educational attainment increases as a function of birth weight, whereas among A2/A2 carriers, birth weight has no effect.

In women, only parental education was related to educational attainment ($P < .001$). The interaction between DRD2 polymorphism and birth weight was not statistically significant, either ($t_{829} = -0.29$; $P = .773$).

DISCUSSION

We found an association between birth weight and educational attainment in men. This association remained largely unchanged after adjustment for gestational age and parental education, but it depended on a genetic variant of the DRD2 gene such that birth weight correlated with educational attainment in A1 carriers (ie, in the A1/A1 and A1/A2 genotype groups but not in the A2/A2 group). No corresponding associations or genetic interactions were seen among women. In both genders, parental educational level but not DRD2 gene Taq1A (C32806T) polymorphism predicted participant's educational attainment.

In previous studies, an association between low birth weight and adulthood academic attainment, especially poor educational achievement and lack of postsecondary studies, was found for both genders^{3,24} and in line with our findings, especially in men.² Conflicting findings exist, however, suggesting a lack of relationship between birth weight and years of education in adulthood.²⁵ The present study suggests that this relationship might be modified by a genetic background.

Among A1 carriers, birth weight predicted later educational attainment across the whole birth weight range, so compared with A2/A2 carriers, they were more vulnerable to the adverse effects of low birth weight but

capitalized on an optimal birth weight. Birth weight had no association with educational attainment among the A2/A2 carriers. In agreement with our results linking A1 genotype with negative outcomes, Berman and Noble²⁶ showed that family stress correlated with poor cognitive functioning in boys carrying the A1 allele of the DRD2 but not in others. In the same sample, Ozkaragoz and Noble²⁷ reported that the association between parental alcoholism and extraversion was moderated by the DRD2, such that living in an alcoholic home was associated with high extraversion among boys carrying A1 allele of the DRD2 but not among those carrying the A2 allele. High extraversion, in turn, has been shown to correlate with a risk-taking, novelty-seeking behavior, leading to a low educational attainment.²⁸

An association between the A1(T) allele and lower mean relative glucose metabolic rate in dopaminergic regions in the human brain has been suggested. Some studies also suggest that the homozygous status for the A1 allele of the DRD2 Taq I polymorphism is associated with better general cognitive functioning and long-term verbal memory,¹⁴ and the DRD2 A1/A1 genotype correlated with higher IQ.¹⁵ Our findings are in line with both adverse and favorable correlates of A1 genotype, because an association between A1 genotype and good cognitive functioning was present in children with optimal birth weight, whereas low birth weight combined with this genotype resulted in poor educational outcome.

In agreement with previous studies,^{10,11} social background predicted academic achievement, whereas the association between birth weight and educational attainment was independent of familial socioeconomic situation among men in this study, as well as among participants of several previous studies.^{3,9–11} At first glance, this might suggest a role of biological factors in favor of environmental factors in this association. Gender-related difference, however, may challenge this interpretation and suggests that part of the association between low birth weight and educational level is attributable to adverse early circumstances.

Allelic distribution was similar in men and in women, but the effect of genotypic variance was apparent only in men. In women, environmental factors were of primary importance and may have masked the potential effect of biological background. This may relate to gender-specific cultural influences. It is well documented that at school, boys are at a higher risk for different kinds of problems and adversities than girls.²¹ Boys are overrepresented in all areas of school difficulties. For instance, in Finland, 12% of the age class needs special education because of learning difficulties, and more than two thirds of them are boys.²¹ This gender difference has been explained by the better fitting between girls' way to behave and learn and schools' expectations.²⁹ For cultural reasons, going to school is easier for girls, especially in adolescence, and

this difference has long-lasting consequences. Thus, boys with "vulnerable" genetic background may be at higher risk, whereas for girls, environment is more likely to eliminate this risk.

CONCLUSIONS

The findings of this study increase our understanding of the significance of birth weight on later educational attainment. Additional studies with other genetic variants, however, are needed to determine the generalizability of these findings. In addition, the amount of VLBW children was low in this population-based sample. Therefore, replications that focus on VLBW children would also be needed.

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ELECTRONIC MEDICAL RECORDS DON'T IMPROVE QUALITY

“Electronic health records—touted by policymakers as a way to improve the quality of health care—failed to boost care delivered in routine doctor visits, US researchers said. Of 17 measures of quality assessed, electronic health records made no difference in 14 measures, according to a study published in the *Archives of Internal Medicine*. The study by researchers at Stanford and Harvard Universities was based on a survey of 1.8 billion physician visits in 2003 and 2004. Electronic health records were used in 18 percent of them. In two areas, better quality was associated with electronic records, while worse quality was found in one area, they said. Many experts believe electronic records can help prevent costly medical mistakes, but few studies have evaluated whether the records actually improve the level of care when compared with paper records. ‘Our findings were a bit of a surprise. We did expect practices (with electronic medical records) would have better quality of care,’ said Dr Randall Stafford of Stanford University. ‘They really performed about the same,’ he said in a telephone interview.”

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