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Glucocorticoid receptor (NR3C1) gene polymorphisms and onset of alcohol abuse in adolescents

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Abstract

Onset of alcohol use at an early age increases the risk for later alcohol dependence. We investigated the role of the glucocorticoid receptor (GR) gene (*NR3C1*) in onset of alcohol use and abuse in 14-year-old adolescents ($n = 4534$). Several *NR3C1* polymorphisms were associated with onset of alcohol drinking or drunkenness at this age. Strongest associations were observed in females, with one marker (rs244465) remaining significant after correction for multiple testing ($P_{\text{adj}} = 0.0067$; odds ratio = 1.7, for drunkenness). Our data provide the first evidence that GR modulates initiation of alcohol abuse and reveal a polymorphism that might contribute to susceptibility to addiction.

Keywords

Addiction; adolescent; alcohol; glucocorticoid receptor; *NR3C1*; polymorphism

Age of onset of alcohol drinking is an important determinant in the addiction process. Early drinking has been found to be a strong predictor of later alcohol abuse and dependence

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Authors Contributions

SD and GS conceived and designed the study. MK, AP, A-LH, MI, PC, LP, NF, M-RJ and PE contributed to acquisition of the human sample and genotyping. SD, AL and FD performed statistical analysis. CPW and CM performed experiments. SD wrote the manuscript. All authors critically reviewed content and have approved the final manuscript.

SUPPORTING INFORMATION

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(Grant & Dawson 1997; DeWit *et al.* 2000). The rates of lifetime alcohol dependence drops from more than 40% among adolescents who started drinking at ages 14 or younger to approximately 10% among individuals who started drinking after age 20 (Grant & Dawson 1997); the odds of dependence decreasing by 14% with each increasing year of age at onset of use. Thus, the age range (11–14 years) has been identified as critical for mediating elevated risk of developing alcohol-related disorders (DeWit *et al.* 2000). Given the link between early onset of drinking and later alcohol problems, it is essential to develop a better understanding of the factors that influence consumption patterns in adolescence.

Environmental influences are a more important determinant of alcohol consumption during adolescence than in adulthood (Kendler *et al.* 2008). In addition to a well-documented role in mediating responses to environmental factors like stress, a recent study demonstrated role for glucocorticoid receptor (GR) in the reinforcing properties of cocaine (Ambroggi *et al.* 2009). However, a role for GR in initiation of drug use has not yet been elucidated.

We performed a genetic screen in humans to investigate if genetic variations of *NR3C1*, the gene encoding GR, are associated with early onset of harmful drinking. For this, we analysed 14-year-old adolescents, a subset from the prospective general population-based Northern Finland Birth Cohort 1966 (NFBC 1966; Rantakallio 1988). Genotyping was described previously (Sabatti *et al.* 2009). For the current analyses, 26 single nucleotide polymorphisms (SNPs) covering the *NR3C1* locus were selected from the whole genome data. Phenotypic characteristics of the sample and list of SNPs investigated are displayed in Table 1 and Supporting Information Table 1, respectively.

Association between SNPs and alcohol-related phenotypes was performed within gender using logistic regression analysis (additive model) using PLINK v1.06 (<http://pngu.mgh.harvard.edu/~purcell/plink/>) (Purcell *et al.* 2007). Threshold for filters were 0.01 for allele frequency, 0.1 for missingness per individual, 0.1 for missingness per marker and 0.01 for the Hardy–Weinberg equilibrium. Benjamini & Hochberg's (1995) step-up false discovery rate procedure was used to estimate uncertainty due to multiple testing within the *NR3C1* locus. These analyses revealed several markers showing nominal, gender-specific association with alcohol drinking behaviour (Table 2, Supporting Information Fig. S1). Effects of polymorphisms on early onset of alcohol use were assessed by comparing adolescents who had never drunk alcohol or tasted only once (i.e. non-drinkers) versus those who had repeatedly drunk alcohol (drunk a few times or more often). This revealed strongest associations for three markers (rs244465, rs4607376 and rs7721458) in females. While the minor alleles at rs244465 (A) and rs7721458 (A) were more common among repeated alcohol drinkers than female non-drinkers [*P* value, odds ratio (OR) [95% confidence interval (95% CI)]: *P* = 0.0021, 1.56 (1.18–2.07) and *P* = 0.0180, 1.20 (1.03–1.40), respectively], minor allele at rs4607376 (A) appeared to be protective [*P* value, OR (95% CI): *P* = 0.0083, 0.84 (0.74–0.96)]. Likewise, comparison of adolescents who had never been drunk versus those having been drunk at least once uncovered markers that associated with drunkenness in females, not in males. As for initiation of drinking, the strongest association was at rs244465, an association that remained significant after gene-wide correction for multiple testing (*P*_{adj} = 0.0067; OR (95% CI), 1.69 (1.28–2.25); Table 2).

These results indicate that genetic variation in *NR3C1* may contribute to establishment of alcohol abuse, and that the minor (A) allele at rs244465 might increase this risk in females. Such genetic variation could potentially alter not only stress-related behaviours, but directly influence the motivation to drink alcohol. Existence of such independent and dissociable function of GR is supported by a recent study (Ambroggi *et al.* 2009) showing that, while inactivation of *Nr3c1* in the entire mouse brain decreases both stress-related behaviours and

motivation to self-administer cocaine, inactivation of *Nr3c1* in dopaminoceptive neurons specifically inhibits cocaine self-administration.

A recent survey (WHO 2009) indicated that although drinking among adolescents increased markedly in recent years in Europe with large variations across countries, patterns of drinking observed in the NFBC 1966 cohort persisted over the years. While frequency of drinking in early adolescence is low in Finland, with 3% of 13-year-olds having reported drinking alcohol at least weekly, early onset of alcohol abuse is more common in Finland compared with most other countries, with 23% boys and 22% girls having been drunk by the age of 13 (WHO 2009). These numbers, similar to results displayed in Table 1, indicate that the NFBC 1966 still reflects some current adolescent drinking patterns. Further studies using appropriately selected samples are required to replicate our findings. In addition, taking into consideration gene–environment interactions by including covariates like adverse life events, parental substance use and peer influence, which might play a significant role in the development of alcohol use disorders (Sher, Grekin & Williams 2005), will help to definitely gauge role of GR in alcoholism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Phenotypic characterization of the Northern Finland Birth Cohort 1966 sample at age 14.

<i>Variable</i>	<i>N(%)</i>
Gender	
Males	2151(47.44)
Females	2383(52.56)
Total	4534(100)
Alcohol drinking	
Never drunk any	1857(40.96)
Males	902(41.93)
Females	955(40.08)
Tasted once	1562 (34.45)
Males	753 (35.01)
Females	809 (33.95)
Drunk a few times	1004 (22.14)
Males	461 (21.43)
Females	543 (22.79)
Drink alcohol monthly	99 (2.18)
Males	31 (1.44)
Females	68 (2.85)
Drink alcohol weekly	29(0.64)
Males	10 (0.46)
Females	19(0.80)
Drunkenness	
Never been drunk	3399(74.97)
Males	1631 (75.83)
Females	1768(74.19)
Once, slightly	425(9.37)
Males	218(10.13)
Females	207 (8.69)
More often, slightly	370 (8.16)
Males	151 (7.02)
Females	219(9.19)
Once very much	143 (3.15)
Males	71 (3.30)
Females	72 (3.02)
2–4 times, very much	137(3.02)
Males	57 (2.65)
Females	80 (3.36)
More often, very much	60 (1.32)
Males	23 (1.07)
Females	37(1.55)

Table 2
NR3C1 polymorphisms associated with alcohol drinking patterns in 14-year-old adolescents.

SNP	AI	Alcohol drinking females (629 drinkers, 1761 non-drinkers)					Alcohol drinking males (502 drinkers, 1654 non-drinkers)						
		OR	SE	I95	U95	STAT	P	OR	SE	I95	U95	STAT	P
rs860465	G	1.06	0.08	0.91	1.24	0.75	0.4546	1.19	0.09	1	1.41	1.97	0.0491
rs853184	A	1.07	0.08	0.91	1.25	0.83	0.4057	1.19	0.09	1.01	1.41	2.06	0.0391
rs244465	A	1.56	0.14	1.18	2.07	3.08	0.0021	0.84	0.18	0.59	1.2	-0.95	0.3405
rs2963154	G	1.09	0.08	0.93	1.27	1.02	0.3102	1.2	0.09	1.02	1.43	2.14	0.032
rs9324918	G	1.08	0.08	0.92	1.26	0.95	0.3428	1.23	0.09	1.04	1.46	2.41	0.0159
rs10052957	A	1.03	0.07	0.89	1.19	0.35	0.7228	1.18	0.08	1.01	1.38	2.12	0.0344
rs4607376	A	0.84	0.07	0.74	0.96	-2.64	0.0083	0.93	0.07	0.81	1.07	-1.05	0.2926
rs7721458	A	1.2	0.08	1.03	1.4	2.37	0.018	0.91	0.08	0.77	1.07	-1.16	0.2469
<i>Drunkness, females (614 at least once, 1765 never)</i>													
rs864354	A	1.15	0.07	1.01	1.31	2.11	0.0348	0.88	0.07	0.77	1.02	-1.73	0.0833
rs244465	A	1.69	0.14	1.28	2.25	3.65	0.0003*	0.87	0.18	0.61	1.23	-0.8	0.423
rs33383	A	1.16	0.07	1.01	1.32	2.15	0.0314	0.91	0.07	0.79	1.04	-1.38	0.1663
rs6877893	A	1.15	0.07	1.01	1.31	2.08	0.0376	0.9	0.07	0.78	1.04	-1.48	0.1386
rs2963156	A	0.84	0.08	0.72	0.98	-2.19	0.0284	0.98	0.09	0.83	1.16	-0.22	0.8294
rs7721458	A	1.19	0.08	1.03	1.39	2.28	0.0227	1.02	0.08	0.87	1.19	0.19	0.8493

Associations attaining nominal significance (P 0.05) are highlighted in bold. Those attaining the threshold level for gene-wide false discovery rate (FDR 0.05) are marked by an asterisk.

AI = minor allele name (based on whole sample); L95 = lower bound of 95% confidence interval for odds ratio; OR = estimated odds ratio for AI; P = asymptotic P value for t -statistic; STAT = t -statistic; U95 = upper bound of 95% confidence interval for odds ratio.