The association of alcohol intake with gamma-glutamyl transferase (GGT) levels: evidence for correlated genetic effects

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Supplementary Methods

Number of participants and reasons for exclusion

Information on GGT levels was present for 8,754 individuals (aged ≥18). Analyses were performed on data from 6,465 individuals for whom data on alcohol intake and levels of GGT were present (3,193 twins, 1,304 siblings, and 1,968 parents). Data were excluded for 11 individuals with known liver disease (ICD-10 codes K70-K77), 1,523 individuals who did not participate in the 2002-2009 surveys, and 121 individuals who reported to have never drunk any alcohol. For 133 persons who participated in the 2002-2009 surveys, data on alcohol intake were missing, and for 31 individuals excluded during data cleaning (because of extreme/impossible values, see Van Beek et al., 2013b). For 470 individuals, data were excluded, since they were not biological relatives of the twins (N=26), zygosity was not yet known (N=2), they formed part of a triplet (N=2), were sibling in a family with more than two same sex siblings (N=64; a maximum of two same sex siblings was included per family), or had another relation to the twin than co-twin, sibling or parent (mostly spouse of twin, N=315; other relationships, e.g. child, N=61).

Description bivariate genetic analysis

Bivariate genetic analysis was performed with saturated models and structural equation models.

The bivariate saturated model estimated 30 familial correlations. Ten familial correlations were estimated for alcohol intake, nine for GGT and eleven cross-trait correlations for the relation of alcohol intake with GGT. For alcohol intake, GGT and the cross-trait covariance of alcohol intake with GGT, these were five offspring correlations (MZM twin pairs, MZF twin

pairs, male-male DZ/sibling pairs, female-female DZ/sibling pairs, and opposite sex twin/sibling pairs), and four parent-offspring correlations (father-son, mother-daughter, father-daughter, mother-son) (thus, 27 in total). In addition, two within-person cross-trait correlations (males, females) were estimated for the relation between alcohol intake and GGT, and one spouse correlation for alcohol intake. As spousal resemblance for GGT was negligible (Van Beek et al., 2013a), this was not included, nor was cross-trait spousal resemblance for alcohol intake with GGT.

Structural equation models were informed by the results based on univariate genetic structural equation models performed on alcohol intake (Van Beek et al., 2013b) and GGT (Van Beek et al., 2013a). Variation in alcohol intake was best explained by effects of additive and non-additive gene action as well as individual-specific environmental effects for both men and women (Van Beek et al., 2013b). Results for GGT differed over sex. Variation in GGT among women was explained by additive genetic, non-additive genetic and non-shared individual-specific environmental factors, whereas for men, non-additive genetic effects were not significant, but shared environmental effects were (Van Beek et al., 2013a). In the structural equation models of this study (see Figure S1), based on these previous results, alcohol intake of fathers, mothers, sons and daughters (depicted as ALC_{FA}, ALC_{MO}, ALC_{SO}, ALC_{DA} respectively) was regressed on factors representing additive genetic (A_1), non-additive genetic (D_1), and individual-specific environmental effects (E_1). The factor loadings (a_1, d_1, e_1) were allowed to differ over sex (represented as $a_{1,m}$, $a_{1,f}$, $d_{1,m}$, $d_{1,f}$, $e_{1,m}$, $e_{1,f}$). Variation in GGT levels among females (mothers depicted as GGT_{MO}, daughters as GGT_{DA}) could also be ascribed to additive genetic (A), non-additive (D) genetic and individual-specific environmental effects. If GGT levels would be uncorrelated with levels of alcohol intake, variation in GGT would be solely

regressed on factors that were specific to GGT, that is on $A_{2,f}$, $D_{2,f}$ and $E_{2,f}$ (the factors loadings $a_{21,f}$, $d_{21,f}$, and $e_{21,f}$ would be set to zero). As can be seen in Figure S1, GGT levels are assumed to be correlated with alcohol intake and this correlation is specified through the factor loadings $a_{21,f}$, $d_{21,f}$, $e_{21,f}$ that run from the factors for alcohol intake ($A_{1,f}$, $D_{1,f}$, $E_{1,f}$) to GGT. For males, the same principle holds true. The association of alcohol intake with GGT among males was modeled to be influenced by alcohol-effects ($A_{1,m}$, $D_{1,m}$, $E_{1,m}$ with factor loadings $a_{21,m}$, $d_{21,m}$, and $e_{21,m}$ and GGT-specific effects (A_2, C_2, E_2 with factor loadings $a_{2,m}$, $c_{2,m}$, and $e_{2,m}$).

The amount of variance and covariance ascribed to genetic and environmental factors, can be estimated by the fact that family members share their genetic and environmental background to different degrees. MZ twin pairs are assumed to share their entire genetic material (that is, the additive genetic factors (A) were modeled to correlate 1 within twin pairs), whereas DZ twin pairs, siblings, and parent and offspring are estimated to share half of their genes (A factors were modeled to correlate .5 for DZ twin, sibling and parent-offspring pairs). Non-additive genetic influences (D) can be estimated by assuming that MZ twin pairs share all their genetic material with each other including non-additive genetic factors (that is: D factors are correlated 1), DZ twins and sibling pairs share on average a quarter of the non-additive genetic factors (D factors are correlated .25), and parent-offspring pairs share none of their non-additive genetic factors. Shared-environmental influences (represented by C factors) on GGT in males were correlated 1 among co-twin/siblings and 0 with their parents. Variance and covariance that was individual-specific (not shared between family members) was estimated as E.

GGT levels were assumed to be independent among parents. Spousal resemblance for alcohol intake was modeled to run via the Δ-path that represents the correlations between the latent genetic and environmental factors influencing the phenotypes of the parents, that result

from phenotypic assortment. The increase in the additive genetic variance (R_A) that results from the presence of phenotypic assortment for alcohol intake was modeled through the additive genetic variance component. The variance of the additive genetic factors in the offspring generation (.5) reflects the segregation variance that emerges due to recombination. This within-family additive genetic variance emerges since parents pass their alleles, not genotypes, giving rise to new genetic variance in the offspring generation (Keller et al., 2009).

Constraints were equal to those in the univariate models: two means (males/females), one variance (equal over sex) for alcohol intake (Van Beek et al., 2013b) and four means (male twins/siblings, female twins/siblings, fathers, mothers) and three variances (male twin/siblings, female twin/siblings, parents) for GGT (Van Beek et al., 2013a).

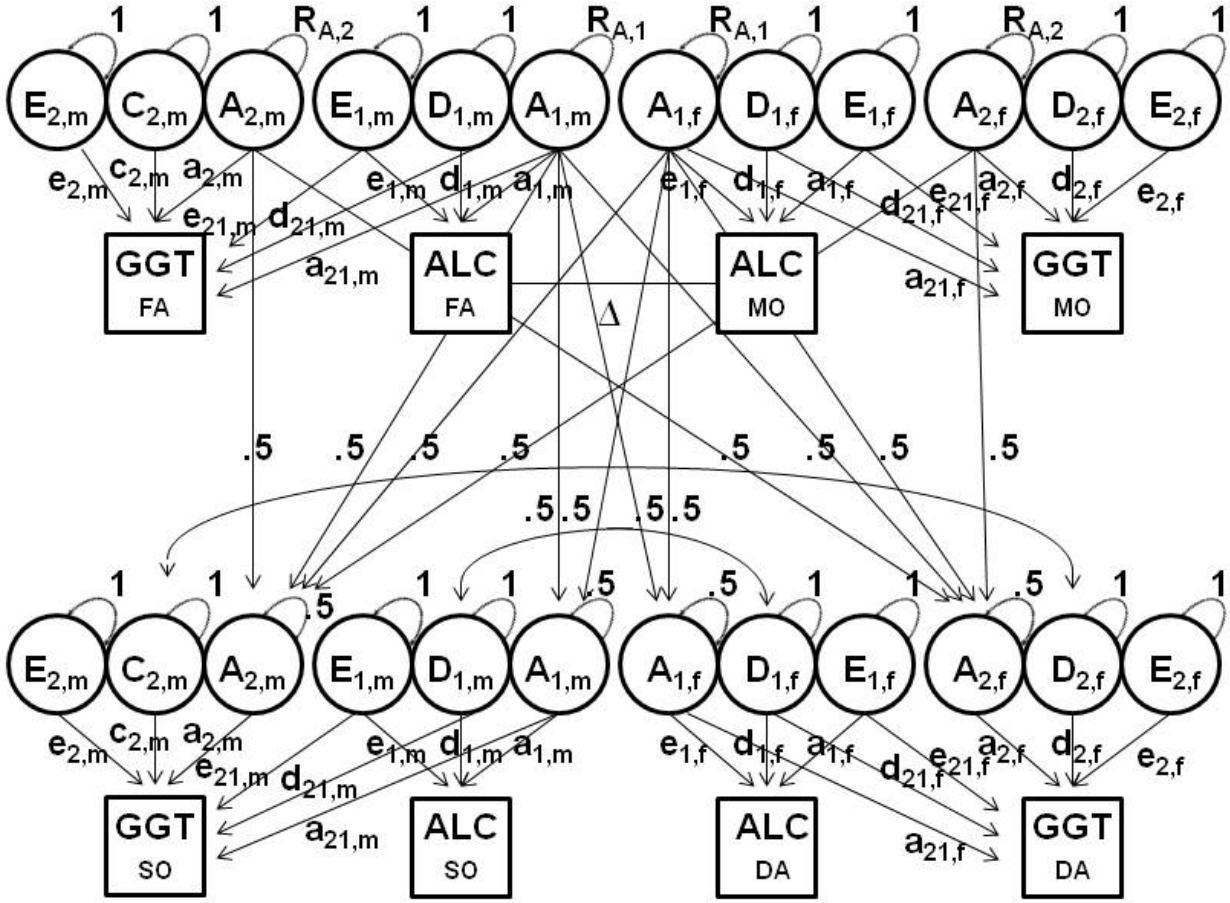

Figure S1 Path diagram for variance decomposition with extended twin family design (ETFD) (shown for DZ twin pair with parents)

Explanation of symbols used in Figure S1:

ALC_{FA}, ALC_{MO}, ALC_{SO}, ALC_{DA} = alcohol intake of fathers, mothers, sons, daughters

GGT_{FA}, GGT_{MO}, GGT_{SO}, GGT_{DA} = GGT of fathers, mothers, sons, daughters

A=additive genetic factor with variance R_A (differs from 1 in the case of phenotypic assortment)

D=non-additive genetic factor

C=shared environmental factor

E=individual-specific environmental factor

$a_{1,m}$,$d_{1,m}$,$e_{1,m}$= path loadings for alcohol intake, males

$a_{1,f}$,$d_{1,f}$,$e_{1,f}$= path loadings for alcohol intake, females

$a_{2,m}$,$c_{2,m}$, $e_{2,m}$= path loadings for GGT, males

$a_{2,f}$, $d_{2,f}$,$e_{2,f}$= path loadings for GGT, females

$a_{21,m}$,$d_{21,m}$,$e_{21,m}$= cross-path loadings alcohol intake - GGT, males

$a_{21,f}$,$d_{21,f}$,$e_{21,f}$= cross-path loadings alcohol intake - GGT, females

Δ=path representing correlations between parental alcohol intake induced by phenotypic assortment

References

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