Genetic and Family and Community Environmental Effects on Drug Abuse in Adolescence: A Swedish National Twin and Sibling Study

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Supplementary Methods

Our database contained ten sources:

1. The Swedish Hospital Discharge Register included all hospitalizations for people in Sweden from 1964-2009.

2. The Swedish Prescribed Drug Register included all prescriptions in Sweden picked up by patients from July 1, 2005 through 2009.

3. The Swedish mortality register contained all causes of death and time of death from 1961-2010.

4. The Population and Housing Censuses (In Swedish, FoB) provided information on household and geographical status in 1960, 1965, 1970, 1975, 1980, 1985, and 1990.

5. The Statistics Sweden's Total Population Register included annual census data on family and geographical status in 1990-2010.

6. The Multi-Generation Register included information on family relationships for all individuals born in Sweden in 1932 and later.

7. The Outpatient Care Register included information from outpatient clinics covering all geographic regions in Sweden from 2001-2009, with information on an increasing number of clinics for each year during this period.

8. The Primary Health Care Register included outpatient primary care data on diagnoses and time for diagnoses 2001-2007 for 1 million patients from Stockholm and middle Sweden.

9 The Swedish Crime Register included national complete data on all convictions, including those for DA, from 1973-2011.

10. The Swedish suspicion register included national complete data on all individuals strongly suspected of crime, including DA, from 1998-2011.

Drug abuse (DA) was identified in the Swedish medical registries by ICD codes (ICD8: Drug dependence (304); ICD9: Drug psychoses (292) and Drug dependence (304); ICD10: Mental and behavioral disorders due to psychoactive substance use (F10-F19), except those due to alcohol (F10) or tobacco (F17)); in the Suspicion register by codes 3070, 5010, 5011, and 5012, which reflect crimes related to DA; and in the Crime register by references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offences (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2). DA was identified in individuals (excluding those suffering from cancer) in the Prescribed Drug Register who had retrieved (in average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives (Anatomical Therapeutic Chemical (ATC) Classification System N05C and N05BA) or Opioids (ATC: N02A). We restricted the diagnosis of DA to individuals above the age of 10 except from the prescribed drug register where the age limit was set at 18 years. Alcohol-related registrations were not considered a form of DA. This study was approved November 2011 by the Ethics Committee of Lund University in Malmö, Sweden.

Sample

The database was created by entering, from the Swedish Twin Registry, all twin pairs with known zygosity, and from the multi-generation registry, all full sibling pairs, all paternal half-sibling pairs and all maternal half-sibling pairs in the Swedish population. To avoid substantial right or left censoring, we excluded all sibling/twin pairs in which: 1) one or both siblings/twins in the pair was born before 1950 or after 1993; 2) one or both siblings/twins had died before 1973; and 3) one or both siblings/twins died before the age of 15. For the twin/sibling analysis we selected all twin pairs and all sibships including up to 4 members. From large sibships (n=30,936), we randomly selected 4 siblings for analyses. The numbers of twin and sibling pairs used for these analyses, broken down by sex, are seen in Table 1 in the published manuscript. Zygosity in the twin registry was assigned using standard self-report items from mailed questionnaires which, when validated against biological markers, were 95-99% accurate (1). The prevalence of DA is lower in both males and females in monozygotic (MZ) and same sex dizygotic (DZ) pairs versus opposite sex (OS) twin pairs and all siblings. This is because only the former were screened for cooperation because at least one member had to return a questionnaire and cooperation was lower in subjects with DA.

For the analysis of years of residence in the same household or community we selected from our database all full sibling, paternal half-sibling and maternal half-sibling pairs. We required that: 1) both siblings could, during the period 1960-2010, be linked to a household and geographical area; 2) the age difference between the siblings did not exceed 17; and 3) at least one sibling was registered with DA during the period 1973-2010. Under 3% of the original pairs did not meet criteria 1 and 2.

From the Statistics Sweden's Total Population Register which uses the population registration as a source and the Housing Census, we included information on household ID number for each sibling. From the total population register, we obtained the family ID number for each sibling within each pair. (A household refers to the person or group of persons

registered in the same municipality, and living in the same dwelling.) This allowed us to calculate the number of years each sibling pair resided within the same household. As the median age of leaving home was approximately 21 in Sweden during this time period (2), we set the upper limit for number of years living in the same household to 21. However, since age differences between siblings set a limit on the number of years of living together, we subtracted the number of years between siblings from 21; e.g., siblings born 2 years apart had 19 possible years of cohabiting. We also excluded sibling pairs who were living in the same household when the oldest sibling turned 29 (the 95th percentile of age at leaving home in Sweden (2), n=12,205 pairs). Preliminary analyses suggested that individuals with chronic mental illness were over-represented in these siblings.

The procedure for retrieving and filtering data on households was repeated for SAMS (small area market statistics, for convenience termed "small residential area") and municipalities in order to calculate the number of years each sibling pair resided within the same SAMS and the same municipality. In Sweden, SAMS are geographical units with boundaries defined by homogeneous building types and have an average of 1,000 to 2,000 inhabitants and approximate the concept of neighborhoods. However, between 1960-1985 we had no information on SAMS areas, and used parishes as a proxy for SAMS. Parishes serve as districts for the Swedish census and elections, and have approximately the same number of inhabitants as SAMS areas. Municipalities in Sweden are its lower-level government entities and are responsible for many local services. Today there are 290 municipalities in Sweden with populations ranging from 3,000 to 870,000. Our data structure was hierarchical. Households nested within SAMS nested within municipalities.

To examine the association between family socioeconomic status (SES) and community-level social depravation (SD), and risk for future DA, we selected all individuals born 1970-1985 registered in Sweden from year of birth to age 15, at age 15 living with at least one parent or grandparent, not registered for DA by age 15 and living in a SAMS with ≥50 individuals. 1,192,089 individuals met these criteria. The neighborhood-level SD variable for each SAMS was derived from register data for all residents aged 25-64 and contained the following: the proportion of residents with low education (9 years or less), the proportion of residents with low household income (below half the median income), the proportion of unemployed residents, and the proportion of individuals on social assistance (3). For each year, we ranked the SAMS areas into three equally sized groups by SD level: high, middle and low. Family SES was defined as annual household income and divided into three groups: high, middle and low. Both our predictor variables were defined when the individual was age 15. We also included in the model gender and parental education (highest education achieved: undergraduate or more (high), high-school diploma (mid), and compulsory school or missing education status (low)).

Statistical Methods

Twin/sibling models were fitted to the raw data using the full-information maximum likelihood estimation procedure available in OpenMx (4, 5). We assumed four potential sources of liability to DA: additive genetic (A), shared (or common) environment (C), special twin environment (T), and unique environment (E) components. Shared environment reflects family and community experiences that increase similarity in all twin/sibling pairs raised together, while T reflects those aspects of the environment that impact only on twins. Unique environment includes random developmental effects, environmental experiences not shared by siblings, and

random error. The importance of A, C, and T can be estimated from the patterns of twin and sibling correlations. A is suspected when correlations in MZ twins are substantially greater than those seen in DZ twins and siblings. C is likely to be present when the correlations in DZ twins and siblings exceed half of those seen in MZ twins (as this is the expected pattern if resemblance is due solely to genetic factors). T is suspected when the resemblance in DZ twins exceeds that seen in siblings.

We also tested for both quantitative sex effects (i.e., is the magnitude of genetic influences on DA the same in both sexes?) as well as qualitative sex effects (i.e., are the same genetic factors influencing risk to DA in men vs. women?) on genetic and environmental sources of variance. The goal of model fitting was to achieve an optimal balance of explanatory power and parsimony. We operationalized this goal using Akaike's information criterion (AIC) (6, 7). Lower values of the AIC indicate relatively better fits.

We tested for equality of thresholds for DA and found that we could equate thresholds across twin 1 and twin 2 within pairs, and across zygosity. We could not equate thresholds of same sex to those of opposite sex siblings or twins. Thresholds could not be equated across sexes. So, all our models assumed 8 thresholds (same sex male & female twin, opposite sex male & female twin, male & female sibling, and opposite sex male & female sibling).

For the analysis of years of residence in the same household or community, we conducted three sets of analyses all stratified by full siblings, paternal half-siblings and maternal half-siblings. First, we looked at aggregation of DA among sibling pairs and examined the dependent variable, DA in both siblings, as a function of the main predictor variable, years living in the same household. We stratified our analysis into five groups of sibling pairs by age difference (0-2, 3-5, 6-8, 9-11, and 12-18 years) because of prior evidence that resemblance for DA within sibling pairs was inversely related to their closeness in age (8). Furthermore, the impact of living in the same household on resemblance for DA in siblings might differ as a function of age differences. For each stratum, we controlled for age difference between siblings and the prevalence of DA in the male Swedish population of sibling pairs with the same number of years living together in the same household. We did this to avoid confounding factors which changed sibling resemblance for DA with those factors that might have impacted only on prevalence.

In our second set of cohabitation analyses, we examined aggregation of DA among sibling pairs as a function of years living in the same SAMS. Since years lived in the same SAMS is highly correlated with years lived in the same household, we could not estimate both parameters in the same model. Therefore, we excluded all sibling pairs that lived in the same household from the birth of the younger sibling until the oldest turned 21. This left us with sibling pairs that had different numbers of years during which they could have lived in the same SAMS. For example, pairs born 2 years apart that had lived in the same household for 10 years had 9 (21-2-10=9) years during which they could have resided in the same SAMS. We stratified our analysis into four strata according to number of years during which the sibling pair could have resided in the same SAMS: 1-5, 6-10, 11-15, and 16-21. In these models, DA in both siblings (yes/no) was used as the dependent variable and number of years living in the same SAMS area as the main predictor variable. In the model for each stratum, we controlled for difference in age between siblings, the prevalence of DA based on the male Swedish population with the same number of years living together in the same household.

In our third set of cohabitation analyses, we examined the aggregation of DA among sibling pairs as a function of years living in the same municipality. As this is highly correlated with number of years living in the same SAMS, we excluded all sibling pairs that had lived in

the same SAMS from the birth of the younger sibling until the oldest turned 21. We stratified the material in the same way as in the second analysis and modeled DA in both siblings as the dependent variable. In the models we controlled for difference in age between siblings, the prevalence of DA based on the male Swedish population with the same number of years living together in the same household, and the number of years living in the SAMS area.

All analyses were performed using generalized estimating equations where we took into account that there could be several sibling pairs from the same family. In all analyses we examined the linear effect of number of years within the same household/SAMS/municipality and we translated the beta-coefficient in the model to odds ratios (OR). In the first set of analyses, the OR represents the relative odds of DA in both siblings for each year the sibling pair shared the same household. In the second analyses, the OR represents the relative odds of DA in both siblings for each year they shared the same SAMS area, over and above the number of years they shared the same household; while in the third analysis it represents the relative odds of DA in both siblings for each year the sibling pair shared the same municipality over and above the number of years in the same SAMS area and household.

These analyses included only male sibling pairs. However, in a complementary analysis we included all sibling pairs (male, female and opposite-sex pairs) investigating the interaction between sibling pair type and the main predictor variables (number of years within the same household/SAMS/municipality). Because of different exposure periods based on time of birth, to examine the association between family SES and neighborhood-level SD, and subsequent DA in individuals, we utilized Cox Proportional Hazard regression where we investigated, from age 15, time to first registration of DA, death or end of follow-up (year 2011), whichever came first. As siblings from the same family could be included in the analysis, we adjusted for non-independence with a robust sandwich estimator. In the model we also included gender, parental education, the interaction between gender and family SES, and the interaction between gender and neighborhood-level SD. All statistical analyses were performed using SAS 9.2 (4). Although we had clear directional hypotheses – for example that residence in the same household, SAMS or municipality increased concordance for DA in sib pairs — to be conservative, we report two-tailed p values.

Supplementary Results

Model Fitting

As outlined in Table S2, we began with a full ACTE model with separate parameter estimates in the two sexes (i.e., quantitative sex effects). When compared with this full model, the fit was not improved by adding qualitative sex effects for additive genetic (model 2), shared environmental (model 3) or twin environmental factors (model 4).

We then constrained parameters to equality in the sexes. Again, compared to the full model, this could not be done for additive genetic effects (model 5), shared environment (model 6) or the twin environment (model 7).

Next, we tried to simplify the model by dropping parameters. We could not drop genetic effects when both sexes where considered together or separately (models 8-10). We could not drop shared environmental effects in both sexes or in males (models 11-12), but the model fit improved when it was dropped in females only (model 13). We could not drop twin environmental effects in both sexes or in males (models 14-15), but could drop them in females

only (model 16). We then fitted a model with no shared or twin environmental effects in females (model 17) which produced the best fit.

Descriptive Statistics for Full and Half-Siblings

Our twin-sibling modelling found that familial-environmental effects contributed substantially to risk for DA in males. Therefore, our second major set of analyses explored possible mechanisms for these effects. In particular, was resemblance for DA in sibling pairs associated with residing, during childhood and adolescence, in the same household or community? The sample size of MZ and DZ pairs containing at least one member with DA were too small to be useful for these analyses. To provide us the ability to replicate and extend findings from full siblings, however, we included maternal and paternal half-siblings.

Tables S3 and S4 provide descriptive statistics for, respectively, all male-male full and half-siblings pairs in Sweden born 1950-1993, and all pairs containing at least one member with DA divided by the difference in years apart of their birth.

Three trends are noteworthy. First, sibling resemblance is greatest in full siblings, intermediate in maternal half-siblings and lowest in paternal half-siblings. Second, as reported previously (8), controlling for the degree of genetic relationship, sibling similarity for DA is higher for siblings similar in age to those born many years apart. Third, we have considerably more full sibling pairs containing at least one member with DA (n= 66,251), than paternal (n=21,389) or maternal half-siblings (n=17,426).

Of the full sibling pairs containing at least one member with DA, 54.6% (36,205/66,251) did not live in the same household for the entire follow-up time period (until the older sibling turned 21). The parallel figures for maternal and paternal half siblings were, respectively 74.6% (12,994/17,426) and 96.1% (20,546/21,389). For those not living together for the entire follow-up period, paternal half-siblings were the most likely and full siblings the least likely to live apart for long periods of time. For example, of those not cohabiting for the entire follow-up period, only 6.5% (2,342/36,205) of full siblings lived apart for more than 10 years while the parallel figures were 22.6% for maternal (2,943/12,994) and 63.2% for paternal half-sibs (12,986/20,546). For those full siblings not living together during the entire follow-up period, 40.4% (14,618/36,205) resided for the entire period within the same SAMS. The parallel figures for maternal and paternal half-siblings were respectively 28.1% (3,647/12,944) and 9.3% (1,908/20,546).

Discussion of Limitations

These results should be interpreted in the context of seven potentially important methodological limitations. First, we detected subjects with DA from medical, legal and pharmacy records, with no need for accurate respondent recall. However, such administrative data contains both false negative and false positive diagnoses, the frequency of which we cannot estimate. An epidemiological study of DA conducted in neighboring Norway, which has similar rates of drug use and abuse (9, 10), found lifetime prevalence rates of DSM-III-R (11) DA similar to those found using our registry based methods (12). Substantial under-ascertainment of DA is unlikely.

Second, information on the specific drug abused was only available from the discharge and out-patients registries and so could not be utilized in our main analyses. For the 67,693

unique DA cases born between 1950 and 1993 and ascertained after 1997 – when ICD-10 was in use – from these registers, the four most common drug classes, in order, (and the % of sums to greater than 100% because subjects had multiple diagnoses) were: sedative/hypnotic (73%), stimulant (24%), opiate (22%), and cannabis (20%).

Third, we were only able to include same-sex twins whose zygosity was known as a result of at least one member responding to a mailed questionnaire. DA was associated with a reduced probability of returning questionnaires so the rate of DA was lower in pairs with known zygosity. This is a form of "concordance-dependent" ascertainment where the probability of known zygosity will be lowest in pairs concordant for DA, intermediate in those discordant for DA and highest in those where neither twin has DA (13). Simulations suggest that with the moderate level of differential ascertainment expected in our data given the observed prevalence differences, biases in parameter estimates are likely to be small with slight underestimations of genetic and shared environmental effects and overestimation of the effects of the individual-specific environment (13).

Fourth, a modest increase in rates of DA in Sweden is seen in recent years resulting partly from new detection methods (e.g., the out-patient and pharmacy registries) and partly from increased prevalence (Giordano et al, in review). Because cohort effects could simulate c^2 in twin models, we repeated our analyses using only the long stable in-patient, mortality and crime registries. Evidence for c^2 in males declined very slightly (from 0.23 to 0.21) indicating that evidence for shared environment does not result from the inclusion of newer forms of DA ascertainment. We also added cohort effects to our cohabitation analyses and saw no impact on results in our SAMS or municipalities analyses but with households saw a modest decline in cohabitation effects in full but not maternal or paternal half-siblings. We concluded that cohort effects were not substantially biasing our estimates of the impact of cohabitation on relative resemblance for DA.

Fifth, could our results artifactually arise from police practices? If an individual was arrested for DA, would police provide closer surveillance to a sibling living in the same household or nearby? To examine this possible bias, we repeated the cohabitation analyses presented here removing cases of DA identified only through the crime register. In no case did the pattern of findings substantially change.

Sixth, we previously showed in Sweden that DA is more frequently transmitted from older to younger siblings than vice-versa (8). We investigated whether such an effect could "drive" our cohabitation finding. We found no appreciable relationship between the years full siblings shared the same household and whether only an older or younger sibling had DA or when both had it whether the older vs. younger was registered first.

Seventh, our hypothesis is that residing in the same dwelling, SAMS or municipality increases sibling resemblance for DA. But could the causal effect go the other way? The mean ages (SD) at registration for DA in the older and younger full siblings in our sample were, respectively, 27.8 (9.8) and 25.5 (8.8). At the end of our observation period – when the older sibling is 21 – 12.8% of the older siblings and 6.8% of the younger siblings who would eventually be registered for DA had already been registered. If DA prolonged cohabitation, the effect would need to be very large for this small percentage of cases to drive our findings. We then directly examined, separately by sex and by decade of birth (from 1950-1993), the age at which individuals who were or were not eventually registered for DA leave home. In six of the eight comparisons (we counted birth years of 1980-93 as one decade), those who developed DA left home earlier than those who did not. While causality cannot be proven with observational

data, most of the association between siblings residing in the same home, SAMS or metropolitan area and their resemblance for DA probably results from cohabitation causing concordance.

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Table S1. Number of Twin and Sibling Pairs and the Tetrachoric Correlation for and Prevalence of Drug Abuse in these Pairs*

Sex	Pair type	Number of Complete Pairs	Number of Concordant Pairs	Number of Discordant Pairs	Tetrachoric Correlation	SE	Prevalence of Drug Abuse	
							Male	Female
Male-Male	monozygotic twins	3,899	47	122	+0.79	0.03	2.8%	
Male-Male	dizygotic twins	4,238	24	157	+0.58	0.06	2.7%	
Female-Female	monozygotic twins	4,558	20	98	+0.70	0.05		1.5%
Female-Female	dizygotic twins	4,313	8	110	+0.45	0.09		1.5%
Male-Female	dizygotic twins	12,447	45	663	+0.36	0.05	4.0%	2.1%
Male-Male	Full Siblings	718,276	7,792	49,908	+0.51	0.00	4.6%	
Female-Female	Full Siblings	641,506	1,139	20,133	+0.37	0.01		1.8 %
Male-Female	Full Siblings	1,347,324	4,063	76,392	+0.32	0.01	4.3%	1.7 %

*For full sibling pairs, we took all pairs within sibships up to size 4. With larger sibships, we picked 4 pairs at random.

Table S2. Results of Model Fitting

Model Number	Model	Description of Model – All Are Compared to Model 1	Δ -2Log Likelihood	Δ Degrees of Freedom	Δ AIC
1	ACTE	Full	--	--	--
2	$+R_g$	Estimate genetic correlation between sexes	-1.13	-1	+0.87
3	$+R_c$	Estimate shared environmental correlation between sexes	0.00	-1	+2.00
4	$+R_t$	Estimate twin environmental correlation between sexes	0.00	-1	+2.00
5	Equate a_m&a_f	Equate heritability across sexes	+7.06	+1	+5.06
6	Equate c_m&c_f	Equate shared environment across sexes	+16.42	+1	+14.42
7	Equate t_m&t_f	Equate twin environment across sexes	+11.27	+1	+9.27
8	Drop a_m&a_f	Drop Genetic Effects in both sexes	+421.8	+2	+417.8
9	Drop a_m	Drop Genetic Effects in males	+21.95	+1	+19.95
10	Drop a_f	Drop Genetic Effects in females	+5.43	+1	+3.43
11	Drop c_m&c_f	Drop shared environment in both sexes	+443.0	+2	+439.0
12	Drop c_m	Drop shared environment in males	+107.0	+1	+105.0
13	Drop c_f	Drop shared environment in females	+1.10	+1	-0.90
14	Equate t_m&t_f	Drop twin environment in both sexes	+9.53	+2	+5.53
15	Drop t_m	Drop twin environment in males	+2.01	+1	+0.01
16	Drop t_f	Drop twin environment in females	+0.16	+1	-1.84
17*	Drop t_f&c_f	Drop shared and twin environment in females	+1.22	+2	-2.78

AIC: Akaike's Information Criterion (19). R_g – genetic correlation between the sexes. R_c – shared environmental correlation between the sexes. R_t – twin environmental correlation between the sexes. a – additive genetic effects; c – shared environmental effects; t – special twin environmental effects; m – male; f – female

Table S3. Odds ratios for resemblance of DA between all sibling pairs. Calculated from the entire population of male-male siblings pairs in Sweden with birth years 1950-1993.

	0-2 birth years apart	3-5 birth years apart	6-8 birth years apart	9-11 birth years apart	12-18 birth years apart
Full siblings	8.63 (8.24–9.03)	8.51 (8.17–8.86)	7.23 (6.80–7.69)	6.63 (6.04–7.27)	4.98 (4.38–5.66)
Paternal half sibling	2.04 (1.71–2.42)	2.13 (1.90–2.39)	2.14 (1.93–2.37)	2.16 (1.92–2.42)	1.90 (1.70–2.12)
Maternal half siblings	4.06 (3.27–5.05)	3.29 (2.97–3.65)	2.82 (2.56–3.11)	2.63 (2.34–2.95)	2.29 (2.03–2.59)

Table S4. Descriptive statistics of the number of male-male sibling pairs in Sweden with birth years 1950-1993 where at least one was identified as a drug abuser. Divided by number of birth years apart and into full siblings, paternal half siblings and maternal half siblings.

	0-2 birth years apart	3-5 birth years apart	6-8 birth years apart	9-11 birth years apart	12-18 birth years apart
Full siblings					
N pairs	19,707	26,736	11,817	5,118	2,873
Concordant pairs (DA)	2,987 (15.2%)	3,459 (12.9%)	1,382 (11.7%)	558 (10.9%)	245 (8.5%)
Paternal half sibling					
N pairs	1,999	4,181	5,204	4,439	5,566
Concordant pairs	178 (8.9%)	405 (9.7%)	499 (9.6%)	386 (8.7%)	408 (7.3%)
Maternal half siblings					
N pairs	844	4,096	4,999	3,776	3,711
Concordant pairs	134 (15.9%)	568 (13.9%)	593 (11.9%)	374 (9.9%)	295 (8.0%)

Table S5. Odds Ratio (95% CIs) for Degree of Resemblance for Drug Abuse in Maternal versus Paternal Half-Siblings As A Function of Years Difference in Birth

	Model A (OR)	Model B (OR)	Model C (OR)
0-2 years apart	1.83 (1.42; 2.37)	1.08 (0.76; 1.55)	1.05 (0.72; 1.54)
3-5 years apart	1.50 (1.31; 1.72)	1.08 (0.90;1.29)	1.07 (0.88;1.29)
6-8 years apart	1.27 (1.12; 1.44)	0.98 (0.83; 1.16)	0.96 (0.81; 1.14)
9-11 years apart	1.15 (0.99; 1.34)	1.06 (0.88; 1.28)	1.02 (0.84; 1.24)
12-18 years apart	1.08 (0.93; 1.27)	1.04 (0.87; 1.25)	0.98 (0.93; 1.03)

Model A contains no covariates. In model B, we covary for the number of years residing together in the same home up to age 21 in the older siblings. In model C, we covary for the number of years residing together in the same home, number of years living in the same SAMS (when not living in the same home) and number of years living in the same municipality (when not living in the same home/SAMS) up to age 21 in the older sibling.