NOS1 gene Ex1f-VNTR polymorphism influences alcohol consumption in humans

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Rationale

Neuronal nitric oxide synthase (NOS1) gene promoter polymorphism Ex1f-VNTR influences both impulsivity-related traits and psychopathology [1]. The short (S) allele with decreased transcriptional activity is considered the risk-allele as opposed to the long (L) allele. Impulsivity in turn is linked to alcohol consumption but any *NOS1* effect on consumption of alcoholic beverages in humans is not known yet. In animal studies NOS1 gene knockout reduced the neurobehavioral effects of alcohol [2], suggesting that for alcohol consumption in humans, the long allele of *NOS1* Ex1f-VNTR could be the risk allele.

Objective

We explored whether NOS1 Ex1f-VNTR influences consumption of alcoholic beverages in a population based sample controlling for impulsivity.

Methods

The sample: The older cohort of a population-representative sample of Estonian young adults (N=593) measured at three waves [3].

Self-reported measures: Use of alcoholic beverages at ages 15 (n=577), 18 (n=388) and 25 (n=537);
Impulsivity scales (Adaptive and Maladaptive Impulsivity Scale) at ages 18 (n=336) and 25 (n=510).

NOS1 gene Ex1-VNTR polymorphism: Genotyping was carried out as previously described [1]. L/L n=113, S/L n=229 and S/S n=95.

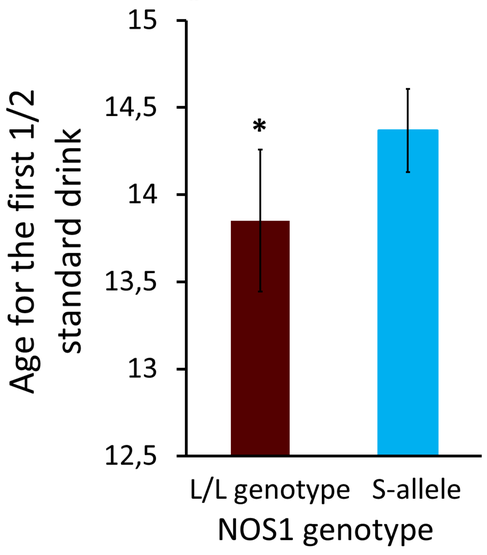
Statistics: Analysis of variance, X^2 test, logistic regression and Mann-Whitney U-test

Results

Men consumed alcohol more than women at all ages.

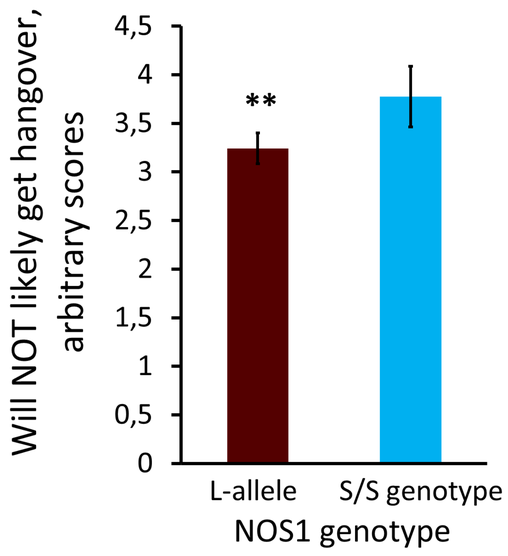
Subjects with L/L genotype had their first ½ standard drink at earlier age (median 14 y) compared to short allele carriers (median 15 y) (p=0.033). Whiskers indicate 95% CI.

NOS1 main effect on age when having the first drink



Subjects with L-allele reported more often that hangover is likely when drinking (p=0.003). However, the effect did not emerge because of drinking more, as controlling for total alcohol consumption did not change the genotype effect.

NOS1 main effect on hangover

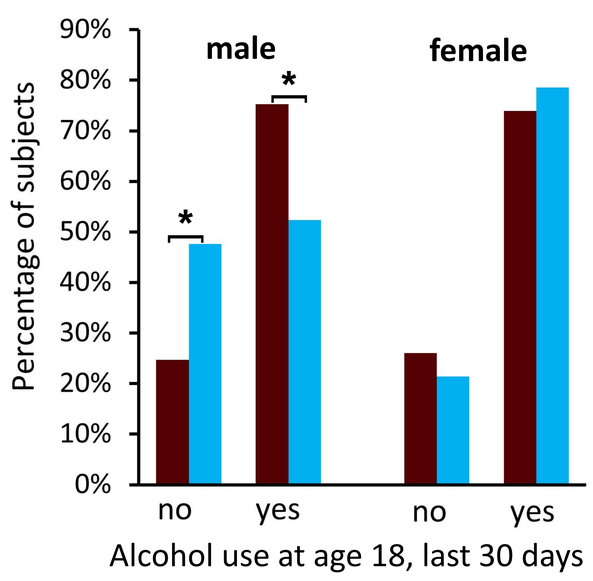


At age 15, no NOS1 Ex1f-VNTR genotype effect on alcohol consumption was observed.

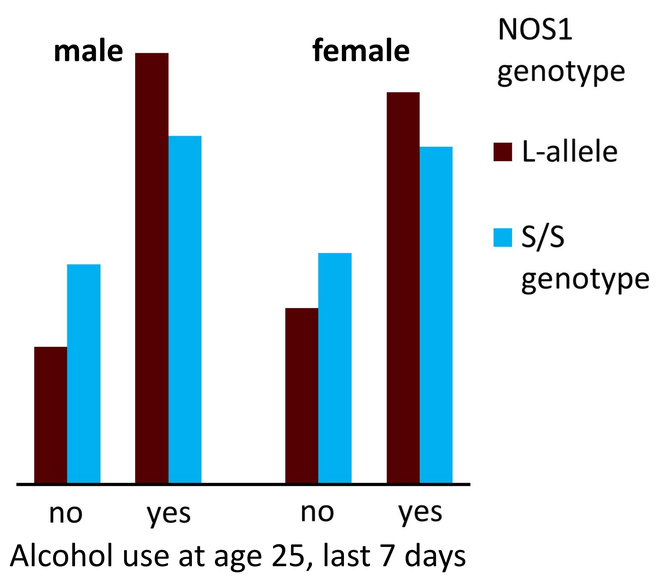
At age 18 NOS1 x Sex effect appeared where *male* L-allele carriers consumed more alcohol: they consumed more per drinking session (p=0.006, not shown); there was an excess of male L-allele carriers among frequent alcohol users (p=0.019, not shown) and in the upper and interquartile range of total alcohol consumption (p=0.036). * - p<0.05, genotype difference in males.

At age 25 NOS1 main effect evolved where L-allele carriers consumed more alcohol regardless of gender: there was an excess of L-allele carriers in the interquartile range and upper quartiles of total alcohol consumption (main effect p=0.024; for males p=0.095, for females p=0.160).

NOS1 x Sex interaction effect on alcohol use at age 18



NOS1 main effect on alcohol use at age 25, divided by gender for comparison with age 18



For illustrative purposes, the subjects were categorised for alcohol use as: ***no*** – have not consumed or consumed small quantities (lower quartile of alcohol consumption period); yes – consumed medium or large quantities (alcohol consumption interquartile range and upper quartile).

The NOS1 x Sex effect on alcohol consumption at age 18 disappeared when accounting with impulsivity but at age 25 the main genotype effect strengthened (p=0.014).

Conclusions

Subjects carrying the *NOS1* Ex1f-VNTR long allele (compared to short/short genotype)...

- have their first ½ drink at earlier age
- consume more alcohol
- report alcohol effects stronger

✓ These effects are not fully explained by impulsivity.

✓ The short allele of the NOS1 Ex1f-VNTR polymorphism is protective against alcohol consumption (although it is presumed that the short allele is the impulsivity-related psychiatric risk allele).

✓ This is in accordance with animal studies [2] where inhibition of NOS1 attenuates alcohol consumption.

Acknowledgements

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Disclosure

The authors report no conflict of interest.

References

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