Modeling Extended Twin Family Data II: Power Associated With Different Family Structures

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Modeling the data from extended twin pedigrees allows the estimation of increasing complex covariance relationships in which the effects of cultural transmission, nonrandom mating and genotype x environment covariation can be incorporated. However, the power to detect these effects in existing data sets has not yet been examined. The present study examined the effects that different family structures (i.e., the ratio of MZ to DZ families and the importance of cousins vs. avuncular relatives) have on statistical power. In addition, we examined the power to detect genetic and environmental effects within the context of two large data sets (VA30K and the OZVA60K). We found that power to detect additive genetic and cultural transmission effects were maximized by over sampling MZ families. In terms of ascertainment, there was little difference in power between samples that had focused on recruiting a third generation (the children of twins) versus those that had focused on recruiting the siblings of the twins. In addition, we examined the power to detect additive and dominant genetic effects, cultural transmission and assortative mating in the existing VA30K and OZVA60K samples, under two different models of mating: phenotypic assortment and social homogamy. There was nearly 100% power to detect assortative mating and cultural transmission, against a background of small additive and dominant genetic and familial environmental effects. In addition, the power to detect additive or dominant genetic effects quickly asymptoted, so that there was almost 100% power to detect effects explaining 20% or more of the total variance. These results demonstrate that the *Cascade* model has sufficient power to detect parameters of interest in existing datasets. Mx scripts are available from www.vipbg.vcu.edu/~sarahme/cascade.

Keywords: Structural equation modeling, Multigenerational pedigrees, Cascade/Stealth model

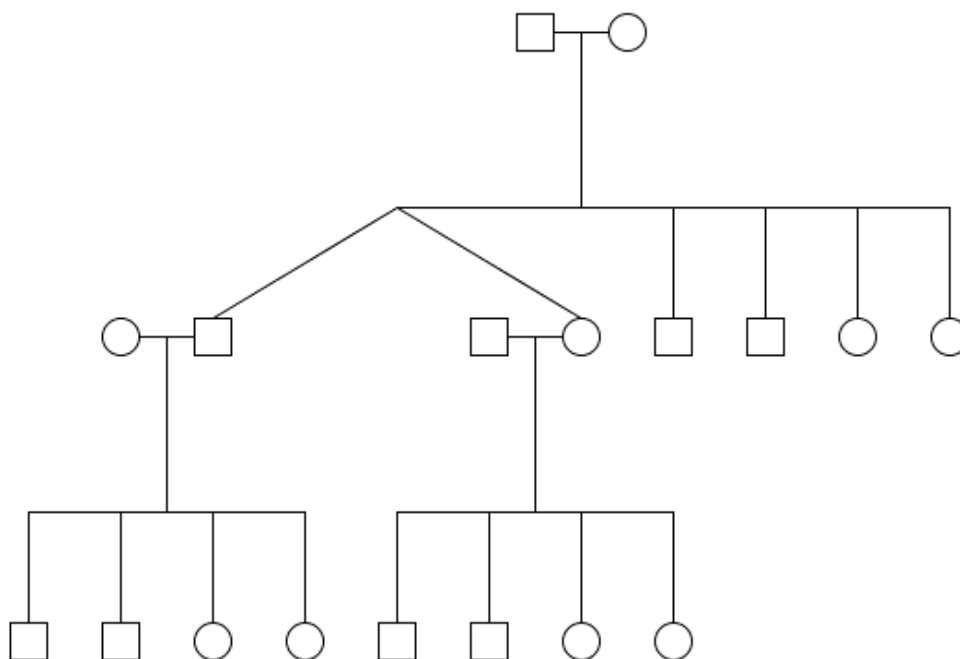By incorporating increasingly complex models of assortment and vertical transmission, the estimates of the genetic and environmental effects provided by the *Stealth* (Eaves et al., 1999) and *Cascade* model (Keller et al., 2008) may provide more accurate models of inheritance than those specified by more models that require more assumptions, such as the classical twin design. However, for the majority of traits analyzed to date (Eaves, 2008; Eaves et al., 1999) there has been little or no evidence of vertical transmissions, and several traits have shown no evidence of mate assortment. One possible explanation for these null results is that there was insufficient power to detect small effects with the samples analyzed.

Previous work by Heath et al. (1985) examined the power of various extended twin, adoptive and nuclear family designs to detect genetic and environmental effects influencing the covariation between relatives. Heath et al. considered the power of four extended-twin models consisting of (a) MZ and DZ twins and their parents, (b) MZ twins and the children of one twin (c) MZ twins and the children of both twins and iv) MZ and DZ twins and their children. They found that the twin and parent model was the generally the most powerful extended twin design for detecting both genetic effects and cultural transmission. However, as highlighted within the discussion in their simulations Health et al., assumed the pairs of relatives were sampled independently and with equal frequencies.

The current article aims to extend the work of Heath et al. (1985) by examining the power of the *Cascade* extended twin design, taking into account the dependence and different relationship frequencies which arise when families are ascertained as a whole. Although the *Stealth* and *Cascade* models, allow for the analysis of extended families of up to 18 individuals shown in the pedigree diagram Figure 1, within most contemporary western societies the average family size is reducing. As such, the use of extended family designs involves increasing amounts of missing

Figure 1
Pedigree diagram of the family structure of used within the *Stealth* and *Cascade* models.

data (which may or may not be missing at random). In the first set of simulations we explored the effects of MZ/DZ ratio on power, while the second explored the effects of sample structure (varying the number of families that collected data from either the siblings or the children of the twins). The third set of simulations addressed the issue of power in previous analyses by examining the power to detect effects within the context of the VA30K and OZVA60K samples. In each case the simulations focused on the power to detect the additive (V_A) and nonadditive (V_D) genetic effects, assortative mating and culturally transmitted family environmental (V_F) effects using the *Cascade* model.

MZ:DZ Ratio

Due to the differential sharing of genetic and environmental effects between MZ and DZ twins, the zygosity ratio of a sample influences the power to detect genetic and environmental effects. For example, within the context of the classical twin design the power to detect additive genetic effects when the covariation between relatives is due solely to additive genetic effects is maximized when the ratio of MZ to DZ twins is 2:1. While, power to detect non-additive genetic effects is maximized when the ratio is 4:1 (Martin et al., 1978; Neale et al., 1994; Visscher, 2004; Visscher et al., 2008). Thus, even in the simple case of the classical twin design in which only two relative types are modeled, the maximally informative ascertainment strategy is not readily apparent.

This problem is magnified in the context of extended twin family models. When allowing for sex differences in relative pairings the *Stealth* and *Cascade* models incorporate data from 88 relative types. In the absence of sex differences this reduces to the 19 relative types shown in Table 1. Given that most extended twin family studies begin by collecting the central twin pair, and then grow outwards, we examined the affects of the MZ:DZ ratio on power.

Methods
GeneEvolve (a simulation package which allows population level simulation across generations allowing for assortment and vertical transmission, available for download at www.matthewckeller.com) was used to simulate variance/covariance matrices. Data were sampled from the simulated population in which additive genetic (V_A) effects accounted for 18% of the variance, non-additive genetic (V_D) and culturally transmitted familial effects (V_F) each accounted for 16% of the variance and unique environmental influences (including measurement error: V_E) accounted for 34% of the variance. Within the data, the trait values of spouses correlated at .2 due to total phenotypic assortment. The presence of vertical transmission induced a correlation between the additive genetic and familial environmental factors which explained the remaining 16% of the variance (CV_{AF}). No twin (V_T) or sibling specific (V_S) environmental effects were included and parameters did not differ between the sexes.

Data were then simulated for a continuous normally distributed trait, using the *mvrnorm* function (empirical = FALSE) within R using the variance/covariance matrix produced by GeneEvolve as input data.[1] Three rounds of data were simulated varying the number of MZ and DZ families (40:160; 100:100; 160:40). Each family contained 18 relatives, with no

Table 1

Types and Frequencies of Relationships for the Family Shown in Figure 1 (Collapsing Over Sex) and the Coefficients of Additive and Dominant Genetic Sharing of These Relationships Within the *Cascade* Model

Relationship Type	Frequency by zygosity		Additive genetic coefficients		Dominance coefficients
	MZ	DZ	No assortment	Allowing for assortment*	
Spouse	3	3	0	$\delta^2\mu\delta^2$	0
Parent child	28	28	.5	$.5(\delta + \delta\mu\tau^2)$	0
MZ twin	1	0	1	$1 + \delta^2\mu$	1
DZ twin	0	1	.5	$(1 + \delta^2\mu)-.5$	.25
Sibling (inc twin-sib)	20	20	.5	$(1 + \delta^2\mu)-.5$	.25
Grandparent–Grandchild	16	16	.25	$.25(\delta + \tilde{\delta}\mu\tau^2 + 2\tilde{\delta}\mu\tilde{\Delta})$	0
MZ avuncular	8	0	.5	$.5(\delta + \tilde{\delta}\mu\tilde{\Phi})$	0
DZ avuncular	0	8	.25	$.5(\theta + \tilde{\delta}\mu\bar{\Omega})$	0
Sib avuncular	32	32	.25	$.5(\theta + \tilde{\delta}\mu\tilde{\Xi})$	0
MZ spousal avuncular	8	0	0	$\delta^2\mu\tilde{\Gamma}$	0
DZ spousal avuncular	0	8	0	$\delta^2\mu\bar{\Theta}$	0
MZ cousin	22	0	.25	$.5(\xi + \delta\mu\tilde{\Gamma})$	0
DZ cousin	0	22	.125	$.5(\lambda + \delta\mu\bar{\Theta})$	0
MZ in-law	1	0	0	$\tilde{\Phi}\mu\delta^2$	0
DZ in-law	0	1	0	$\bar{\Omega}\mu\delta^2$	0
Sib in-law	8	8	0	$\tilde{\Xi}\mu\delta^2$	0
Parent in-law	4	4	0	$\delta^2\mu\tilde{\Delta}$	0
MZ spouses in-law	2	0	0	$\delta^2\mu^2\tilde{\Phi}\delta^2$	0
DZ spouses in-law	0	2	0	$\delta^2\mu^2\tilde{\bar{\Omega}}\delta^2$	0
Total	153	153			

Note: * Following the notation of Keller et al. (current issue).

missing data, resulting in a sample size of 3600. In each case we simulated 500 replicates. Each replicate was analyzed using the *Cascade* model in which all effects had been set to be equal between the sexes and there were no twin or sibling environmental effects. For each parameter tested, we compared the minus twice log-likelihoods (–2LL) from the full model to the –2LL's from a series of models in which the Additive genetic, Familial environmental, Dominant genetic parameters, or the Covariation between spouses were set to zero. Note that the additive genetic variance here refers to the total additive genetic variance which includes the influences of assortment on the additive genetic variance. Power was calculated as the percentage of the 500 replicates in which the given effect was significant at a *p* value of .05.

Results and Discussion

The results of the simulations are shown in Table 2. Ceiling effects were observed when attempting to estimate the power to detect nonrandom mating. As the current sample contained 600 spouse pairs, and the covariation between the spouses is modeled as a simple correlation, high power was expected.

Ceiling effects were also observed when trying to estimate the power to detect non-additive genetic effects. In addition to the twin pairs, information regarding dominant genetic effects is gained from the 20 pairs of siblings per family, who are expected to

share both copies of an allele at a locus a quarter of the time. Conversely, dominance does not contribute to the correlations of 132 of the 153 relative pairings arising from the pedigree structure in Figure1, as dominance is not influenced by assortative mating. Thus, high power to detect nonadditivity within the full pedigree structure may be expected.

The contribution of additive genetic effects to the pattern of covariances between relative is much more complex. In the absence of assortment, DZ twins, parent–child, sibling, and MZ avuncular pairs are expected to share on average half their genes. With an additional 56 pairs in DZ families and 70 pairs in MZ families expected to share one quarter of their genes, and 22 cousin pairs in DZ families sharing one eighth of their genetic information.

Allowing for assortative mating increases the coefficient of relatedness and requires the evaluation of a nonlinear constraint, which decreases the precision of the estimates of additive genetic effects, and induces covariation due to additive genetic effects in the 26 pairs who would otherwise be uncorrelated. As a result of this complex pattern of covariation the power to detect additive genetic effects, although high, is not subject to a ceiling effect — a somewhat counter-intuitive finding. As shown in Table 2, the power of detect additive genetic effects is greatest when maximising the number of MZ families ascertained. Similarly, the power to detect familial environmental

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Table 2

Power to Detect Additive Genetic (V_A), Familial Environment (V_F), Nonadditive Genetic Effects (V_D) and Assortative Mating (Am) by MZ:DZ Ratio

Simulation	N MZ families	N DZ families	Sample size	Power			
				V_A	V_F	V_D	Am
1	40	160	3600	0.63	0.92	1	1
2	100	100	3600	0.82	0.98	1	1
3	160	40	3600	0.89	0.99	1	1

effects arising from vertical transmission were also increased, albeit marginally, when the maximising the number of MZ twins. Given the complexity of optimising when allowing both assortment and vertical transmission it appears likely that the observed increase in power to detect A and F as the MZ:DZ ratio increases is due to improvements in the ability to estimate the increase in genetic sharing due to assortative mating, which is bounded by nonlinear constraints.

Most volunteer registries contain more MZ than DZ pairs, and while this imposes limitations on the power when using a classical twin design, the results of the current simulations suggest that this may be a boon when using extended twin family design. In addition, these results highlight the high statistical and exploratory power of extended family designs when dense family data is available. However, as these types of dense pedigrees decreasing within most western populations, we undertook a second round of analyses that examined the relative importance of ascertaining families with children of twins versus avuncular relatives.

Children of Twins Versus Avuncular Relatives

The *Stealth* and *Cascade* model focus on three generational pedigrees, in which the first generation are parents of the twins and the third generation are children of the twins. However, the extent to which this sampling structure is successful depends largely on the age of the twins. In samples centered on older twin pairs, the data from the first generation tends to be sparse, and less sibling data is available. However, this maybe partially ameliorated as data on the first generation is often indirectly available from the twins' reports. Conversely, studies with younger twins tend to have more data from the twins' siblings but little data from the third generation. We examined the effects of these cohort related problems on the power to detect Additive genetic, Familial environmental, Dominant genetic effects, and Assortative mating.

Methods

The data simulation technique, model parameters and procedures described above were used in these simulations. Three rounds of data were simulated varying the number families with data from a third generation (40:160; 100:100; 160:40), and three in which the number families with data from the twins' siblings was varied (40:160; 100:100; 160:40). In each case 500 replicates were simulated. We employed the same

procedures for determining statistical power as described above. Equal number of MZ and DZ families were simulated.

Results and Discussion

The results of the simulations are shown in Table 3. Considering first the simulations that varied the number of families with data from the third generation, the high power to detect assortative mating is again apparent. Even with only 240 pairs of spouses the power to detect assortative mating ($r = .2$) approached 90%. Interestingly, while the power to detect F and D asymptote quickly, the power to detect A increases quite slowly, perhaps as a consequence of nonlinear constraints and the difficulty in estimating the increase in additive genetic variance due to assortment.

Within the simulations that varied the number of families with avuncular data, we once again observed ceiling effects in the power to detect assortative mating and nonadditive genetic effects. Similarly, the power to estimate F asymptotes almost immediately, while the power to detect A slowly increases with sample size. This seemingly unintuitive result was mirrored in sensitivity analyses looking at the variances and covariances of parameter estimates, in which the estimate of A had a high variance relative to estimates of D and F (Keller et al., forthcoming).

As shown from a comparison of simulations 6 and 8 it appears to make little difference in term of power as to whether researchers collect data from the twins' children or their siblings. Thus, to the extent that missing data patterns reflect sampling strategy rather than nonrandom missingness, which might arise if an individuals trait value influenced their chances of finding a mate and producing offspring, the structure of the missingness does not appear to have a marked effect on power. Given these results we went on to examine the power of two existing data sets, the VA 30K and the OZVA0K.

VA30K and OZVA60K

Although extended twin family data is invaluable in examining the etiology of behavior, the intensive nature of the sampling strategy has meant that only a few samples of this type have been collected. The Virginia 30,000 Health and Life-Style Questionnaire for Twins (VA30K) and Australian Health and Life-Style Questionnaire data are notable exceptions. The

Table 3

Power to Detect Additive Genetic (V_A), Familial Environment (V_F), Nonadditive Genetic Effects (V_D) and Assortative Mating (Am) Whilst Varying the Number of Families With Data From (a) the Third Generation (Children of Twins') and (b) Avuncular Relatives (Siblings of Twins')

(a)	Number of families		Sample size	Power			
Simulation	With 3rd generation	No 3rd generation		V_A	V_F	V_D	Am
4	40	160	2000	0.26	0.60	0.72	0.89
5	100	100	2600	0.54	0.83	0.97	0.98
6	160	40	3200	0.71	0.96	1	1
(b)	Number of families		Sample size	Power			
Simulation	with avuncular	No avuncular		V_A	V_F	V_D	Am
7	40	160	2960	0.69	0.89	1	.99
8	100	100	3200	0.75	0.93	1	1
9	160	40	3400	0.77	0.95	1	1

most common family structures within these samples are summarized in Table 4.

The (VA30K) consists of the kinships (n = 30,000) of 14,763 twin men and women aged 18 to 88 years. The data were collected in the late 1980s, and included assessments of political and social attitudes, socio-demographics, personality traits, and life-events. The majority of the twins were recruited from the Mid-Atlantic Twin Registry. However, the inclusion of a subsample recruited from American Association of Retired Persons has meant that data is available for a large number of children of twins. Detailed information on the sample, response rates, and sampling technique can be found in Eaves et al. (1999) and Truett et al. (1994).

The participants of the Australian Health and Life Style (AHLS) studies were originally recruited from the Australian National Health and Medical Research Council Twin Registry (ATR), a volunteer register begun in 1978, which has more than 30,000 twin pairs enrolled in various stages of active contact. The first health and lifestyle questionnaire study, conducted in 1980–1982, was sent to all available twin pairs, and where available their parents and siblings aged over 18

at that time (i.e., born prior to 1965). A second study was conducted in 1988–1990 and focused on those twins who responded to the original survey.

Because of the general nature of both the VA30K and the AHLS studies there are numerous phenotypes that have been collected for both samples. A number of phenotypes, including neuroticism (Lake et al., 2000), religiosity (Kirk et al., 1999) and smoking (Maes et al., forthcoming) have been analyzed jointly in the two samples, which are collectively referred to as the OZVA30K. As suggested by the modal family structures shown in Table 4, the patterns of missingness within the OZVA30K sample is very complex. Thus, to determine the power of previous studies using these data, we examined the power to detect Additive genetic, Familial environmental, Dominant genetic effects, and Assortative mating within the VA30K and the OZVA60K samples.

Methods

Power was examined for a range of scenarios by varying V_A, V_F, V_D or CV_{SPOUSE} from .1 to .5 (with increments of .1) while holding the other parameters constant (CV_{SPOUSE}=.2, V_D =.2, V_F =.2, V_E =.4). No twin

Table 4

Five Most Commonly Observed Family Structures in the Virginia 30K and the Australian Health and Lifestyle Survey Samples

Virginia 30K		Australian Health and Lifestyle	
Most common family structures	*%*	*Most common family structures*	*%*
Twins only	24	Twins only	48
Twins + spouse(s)	14	Twins + spouse(s) + sib(s) + parent(s)	20
Twins + spouse(s) + child(ren) of 1 twin	8	Twins + sib(s) + parent(s)	10
Twins + parent(s)	6	Twins + parent(s)	4
Twins + sib(s)	6	Twins + spouse(s) + parent(s)	3
Summary statistics	*%*	*Summary statistics*	*%*
Families with child(ren) of 1 twin	20	Families with child(ren) of 1 twin	7
Families with child(ren) of both twins	11	Families with child(ren) of both twins	4
MZ families	45	MZ families	43
Families with 3 generations	1.5	Families with 3 generations	5

(V_T) or sibling specific (V_S) environmental effects were included and parameters did not differ between the sexes. Each scenario was simulated once under total phenotypic assortment and once under social homogamy. GeneEvolve was used to simulate variance/covariance matrices from populations with the desired parameters. Using these variance/covariance matrices, data were then simulated for a continuous normally distributed trait, using the *mvrnorm* function (empirical = FALSE) within R. Data sets were simulated under each model following the sample size and missingness patterns observed within the VA30K and OZVA60K samples. The patterns of missingness in these simulations were based on self reported sex, and as such, may differ from those reported for other phenotypes.

This resulted in a total of 80 simulation scenarios (5 variants for each of the 4 variance components examined * assortative mating type * sample). In each case 400 replicates were simulated. Each replicate was analyzed using the *Cascade* model. We employed the same procedures for determining statistical power as described above.

Results and Discussion

Within these simulations there was 100% power to detect assortative mating and familial environmental (i.e., dropping these effects resulted in a significant loss of fit in all 400 simulations). The power to detect additive and dominant genetic effects is summarized in Table 5. Under both total phenotypic assortment and social homogamy, the power to detect additive or dominant genetic effects quickly asymptoted, so that there was almost complete power to detect effects explaining 20% or more of the total variance. Interestingly, the power to detect additive genetic effect was slightly higher under total phenotypic assortment than under social homogamy, whereas the reverse was true for dominant genetic effects. The increase in size of OZVA60K sample over the VA30K alone is reflected in the marked increase in power to detect additive genetic effects accounting for 10% of the variance. In comparison, there were only marginal increases in power to detect dominance when using the OZVA60K, perhaps reflecting the large number of AHLS families composed of a single twin pair. Thus, these simulations have shown that there is more than adequate power to detect assortative mating and vertical transmission within the VA30K and OZVA60K samples, and that there is very good power to detect both additive and dominant genetic effects.

A secondary finding arising from these simulations is that the analyses are highly sensitive to starting values. These analyses were initially run using the same start values for all analyses. For simulation runs where the start values approximated the true values fewer than 10 of the 400 simulations encountered optimization problems (IFAIL codes −1 or 6). However, in senarios where the start values were less precise, up to 60 of the 400 replicates resulted in optimization failures. In the present study we re-ran the analyses using more precise start values. However, in the context of a real data analysis it can be difficult to choose good start values because of the non-linear relationships between the variance components, and trying a 'grid' of start values may be the best solution.

In summary, the three series of simulations have shown the extensive power that can be derived from analysis of dense multigenerational pedigrees. Given the complex multidimensional parameter space of the *Cascade* extended twin family design, the simulated scenarios represent only a small number of situations in which we may be interested in determining power. For example, it would be interesting to examine the power of available samples to detect sex differences in vertical transmission and the extent to which vertical transmission distinguishable from qualitative and quantitative sex differences in genetic effects. To this end, a series of simulations focusing on the effects of model miss-specification and the power to differentiate phenotypic from social assortment is currently underway (Keller et al., 2008). We hope that the

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Table 5

Power to Detect Additive Genetic (V_A), and Nonadditive Genetic Effects (V_D) Within the VA30K and OZVA60K Samples Under Total Phenotypic Assortment and Social Homogamy.

V_A	V_D	VA30K Total phenotypic assortment	VA30K Social homogamy	OZVA60K Total phenotypic assortment	OZVA60K Social homogamy
.1	.2	68	58	92	83
.2	.2	93	89	97	97
.3	.2	98	94	97	99
.4	.2	93	95	96	97
.5	.2	95	93	99	99
.2	.1	42	53	55	61
.2	.2	89	93	87	98
.2	.3	98	97	99	99
.2	.4	99	97	100	99
.2	.5	99	97	100	99

current study will lead to additional investigations of this type and to increased use of extended twin and family designs.

Endnote

1 At present there is no option in GeneEvolve to allow the user to specify the structure of the families simulated. As the aim here was to examine the power to detect effects whilst preserving family structure, we chose to simulate data based on the results of the GeneEvolve results rather than use the raw data from GeneEvolve.

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