Supplementary Appendix for

Correlated Genotypes in Friendship Networks

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Description of Available Genes in the Add Health Study

CYP2A6: Add Health genotyped the *CYP2A6* gene using a single nucleotide polymorphism in exon 3 (rs1801272) (*1*). This gene encodes for an enzyme that catalyzes reactions related to drug metabolism and the synthesis of cholesterol, steroids, and other lipids; different allelic variants may confer reduced metabolic efficiency for coumarin or nicotine. Specifically, this gene maps to 19q12-13.2 on chromosome 19, and the T→A nucleotide substitution results in an amino acid change from leucine to histidine, producing a catalytically inactive protein product (*2*). The *CYP2A6* alleles which result in deficient nicotine metabolism are associated with a reduction in tobacco consumption (*3-5*). *CYP2A6* may also be associated with the personality trait of openness (*6)*.

DRD2: This study focuses on the TaqI A repeat fragment length polymorphism in the *DRD2* gene (*7*). The *DRD2* gene is located on chromosome 11 (11q23) and the TaqI A polymorphism, located 9.4 kb downstream from the coding region of the *DRD2* gene, is not in a known regulatory region. As a result, it remains unclear how this polymorphism affects expression even though it has been associated with reduced D2 receptor binding (*8*). The TaqI A

allele, genotyped as a SNP, is the *DRD2* allele most frequently studied (*9*). There are two *DRD2* alleles, the minor A1 allele and major A2 allele. Impairments of the dopamine system are implicated in neurological, psychiatric and drug addiction disorders, and mental illness, and the D2 receptor has a role in modulating dopamine synthesis, cell firing, and release (*10*). Several studies have found a significant relationship between the dopamine D2 receptor density and social attachment (*11-13*) as well as an association between the A1 allele and social alienation (*14*), antisocial personality disorder (*15*), and avoidant personality types (*16*).

DRD4: a 48 bp VNTR (variable number tandem repeat) in exon 3 resulted in detection of alleles with base-pair (bp) length of 379, 427, 475, 523, 571, 619, 667, 715, 763 and 811. The two most common alleles were the 475 bp (with four repeats of the 48-bp VNTR), and the 619 bp (with seven repeats of the 48-bp VNTR). Following Hopfer et al. (*17*), we group the 379, 427, 475, 523, and 571 bp alleles to form the 4R grouping and 619, 667, 715, and 763 bp alleles into the 7R grouping. Novelty-seeking is thought to be mediated by genetic variability in dopamine transmission (*18*) and a wide variety of genetic association studies have tested the link between polymorphisms of *DRD4* and novelty-seeking behavior with generally positive results (*19-21*). Studies of animals indicate that *DRD4* is involved in cortical excitability and behavioral sensitization. These alterations in cortical arousal affect "approach traits" such as novelty-seeking and sensation-seeking, which in turn affect personality and behavior (*22-25*).

MAOA: MAOA encodes monoamine oxidase A, an enzyme responsible for degrading amine neurotransmitters such as dopamine, norepinephrine, and serotonin. This gene is mapped to Xp11.3-11.4 on the X chromosome, and contains a 30 base pair VNTR in the 5' regulatory region of the gene (*26*) which has been shown to affect its expression (*27*). MAOA has been associated with antisocial behaviors and misconduct but results have been mixed (*28-38*).

SLC6A3: This gene, also known as DAT1, maps to 5p15.3 on chromosome 5 and has a 40 base pair VNTR polymorphism in an untranslated section of the 3' region (*39*). There are between 3 and 11 copies of the VNTR, though the 9-repeat (440 bp) and 10-repeat (480 bp) polymorphisms are the most common alleles in Caucasian, Hispanic, and African American populations (*40*). The VNTR has been associated with the translation of the DAT protein in human striatum (*41*) and the dopamine transporter it encodes has been associated with idiopathic epilepsy, attention-deficit hyperactivity disorder (*42*), dependence on alcohol and cocaine (*43*), susceptibility to Parkinson disease, and protection against nicotine dependence (*44*).

SLC6A4: Known alternately as 5HTT or 5-HTTLPR, this gene maps to the 17q11.1-17q12 region on chromosome 17 and contains a 44 bp VNTR in the 5' regulatory promoter region of the gene (*45*). Variation in the number of repeats is associated with variation in transcriptional activity, and the long variant (528 base pair) is approximately three times more efficient than the shorter variant (484 bp) (*46*). The repeat length polymorphism is thought to affect the role of serotonin uptake. Although the exact role of 5HTT remains to be elucidated, it is among the polymorphisms thought to be related to one's "central sensitivity to the pathogenic effects of the environment" (*47-48*) and it is hypothesized that this polymorphism is directly or indirectly related to some aspect of brain functioning related to buffering stress (*48*). The short variant of 5HTTLPR is associated with anxiety-related, harm avoidant, and negative personality traits (*47*,*49-55*). Behaviorally, short alleles are associated with great anxiety, learned fear, learned helplessness, startle response, reduced aggression, and less exploratory activity (*49*).

Table S1a. Associations Between Subject and Friend's Genotype in the National Longitudinal Study of Adolescent Health

	Dependent Variable: Friend's Genotype								
	Cytochrome P450 CYP2A6 (rs1801272)			*Dopamine Receptor DRD2* (rs1125394)			*Dopamine Receptor DRD4* (R7,R4 VNTR)		
Independent Vars.	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*
***Subject's Genotype Minus Siblings' Mean Genotype* (w)**	**-0.11**	**0.03**	**0.0001**	**0.11**	**0.04**	**0.008**	**0.05**	**0.04**	**0.19**
Siblings' Mean Genotype (b)	-0.06	0.02	0.00	-0.01	0.04	0.78	0.09	0.04	0.01
Subject Female	0.03	0.02	0.06	0.02	0.04	0.63	-0.01	0.04	0.69
Friend Female	-0.02	0.01	0.14	0.02	0.04	0.69	0.06	0.04	0.08
Subject's Age	0.01	0.01	0.11	0.01	0.02	0.45	0.03	0.02	0.07
Friend's Age	-0.02	0.01	0.01	0.01	0.02	0.76	-0.03	0.02	0.06
Subject is Black	-0.05	0.03	0.06	0.11	0.17	0.53	-0.03	0.12	0.81
Friend is Black	-0.04	0.03	0.11	0.31	0.17	0.06	-0.10	0.12	0.38
Subject is Native American	-0.05	0.02	0.02	-0.05	0.06	0.43	0.10	0.09	0.23
Friend is Native American	-0.08	0.01	0.00	0.04	0.07	0.61	0.01	0.08	0.89
Subject is Chinese	0.02	0.02	0.13	0.12	0.26	0.63	-0.15	0.14	0.29
Friend is Chinese	-0.10	0.03	0.00	0.86	0.32	0.01	-0.16	0.14	0.24
Subject is Filipino	-0.04	0.03	0.29	0.59	0.52	0.26	0.05	0.14	0.70
Friend is Filipino	-0.06	0.04	0.11	-0.11	0.55	0.84	-0.23	0.15	0.12
Subject is Korean	-0.06	0.02	0.00	0.74	0.35	0.03	-0.04	0.18	0.82
Friend is Korean	-0.01	0.02	0.62	-0.31	0.40	0.44	-0.31	0.11	0.01
Subject is Puerto Rican	-0.01	0.04	0.82	-0.42	0.12	0.00	-0.38	0.13	0.00
Friend is Puerto Rican	-0.10	0.02	0.00	0.54	0.52	0.30	0.10	0.29	0.73
Subject is Mexican	0.05	0.06	0.42	-0.26	0.13	0.04	0.05	0.12	0.67
Friend is Mexican	-0.09	0.04	0.01	1.03	0.12	0.00	0.09	0.12	0.44
From Saturated School	-0.01	0.02	0.38	0.04	0.04	0.34	0.12	0.04	0.00
Constant	0.19	0.08	0.01	0.02	0.22	0.93	0.21	0.20	0.29
MSE	64.4			397			362		
Null MSE	66.7			457			378		
N	1175			1167			1195		

This table shows results of three separate linear regressions of friend's genotype on subject's genotype with age, sex, and race controls. Models were estimated using a general estimating equation with an independent working covariance structure and errors clustered on family ids. Models with an exchangeable correlation structure yielded poorer fit. MSE fit statistics show sum of squared errors between predicted and observed values for the model and a null model with no covariates. Genotype takes the value 0, 1, or 2 depending on the number of minor alleles. To reduce the likelihood of population stratification, we use the sibling transmission disequilibrium test (Sib-TDT) method, controlling for sibling mean genotype and subtracting this value from the subject's genotype. Because we conducted tests on six genetic markers available in the Add Health study, a Bonferroni correction implies that the threshold for 95% confidence is $p = 0.05 / 6 = 0.008$. The associations between subject and friend genotype for *CYP2A6* and *DRD2* are significant at this level.

Table S1b. Associations Between Subject and Friend's Genotype in the National Longitudinal Study of Adolescent Health

	Dependent Variable: Friend's Genotype								
	Monoamine Oxidase *MAOA* (uVNTR)			*Dopamine Transporter* *SLC6A3* (R9,R10 VNTR)			*Serotonin Transporter* *SLC6A4* (5HTT VNTR)		
Independent Vars.	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*
***Subject's Genotype Minus Siblings' Mean Genotype* (w)**	**-0.04**	**0.04**	**0.24**	**-0.03**	**0.04**	**0.43**	**-0.10**	**0.04**	**0.006**
Siblings' Mean Genotype (b)	-0.05	0.04	0.26	0.06	0.04	0.15	-0.06	0.04	0.10
Subject Female	0.05	0.05	0.40	-0.05	0.04	0.21	-0.02	0.05	0.59
Friend Female	0.01	0.06	0.82	-0.14	0.04	0.00	-0.15	0.05	0.00
Subject's Age	-0.01	0.03	0.70	0.01	0.02	0.74	-0.01	0.02	0.60
Friend's Age	-0.01	0.03	0.61	-0.02	0.02	0.41	0.05	0.02	0.01
Subject is Black	0.41	0.31	0.19	0.26	0.21	0.21	0.10	0.17	0.54
Friend is Black	-0.08	0.32	0.80	-0.33	0.20	0.10	-0.60	0.17	0.00
Subject is Native American	0.29	0.11	0.01	0.06	0.08	0.44	0.07	0.09	0.47
Friend is Native American	0.13	0.12	0.26	0.08	0.08	0.36	0.02	0.08	0.77
Subject is Chinese	-0.51	0.46	0.27	0.15	0.29	0.60	0.73	0.31	0.02
Friend is Chinese	0.88	0.62	0.15	-0.01	0.35	0.97	-0.56	0.34	0.10
Subject is Filipino	0.07	0.30	0.83	0.15	0.16	0.35	-0.24	0.12	0.05
Friend is Filipino	0.41	0.31	0.19	-0.39	0.18	0.03	0.76	0.13	0.00
Subject is Korean	0.62	0.43	0.15	0.12	0.20	0.57	0.01	0.11	0.94
Friend is Korean	0.52	0.31	0.09	-0.47	0.13	0.00	0.51	0.10	0.00
Subject is Puerto Rican	-0.39	0.17	0.02	-0.37	0.12	0.00	0.25	0.13	0.06
Friend is Puerto Rican	0.78	0.40	0.05	-0.32	0.14	0.03	-0.24	0.30	0.43
Subject is Mexican	0.37	0.18	0.04	0.05	0.11	0.64	0.33	0.13	0.01
Friend is Mexican	-0.20	0.15	0.19	-0.16	0.11	0.16	-0.21	0.13	0.10
From Saturated School	0.16	0.06	0.01	0.07	0.04	0.12	0.00	0.05	0.97
Constant	0.89	0.31	0.00	0.85	0.20	0.00	0.60	0.25	0.02
MSE	770			373			527		
Null MSE	804			389			571		
N	1179			1175			1187		

This table shows results of three separate linear regressions of friend's genotype on subject's genotype with age, sex, and race controls. Models were estimated using a general estimating equation with an independent working covariance structure and errors clustered on family ids. Models with an exchangeable correlation structure yielded poorer fit. MSE fit statistics show sum of squared errors between predicted and observed values for the model and a null model with no covariates. Genotype takes the value 0, 1, or 2 depending on the number of minor alleles. To reduce the likelihood of population stratification, we use the sibling transmission disequilibrium test (Sib-TDT) method, controlling for sibling mean genotype and subtracting this value from the subject's genotype. Because we conducted tests on six genetic markers available in the Add Health study, a Bonferroni correction implies that the threshold for 95% confidence is $p = 0.05 / 6 = 0.008$. No associations between subject and friend genotype in this table are significant at this level.

Table S2. Replication of Associations Between Subject and Friend's Genotype in the Framingham Heart Study

	Dependent Variable: Friend's Genotype					
	Cytochrome P450 CYP2A6 (rs1801272)			*Dopamine Receptor DRD2* (rs1125394)		
Independent Vars.	*Coef*	*SE*	*p*	*Coef*	*SE*	*p*
***Subject's Genotype Minus Parental Mean Genotype* (w)**	**-0.08**	**0.03**	**0.02**	**0.17**	**0.06**	**0.006**
Parental Mean Genotype (b)	-0.10	0.02	0.00	-0.08	0.03	0.01
Subject Female	-0.08	0.04	0.06	-0.05	0.05	0.30
Friend Female	0.10	0.04	0.02	0.00	0.05	0.93
Subject's Age	0.00	0.00	0.71	0.00	0.00	0.19
Friend's Age	0.00	0.00	0.95	0.00	0.00	0.54
Constant	0.12	0.06	0.03	0.43	0.08	0.00
MSE	1834			8345		
Null MSE	1871			8578		
N	1988			3316		

This table shows results of three separate linear regressions of friend's genotype on subject's genotype with age and sex controls. Genotype takes the value 0, 1, or 2 depending on the number of minor alleles. Models were estimated using a general estimating equation with an independent working covariance structure and errors clustered on family id. Models with an exchangeable correlation structure yielded poorer fit. MSE fit statistics show sum of squared errors between predicted and observed values for the model and a null model with no covariates. To reduce the likelihood of population stratification, we use the family transmission disequilibrium test (TDT) method, controlling for parental mean genotype and subtracting this value from the subject's genotype. Both associations between subject and friend genotype are significant.

Table S3. Summary Statistics for Models Conducted in the National Longitudinal Study of Adolescent Health in Table S1

Variable Name	Mean	SD
Friend's CYP2A6 Genotype	0.060	0.238
Subject's Genotype Minus Siblings' Mean Genotype (w), *CYP2A6*	0.001	0.202
Siblings' Mean Genotype (b), *CYP2A6*	0.070	0.253
Friend's DRD2 Genotype	0.481	0.626
Subject's Genotype Minus Siblings' Mean Genotype (w), *DRD2*	0.035	0.504
Siblings' Mean Genotype (b), *DRD2*	0.452	0.598
Friend's DRD4 Genotype	0.367	0.563
Subject's Genotype Minus Siblings' Mean Genotype (w), *DRD4*	0.042	0.536
Siblings' Mean Genotype (b), *DRD4*	0.380	0.558
Friend's MAOA Genotype	0.718	0.826
Subject's Genotype Minus Siblings' Mean Genotype (w), *MAOA*	-0.013	0.873
Siblings' Mean Genotype (b), *MAOA*	0.703	0.789
Friend's SLC6A3 Genotype	0.478	0.576
Subject's Genotype Minus Siblings' Mean Genotype (w), *SLC6A3*	0.011	0.620
Siblings' Mean Genotype (b), *SLC6A3*	0.431	0.575
Friend's SLC6A4 Genotype	0.906	0.694
Subject's Genotype Minus Siblings' Mean Genotype (w), *SLC6A4*	-0.019	0.680
Siblings' Mean Genotype (b), *SLC6A4*	0.881	0.701
Subject is Female	0.530	0.499
Friend is Female	0.530	0.499
Subject's Age	15.583	1.684
Friend's Age	15.583	1.684
Subject is Black	0.127	0.333
Friend is Black	0.127	0.333
Subject is Native American	0.068	0.252
Friend is Native American	0.068	0.252
Subject is Chinese	0.012	0.108
Friend is Chinese	0.012	0.108
Subject is Filipino	0.053	0.224
Friend is Filipino	0.053	0.224
Subject is Korean	0.004	0.063
Friend is Korean	0.004	0.063
Subject is Puerto Rican	0.014	0.119
Friend is Puerto Rican	0.014	0.119
Subject is Mexican	0.060	0.237
Friend is Mexican	0.060	0.237
Subject, Friend From Add Health School with "Saturated" Observations	0.278	0.448

Table S4. Summary Statistics for Replication Models Conducted in the Framingham Heart Study in Table S2

	Cytochrome P450 CYP2A6 (rs1801272)		*Dopamine Receptor DRD2* (rs1125394)	
	Mean	*SD*	*Mean*	*SD*
Friend's Genotype	0.09	0.29	0.31	0.51
Subject's Genotype Minus Family's Mean Genotype (w)	0.00	0.17	0.00	0.31
Family's Mean Genotype (b)	0.09	0.29	0.31	0.49
Subject Female	0.50	0.50	0.50	0.50
Friend Female	0.50	0.50	0.50	0.50
Subject's Age	51.73	12.10	51.70	12.13
Friend's Age	51.76	12.13	51.70	12.15
N	1988		3316	

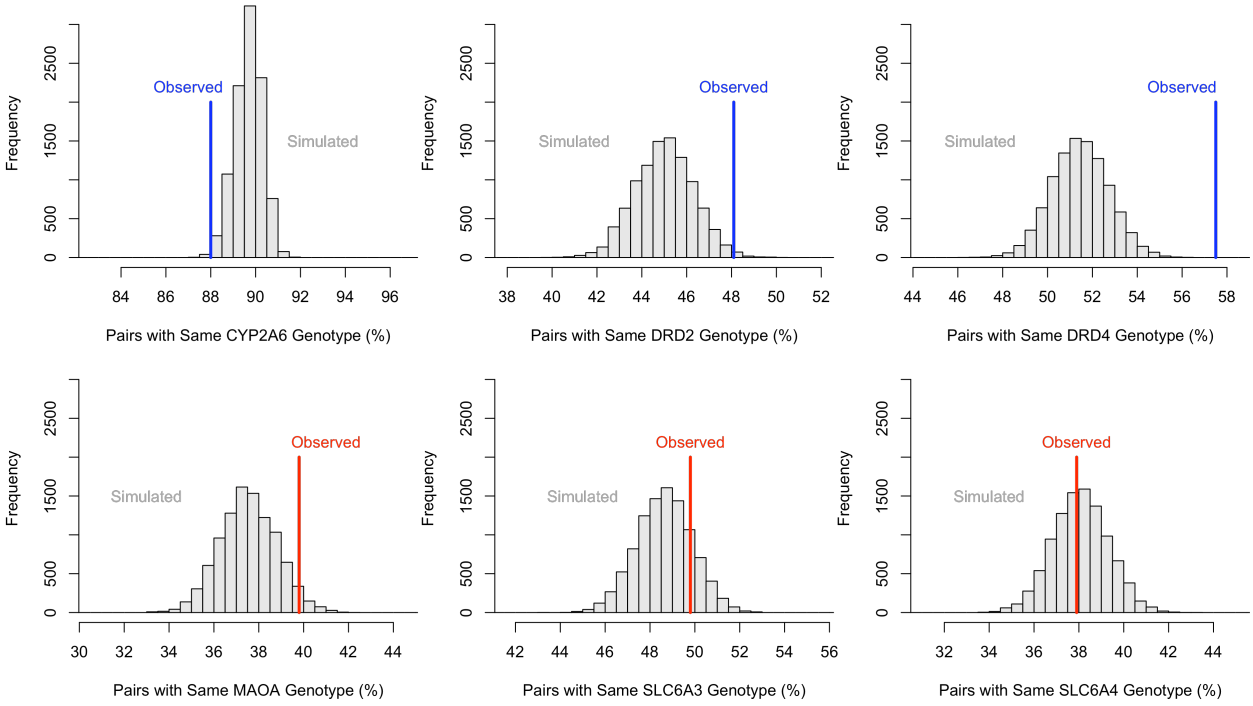
Note: Sample sizes between models differ due to availability of network information and genotypic information for subject and friend.

Table S5. Additional Replication of Association Between Subject and Friend's Genotype in the Framingham Heart Study on Nearby Unimputed SNP in Highest Linkage with rs1801272

	Dependent Variable: Friend's Genotype *Cytochrome P450 CYP2A6* (rs7251418)		
Independent Vars.	*Coef*	*SE*	*p*
***Subject's Genotype Minus Parental Mean Genotype* (w)**	**-0.57**	**0.28**	**0.04**
Parental Mean Genotype (b)	-0.47	0.29	0.10
Subject Female	0.78	0.62	0.20
Friend Female	-0.42	0.59	0.48
Subject's Age	-0.01	0.02	0.61
Friend's Age	0.01	0.02	0.35
Constant	0.20	0.24	0.40
MSE	66.3		
Null MSE	82.2		
N	177		

This table shows results of a linear regression of friend's genotype on subject's genotype with age and sex controls. The genotype used (rs7251418) is not imputed and is the highest linkage SNP near rs1801272 ($r = 0.30$, distance = 12.9k base pairs). Genotype takes the value 0, 1, or 2 depending on the number of minor alleles. Model was estimated using a general estimating equation with an independent working covariance structure and errors clustered on the subject. Models with an exchangeable correlation structure yielded poorer fit. MSE fit statistics show sum of squared errors between predicted and observed values for the model and a null model with no covariates. To reduce the likelihood of population stratification, we use the family transmission disequilibrium test (TDT) method, controlling for parental mean genotype and subtracting this value from the subject's genotype.

Figure S1. Monte Carlo Tests of Genotype Association in Friends



Comparison of observed rate of similar genotypes in friendship pairs to simulated rate in 10,000 Monte Carlo simulations in which friends' genotypes are randomly assigned, keeping the friendship network structure and genotype incidence constant. The results show that observed values fall at extreme percentiles in the tails of the simulated distribution (and therefore are very unlikely due to chance) for *CYP2A6* (0.27%), *DRD2* (99.21%), and *DRD4* (>99.99%). Observed percentiles for the other three genotypes are less extreme, and therefore more likely to have occurred by chance (96.12% for *MAOA*, 81.80% for *SLC6A3*, and 46.30% for *SLC6A4*).

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