



# Effect of neuregulin-1 gene functional variant and environmental factors on alcohol use disorder



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## Introduction

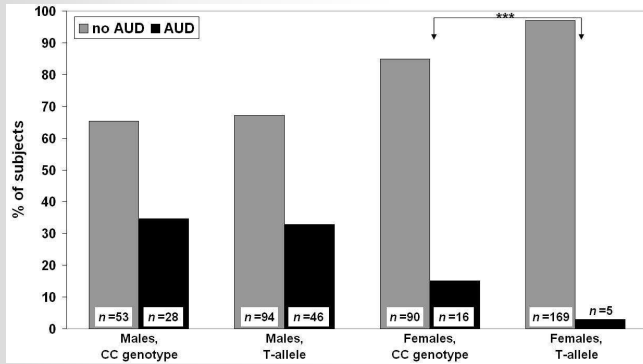
A functional promoter polymorphism in the neuregulin-1 gene (*NRG1*) – SNP8NRG243177/rs6994992; (C/T) in the promoter region of brain-specific type IV *NRG1* – has been found have extensive effects on brain structure [1], frontal lobe activation [2], psychotic illness [3]. The combination of evidence from clinical, postmortem and neuroimaging studies provides mounting evidence of functional effects of variation at SNP8NRG243177. Thus, the effects of *NRG1* on different psychiatric disorders including substance abuse and addiction are of interest.

## Methods

Data from the older birth cohort of the longitudinal Estonian Children Personality Behavior and Health Study [4] were used. Subjects participated at the ages of 15, 18 and 25, reporting their substance use, socioeconomic background, various life events, personality traits, general well-being etc. During the last data collection wave, the subjects went through M.I.N.I. interview for lifetime psychiatric disorders, including alcohol use disorder (AUD). Data on diagnosis were available on 501 subjects, 221 of them male, 280 female.

Minor (T) allele frequency of *NRG1* rs6994992: 0.36; HWE.

## Results



**Fig. 1.** The effect of *NRG1* rs6994992 on the occurrence of AUD.  $***F(1,278)=14.2, p<0.001$

Females with C/C genotype and AUD had experienced more stressful life events by the age of 25 (Table 1). Already by the age 18 they had more likely been victims of rape or attempted rape, and had higher depressiveness scores. They exhibited least aggression, indicating the possibility of internalized negative emotions and inhibited behaviour.

The effect of *NRG1* genotype on AUD was not affected by the onset of alcohol use. However, there was a tendency towards more frequent alcohol use at the age of 18 in females with C/C genotype and AUD referring to the probability of self-medication.

**Table 1.** The effects of *NRG1* rs6994992 genotype and environmental factors on the occurrence of alcohol use disorder (AUD) among women.

	<i>NRG1</i> rs6994992		AUD		<i>NRG1</i> rs6994992 * AUD			
	C/C	T-allele	unaffected	affected	C/C, unaffected	C/C, affected	T-allele, unaffected	T-allele, affected
Stressful life events, 15 yrs	1.9±1.7	1.9±1.8	1.9±1.8	2.1±1.6	1.9±1.7	1.9±1.6	1.8±1.8	2.6±1.5
Stressful life events, 18 yrs	3.1±3.0	2.6±2.5	<b>2.5±2.5***</b>	<b>6.0±3.4</b>	2.5±2.4	6.3±3.8	2.5±2.5	5.0±2.2
Victim of rape/attempted rape, 18 yrs; Ss attacked	21%	15%	<b>15%*</b>	<b>44%</b>	<b>18%</b>	<b>58%***</b>	<b>14%</b>	<b>0%</b>
Stressful life events, 25 yrs	4.1±2.8	4.2±2.8	<b>4.1±2.8*</b>	<b>5.4±2.8</b>	<b>3.8±2.7</b>	<b>6.0±2.6*</b>	<b>4.2±2.8</b>	<b>3.6±2.7</b>
Relationship problems, 25 yrs	63%	60%	<b>59%*</b>	<b>86%</b>	<b>58%</b>	<b>94%*</b>	<b>60%</b>	<b>60%</b>
Depressiveness, MADRS, 18 yrs	12.3±7.0	11.3±6.5	<b>11.3±6.4**</b>	<b>17.1±8.1</b>	<b>11.1±6.1</b>	<b>19.5±7.7*</b>	<b>11.3±6.5</b>	<b>10.5±5.7</b>
Depressiveness, MADRS, 25 yrs	8.6±6.5	8.5±6.4	8.4±6.3	11.1±7.3	8.0±6.1	12.1±7.8	8.6±6.4	8.2±5.0
Aggressive behavior, 18 yrs (1=friendly, 7=insolent)	2.1±1.2	1.9±1.0	2.0±1.1	2.2±1.2	<b>2.2±1.2</b>	<b>1.5±0.8**</b>	<b>1.8±1.0</b>	<b>3.3±1.0</b>
The age of drinking the first half a unit of alcohol	14.7±2.0	14.4±1.8	14.5±1.9	14.8±1.9	14.7±2.0	14.7±2.0	14.4±1.8	15.0±1.7
The frequency of drinking alcohol, 18 yrs	Median & mode: „monthly“	median & mode: „monthly“	<b>median &amp; mode: „monthly“*</b>	<b>median &amp; mode: „weekly“</b>	median & mode: „monthly“	median & mode: „weekly“#	median & mode: „monthly“	median & mode: „monthly“

#p=0.067, \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001 – difference from T-allele carriers with AUD

Men had significantly more alcohol abuse problems ( $F(1,499)=60.6, p<0.001$ ). The prevalence of AUD was affected by *NRG1* genotype only among women (Fig. 1): female subjects with C/C genotype were ~5 times more likely to have AUD by the age of 25.

## Conclusions

*NRG1* genotype affects the risk of developing AUD in females: C/C appears to be the vulnerability genotype. The relationship is affected by stressful life events, especially by sexual victimization.

## Disclosure

No potential conflict of interest.

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