Putting the 'Human' Back in Genetics: Modeling the Extended Kinships of Twins

Lindon Eaves

Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, United States of America

Few papers have attempted to address the potential of extended kinships of twins to resolve the complexities of biological and cultural inheritance in humans. Since the mid-80s these issues have largely been buried beneath the quest for specific genes that contribute to individual differences in complex traits and liability to disease. The articles of Keller et al. and Medland and Keller (current issue) revisit these issues. History will decide whether these new papers represent the final gasp of a paradigm superceded by the 'new' genetics or contain the timely seeds of new birth in the face of a 30-year genetic research program otherwise poised on the cusp of degeneration (Lakatos & Musgrave, 1970).

The Classical Emphasis: Biological Inheritance

The study of human variation in the late 19th and early 20th century was energized by the theory that humans shared much, if not most, in common with other species and that differences could be understood by the same mechanical rules so patiently characterized by Mendel in his experiments in plant hybridization (1865) and by Pearson and Lee (1903) in their attempt to induce 'the laws of inheritance in man' from the correlations between relatives. Karl Pearson was the most forceful exponent of the view that even the 'inheritance of mental and moral characteristics in man' (1904) could be understood by the same principles of family resemblance that explained the inheritance of the 'protopodite of the waterflea'. The brilliant syntheses of Ronald Fisher's elaboration of the Mendelian polygenic theory of quantitative inheritance (1918) and the Genetical Theory of Natural Selection (1930) have retained their explanatory and heuristic power well into a new century. Indeed, linkage and genome-wide association studies of a magnitude that was almost inconceivable even a decade ago appear to vindicate the Fisherian paradigm of polygenic inheritance and confirm that the inheritance of many complex traits depends on the relatively small individual effects segregating at a remarkably large number of genes.

Taking the Environment Seriously

The triumphal procession of essentially 'biological' anthropology relegated the environment to a nuisance variable accounting for superficial differences that have no real scientific or practical significance. Fisher's detailed analysis of kinship correlations between multiple degrees of biological relatives for stature showed that this assumption appeared to be justified for physical traits. Pearson's earlier sweeping generalization of nineteenth century biology to behavioral differences (1904), based as it was upon ratings of sibling behavior only, savored of the same hubris implicit in the oft-repeated modern claim that 'molecular genetics will sort it all out'. Humans, however, 'do things' that have etiological implications. They structure and manage their social interactions, choose their mates, educate their children and seek to influence those around them whether or not to their benefit.

Francis Galton, though driven by fascination with the laws of family resemblance in humans (1869), recognized that a strictly biological interpretation might be unwarranted if families sharing biological advantages also had more than their fair share of significant social advantage. For Galton (1883) the 'history of twins' provided the key to unraveling the developmental implications of the environment. However, his depiction of the environment by analogy to the short-term effects of random eddies in the overwhelming downstream force of the current from birth to death reinforced a mechanical and reductionist model for human variation that left little room for human agency (e.g., Murphy & Brown, 2007).

Galton's early twin study fell far short of the standards of sampling and measurement that are prerequisites for modern studies. From the late 1920s to the end of the 1960s vast numbers of twin studies demonstrated that almost every measurable human trait — physical, physiological or behavioral — showed a significant heritable component. If the criticisms of twin studies could be disregarded, the case for the role of genes in human variation, and even in human behavior, was insurmountable. It was a matter of jest

Received 17 November, 2008; accepted 24 November, 2008.

Address for correspondence: Lindon Eaves, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA. Email: eaves.lindon@gmail.com

that, when clinicians were devoid of better ideas, they conducted a twin study to see if their favorite trait 'had' a heritability.

There were some exceptions, but such studies focused on resolving the sources of variation for those contributing to differences within pairs reared together. The 'equal environments assumption' notwithstanding, the twin study was presumed to control for the effects of the environment shared by family members, and its effects were largely unexamined.

There were occasional and significant exceptions. Empirical studies were not confined exclusively to twins living together. There were important studies of other relationships, notably separated twins (e.g., Bouchard et al., 1990; Shields, 1962) and adoption studies (e.g., Cadoret, 1978; Plomin & DeFries, 1985) that attempted to test for the effects of the shared home environment on human traits. From a theoretical perspective, psychologist Cyril Burt (Burt & Howard, 1965) recovered Fisher's model (1918) and explained it to a less technical readership. His inclusion of separated twins and adopted siblings permitted a primitive analysis of the effects of the home environment, though he noted that the effects of nonrandom placement might inflate the resemblance of foster siblings (Burt, 1966). Raymond Cattell (e.g., 1963) emphasized that human agency would lead to family resemblance for environmental as well as genetic influences, especially for behavioral traits, and offered the first illuminating exposition of genotype environment correlation between and within families. Subsequently, John Loehlin (1965) provided significant corrections to Cattell's initial equations, and Cattell's seminal work in this area was largely eclipsed by the conceptual, statistical and computational developments of the next decade.

The sheer number and complexity of Cattell's equations posed a problem for estimation and hypothesis testing that was, in part, resolved by John Jinks and David Fulker in their (1970) classic application of weighted least squares to the comparison of more parsimonious (linear) models.

Had behavioral genetics remained an arcane pursuit without social implications, the analysis of family resemblance might have proceeded slowly. However, Burt's espousal of a predominately genetic theory of differences in IQ were regarded by some as lying behind the marked inequalities of expenditure on secondary education in the United Kingdom. Arthur Jensen's (1969) attribution of race differences in measured IQ to genetic differences was viewed, rightly or wrongly, as an attempt to provide a core of scientific justification for the continuation of racism.

The standard of scientific debate was raised during the 1970s by a concern to 'get it right' and to permit genetic and social theories of human diversity to compete on a level playing field. Among the critical developments of that period were the extension of the theory of particulate Mendelian inheritance to model the nongenetic transmission and cultural evolution of human behavior (Cavalli-Sforza & Feldman, 1973; 1981), the recognition that social attitudes might provide a model system for testing the assumptions of a purely genetic model and exploring the implications of cultural inheritance (Eaves & Eysenck, 1974; Feldman & Cavailli-Sforza et al., 1982). The recovery of Sewall Wright's (1921) method of path analysis by Newton Morton (1973) and its application to family resemblance in IQ and education (e.g., Jencks et al., 1972; Rao et al., 1977,) provided the first attempt to integrate polygenic and cultural theories of inheritance. Whereas the models of Cavalli-Sforza and Feldman were largely binary, in the tradition of classical population genetics, the development of path models enabled the application of a unified model of quantitative inheritance to family resemblance. The principal feature of models for cultural inheritance was the nongenetic transmission of information between individuals in families and society (see also Eaves, 1976). The powerful critical and corrective appraisal of Arthur Goldberger (e.g., 1977, 1978) was motivated in part by the need for a thorough evaluation of this work by social scientists. This need became still more urgent following publication (Behrman et al., 1980) of the first twin study of inequality income and occupational attainment. Much of the empirical data underlying these studies were reviewed cogently in a series of lucid chapters by the late David Fulker (Fulker & Eysenck, 1979).

Integrating Biological and Cultural Inheritance

Different early models of biological and cultural inheritance made a variety of more or less arbitrary assumptions about the mechanisms of cultural inheritance and mate selection largely as a matter of prior conviction or mathematical convenience. The model of mate selection employed in many analyses of IQ in the United Kingdom (e.g., Burt, 1966; Eaves, 1973, 1975; Jinks and Fulker, 1970) followed the model that Fisher had applied to stature that assumed mate selection was based on the measured phenotype ('phenotypic assortative mating') or on a latent 'true' phenotype that was subject to measurement error ('phenotypic assortative mating with error', Heath et al., 1985). The first applications of path analysis in the same period assumed that assortment was based on socially determined covariates of the phenotype ('social homogamy', Morton, 1973). Similarly, the nongenetic transmission of information from parent to child was variously assumed to reinforce genetic (typically maternal) differences between the families ('G to E transmission'; e.g., Corey and Nance, 1974), depend on the social correlates of the phenotype ('E to E transmission'; e.g., Rice et al., 1978) or direct intergenerational influence of parents on children ('P to E transmission'; e.g., Eaves, 1976). The effects of cultural inheritance in the presence of genetic resemblance between relatives lead to correlation

https://doi.org/10.1375/twin.12.1.1 Published online by Cambridge University Press

between genetic and environmental effects shared by family members. In parallel with these developments, the possible interaction of familial differences with age and sex were considered (e.g., Eaves, 1977; Tambs et al., 1993). The 1970s were a decade of refining numerical methods for fitting constrained nonlinear models for family resemblance and exploring the algebra for different models of familial transmission.

This exploratory period culminated in 1979 with the publication by Robert Cloninger and his colleagues at St. Louis of the first path model that integrated Fisher's model of phenotypic assortative mating with the effects of vertical cultural inheritance ('P to E transmission'). This development provided the impetus to the systematic developments of the 1980s that lie behind the articles in this edition of *Twin Research and Human Genetics*.

Towards a General Model

By 1980, it was clear that future studies needed to address the nuances of mate selection, genetic and nongenetic inheritance, nonadditive genetic effects, and the effects of age and sex on the expression of genetic and environmental factors. Power calculations (e.g., Eaves, 1972; Martin et al., 1978) had shown that even classical twin studies needed to be one or two orders of magnitude larger to yield sufficiently precise parameter estimates for all but the most trivial models. The most appealing designs for the study of nongenetic inheritance involved adoptees or separated twins. These studies are powerful but difficult to conduct in the face of justifiable need to protect the privacy of adoptees and their families, and may require that the biases of placement and sampling be modeled in addition to those of genetic and nongenetic inheritance. A series of papers in the early 1980s recognized that the resolution of mechanisms of mate selection would be facilitated by the study of the spouses of related individuals such as twins (Eaves, 1980; Eaves & Heath, 1981) and/or siblings (Heath et al., 1985). Heath (1987) pointed out that the spouses of twins and siblings could also resolve the effects of mate selection on spousal resemblance from those on spousal interaction without recourse to longitudinal follow-up data on spouse pairs. Seminal work by Van Erdewegh (1982) on modeling mate selection in multivariate systems provided the intellectual foundations for a more general treatment of the nuances of mate selection. David Fulker provided a lucid exposition of the elements of an integrated model for mate selection and cultural inheritance (1989).

The effects of biological and cultural inheritance are confounded in studies of nuclear families. Rao et al. sought to identify the model by including 'environmental indices' (1974), but their use depended on the untested assumption that such indices were not themselves a function of genetic differences. This assumption is not warranted for many socio-economic covariates and behavioral covariates of liability to disease. Resolution of the effects of genes and shared family environment in studies of twins reared together depends critically on the assumption that mating is random and gene action is additive (see, e.g., Neale & Cardon, 1992). The study of twins and their parents combines the value of the twin study for estimating genetic effects with those of the nuclear family for estimating the effects of assortative mating and intergenerational transmission permitting some joint analysis of the effects of genetic and cultural inheritance (e.g., Fulker, 1982; Young et al., 1980).

Early work on the kinships of twins exploited the offspring of MZ twins ('MZ half siblings', Corey and Nance, 1974) to model the environmental effects of the maternal genotype. Hayley and Jinks (1983) extended the 'children of twins' design to include other parental relationships and to consider the implications of sex-linked and sex-limited inheritance. This early work provided the basic insight that the study of twins and their children might provide an alternative to the adoption study for the resolution of the biological and social effects of parents on their children. The basic logic is simple, though not foolproof. The monozygotic-cotwin of a biological parent is genetically identical to a parent but is socially an uncle or aunt. C*eteris paribus,* the excess of the biological parent offspring correlation over the 'monozygotic aunt–nephew/niece' correlation yields information about the nongenetic impact of parents on their children. Strictly, this is only unambiguously the case if mating is random, but the ambiguity can be resolved, with implications for power, by appropriate extensions of the design.

Putting it Together: The Extended Twin Kinship Design

Each of the component family-based designs — nuclear families, twins, twins and parents, twins and children, spouses of twins — provides information about some of the critical parameters of biological and cultural inheritance but none, by itself, could estimate them all and provide a test of the underlying model. It was not a major leap to see that combining all these elements into a single design might provide sufficient unique biological and social relationships to identify and estimate the parameters of a fairly general model and provide a test of goodness of fit. Thus, the 'Extended Twin Kinship Design' was born, comprising twins, their parents, spouses, offspring and siblings (see, e.g., Eaves et al., 2000). The addition of siblings of twins provided a test of the representativeness of twins and twin resemblance.

If analysis of the extended twin kinship design was confined to collateral relatives and relatives separated by only one generation (i.e., assuming that it would be difficult to obtain large enough adult samples to span three generations with self-report or face-to-face assessment) the design provided 88 unique biological and social relationships (i.e., distinct correlations

https://doi.org/10.1375/twin.12.1.1 Published online by Cambridge University Press

between relatives) allowing for the various unique configurations with respect to sex — more than enough to identify the parameters of quite general models for biological and cultural inheritance in the presence of assortative mating.

The first attempt to collect data systematically using the extended twin kinship design was undertaken in the mid-1980s under the auspices of the Virginia 30,000 (VA30K), followed by a comparable Australian study (the OZ25K) using many of the same measures.

In parallel with data collection, Eaves derived the first set of complete expectations for the 88 correlations under a model that allowed for phenotypic assortative mating, additive and dominant genetic effects, vertical phenotype to environment cultural inheritance, excess twin environmental resemblance and measurement error. The model allowed for different genes to be expressed in males and females (sex limitation) and for different cultural inheritance parameters as a function of the sexes of the parents and offspring and assumed that the effects of assortative mating and cultural inheritance on genetic correlations and genotype–environment correlations had reached equilibrium. The model was coded initially in FORTRAN with help from John Hewitt, Andrew Heath and Hermine Maes, and subsequently in programmed in Mx by Hermine Maes. The first application was published by Truett et al. (1994) using Church Attendance as a model variable likely to engage most of the nuances of a joint model for the effects of genes and environment.

The appearance of the path diagram (see, e.g., Eaves et al., 1999) led Lon Cardon to coin the name 'Stealth Model' because of superficial resemblance to the silhouette of a Stealth Bomber. David Fulker responded characteristically that 'you could shoot peas through it'.

The Stealth model has been applied to numerous variables, from the VA30K and OZ25K, including stature and conservatism (Eaves et al., 1999), church attendance (Truett, 1994; Kirk et al., 1999), personality and social attitudes (Eaves et al., 1999), mood (Kendler et al., 1994), BMI (Maes et al., 1997), alcohol consumption and church attendance (Maes et al., 1999). The latter application involved the first extension of the model beyond the univariate case and comprises part of the significant background to the generalizations described here.

Beyond 'Stealth'

The limitations of the Stealth model are numerous and obvious. The assumption of phenotypic assortment, with or without measurement error, is arbitrary and restricting, especially given that part of the appeal of the design its provision for testing alternative models of mate selection. Similarly, the model for vertical cultural inheritance assumes 'P to E' transmission. Furthermore, the model currently ignores any interaction between genetic or environmental effects and age. The latter is a particular problem because it is likely to inflate twin resemblance (because genetic effects are assessed at identical ages in cross-sectional data) and reduce intergenerational correlations relative to those between collateral relatives (because collateral relatives are more similar in age). These effects are likely to introduce biases that resemble the effects of genetic nonadditivity and special twin environment effects.

The articles in this edition of *Twin Research and Human Genetics* represent the first significant progress in modeling the extended kinships of twins in more than a decade. Discussion among the authors identified two necessary first goals. First, the model needed to be generalized to allow more flexible specification of the mechanism of mate selection and nongenetic inheritance. Achievement of this goal was facilitated by the recognition that many of the nuances of a more general univariate model for extended twin kinships could be captured as special cases imposed by varieties of constraints on a more generate bivariate version of the original Stealth model. This model has been appropriately renamed the 'Cascade' model by Sarah Medland in the attempt to minimize the military associations of 'stealth' and better to capture the essential 'cascading' qualities of vertical familial transmission. Second, a flexible algorithm for the simulation of extended twin kinships was needed if the biases introduced by the complexities of nonadditive genetic effects, genotype × age interaction and G × E interaction were to be explored and, ultimately, be modeled. A simulation program, *GeneEvolve* (available for download at http://www.matthewckeller.com/html/geneevolve.html), accurately simulates these and other complexities in genetically informative data. Early results indicate that extended twin family models work as designed, and that results are fairly accurate even in the presence of genotype × age and G × E interactions (Keller, Medland, & Duncan, in prep). It is a testimony to the industry and ability of a new generation of young scholars that they have accomplished what others had found too daunting.

Who Cares?

Thirty years ago, a workshop at Snowbird Utah (see Sing & Skolnick, 1979) heralded a new generation of optimism that the individual genes responsible for liability to complex disease would soon be identified, initially by segregation analysis of extended pedigrees (e.g., Elston & Stewart, 1971) then by genome-wide linkage analysis (e.g. Kruglyak & Lander, 1995) and, most recently, by genome-wide association analysis of increasingly large samples of cases and controls. As the hard-won findings of these studies are established (e.g., Diabetes Genetics Initiative, 2007; Easton & Eeles., 2008; Sklar et al., 2008), there is growing awareness that Fisher may have been right in 1918 and that the genetic component of quantitative variation indeed represents the cumulative effects of large numbers of genes of relatively small individual effect.

https://doi.org/10.1375/twin.12.1.1 Published online by Cambridge University Press

The optimism that molecular genetics, served by statistical genetics when needed, holds the principal key to prevention and treatment continues, but there are reasons to question that assumption in some circumstances. Improvement in quality of life and health may benefit as much from understanding the nature, distribution and transmission of social risk factors as their biological etiology. The genetic contribution to a wide range of human traits is often moderate at best. The environment and perhaps its interaction with genotype may still bear much of the burden of risk. Many of the salient environmental risk factors are familial, stratified in human populations and conceivably correlated with genetic differences. Although there are exceptions, the biological and social study of human differences have followed separate trajectories and been the source of unproductive misunderstanding, even antipathy, between the life and social sciences. The articles that follow represent an attempt to provide a deeper understanding of the subtleties of biological and cultural inheritance that may challenge the separation of the two research programs and provide new insight to both about intricacies that each has tended to ignore.

Acknowledgments

Model development, data collection and analysis have been supported by grants from the DHSS, the John M Templeton Foundation and RJR Nabisco.

References

Behrman, J. R., Hrubec, A., Taubman, P. & Wales, T. J. (1980). *Socioeconomic success: A study of the effects of genetic endowments, family environment and schooling*. Amsterdam: Elsevier.

Bouchard, T. J. Jr., Lykken, D. T., McGue, M., Segal, N. L., & Tellegen, A. (1990) Sources of human psychological differences, the Minnesota Study of Twins Reared Apart. *Science*, 223–228

Burt, C., & Howard, M. (1965) The multifactorial theory of inheritance and its application to intelligence. *British Journal of Psychology, 57*, 137–153.

Burt C. (1966) The genetic determination of differences in intelligence. *British Journal of Statistical Psychology, 9,* 95–131.

Cadoret, R. J. (1978) Psychopathology in adopted-away offspring of biologic parents with antisocial behavior. *Archives of General Psychiatry, 35,* 176–184.

Carey, G. (1986). Sibling imitation and contrast effects. *Behavior Genetics*, *16,* 319–341.

Cattell, R. B. (1963). The interaction of heredity and environmental influences. *British Journal of Statistical Psychology, 16,* 191–210.

Cavalli-Sforza, L. L., & Feldman, M. W. (1973). Cultural versus biological inheritance: Phenotypic transmission from parent to children (a theory of the effect of parental phenotypes on childrens' phenotypes). *American Journal of Human Genetics, 23,* 618–637.

Cavalli-Sforza, L. L., & Feldman, M. W. (1981). *Cultural transmission and evolution: A quantitative approach*. Princeton, NJ: Princeton University Press.

Cavalli-Sforza, L.L., Feldman, M. W., Chen, K. H., & Dornbusch, S. M. (1982). Theory and observation in cultural transmission. *Science, 218,* 19–27.

Cloninger, C. R., Rice, J., & Reich, T. (1979). Mutifactorial inheritance with cultural inheritance and assortative mating. *American Journal of Human Genetics, 31,* 178–188.

Cloninger, C. R., Bohman, M., Sigvardsson, S., & von Knorring., A. L. (1985). Psychopathology in adopted-out children of alcoholics: The Stockholm adoption study. In Galanter, M. (Ed.). *Recent Developments in Alcoholism* (3rd ed., pp. 37–51). New York: Plenum Press.

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena, R., Voight, B. F., Lyssenko, V., Burtt, N. P., de Bakker, P. I., Chen, H., Roix, J. J., Kathiresan, S., Hirschhorn, J. N., Daly, M. J., Hughes, T. E., Groop, L., Altshuler, D., Almgren, P., Florez, J. C., Meyer, J., Ardlie, K., Bengtsson Boström, K., Isomaa, B., Lettre, G., Lindblad, U., Lyon, H. N., Melander, O., Newton-Cheh, C., Nilsson, P., Orho-Melander, M., Råstam, L., Speliotes, E. K., Taskinen, M. R., Tuomi, T., Guiducci, C., Berglund, A., Carlson, J., Gianniny, L., Hackett, R., Hall, L., Holmkvist, J., Laurila, E., Sjögren, M., Sterner, M., Surti, A., Svensson, M., Svensson, M., Tewhey, R., Blumenstiel, B., Parkin, M., Defelice, M., Barry, R., Brodeur, W., Camarata, J., Chia, N., Fava, M., Gibbons, J., Handsaker, B., Healy, C., Nguyen, K., Gates, C., Sougnez, C., Gage, D., Nizzari, M., Gabriel, S. B., Chirn, G. W., Ma, Q., Parikh, H., Richardson, D., Ricke, D., & Purcell S. (2007) Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science, 316,* 1331–1336.

Easton, D. F., & Eeles, R. A. (2008). Genome-wide association studies in cancer. *Human Molecular Genetics, 17,* R109–115.

Eaves, L. J. (1972). Computer simulation of sample size and experimental design in human psychogenetics. *Psychological Bulletin, 77,* 144–152.

Eaves, L. J. (1976). The effect of cultural transmission on continuous variation. *Heredity, 37,* 69–81.

Eaves, L. J. (1977). Inferring the causes of human variation. *Journal of the Royal Statistical Society, 140,* 324–355.

Eaves, L. J. (1979). The use of twins in the analysis of assortative mating. *Heredity, 43,* 399–409.

Eaves, L. J., & Heath, A. C. (1981). Detection of the effects of asymmetric assortative mating. *Nature, 289,* 205–206.

https://doi.org/10.1375/twin.12.1.1 Published online by Cambridge University Press

Eaves, L. J., Heath, A. C., Martin, N.G., Neale, M. C., Meyer, J. M., Silberg, J. L., Corey, L. A., Truett, K., & Walters, E. (1999). Biological and cultural inheritance of stature and attitudes. In C. R. Cloninger (Ed.), *Personality and psychopathology* (pp. 269–309). New York: American Psychiatric Pub.

Eaves, L. J., Heath, A. C., Martin, N. G., Maes, H. H., Neale, M. C., Kendler, K. S., Kirk, K. M., & Corey, L. A. (1999). Comparing the biological and cultural inheritance of personality and social attitudes in the Virginia 30,000 study of twins and their relatives. *Twin Research, 2,* 62–80.

Elston, R. C., & Stewart, J. (1971). A general model for the genetic analysis of pedigree data. *Human Heredity, 21,* 523–542.

Fisher, R. A. (1918). The correlation between relatives on the supposition of Mendelian inheritance. *Transactions of the Royal Society of Edinburgh, 52,* 399–433.

Fisher, R. A. (1930) *The genetical theory of natural selection.* Oxford: Clarendon Press.

Fulker, D. W., & Eysenck, H. J. (1979). Nature and nurture. In H. J. Eysenck (Ed.), *The structure and measurement of intelligence* (pp. 102–174). New York: Springer-Verlag.

Fulker, D. W. (1982). Extensions to the classical twin method. In Bonne-Tamir B, Cohen T, Goodman RM (Eds.). *Human genetics, part A: The unfolding genome* (pp. 395–406). New York: Alan R. Liss.

Fulker, D. W. (1988). Genetic and cultural transmission in human behavior. In B. S. Weir, E..J. Eisen, M. M. Goodman, & G. Namkoong (Eds.), *Proceedings of the Second International Conference on Quantitative Genetics* (pp. 318–340). Sunderland, MA: Sinauer.

Galton, F. (1869). *Hereditary genius: An inquiry into its laws and consequences*. London: MacMillan.

Galton, F. (1883). *Inquiries into human faculty and its development*. New York: AMS Press.

Goldberger, A. S. (1977). Twin methods: A skeptical view. In P. Taubman (Ed.), *Kinometics: Determinants of socioeconomic success within and between families* (pp. 299–324). Amsterdam: North Holland.

Goldberger, A. S. (1978). The non-resolution of IQ inheritance by path analysis. *American Journal of Human Genetics, 30,* 442–445.

Haley, C. S., Jinks, J. L., & Last, K. (1981) The monozygotic twin half-sib method for analysing maternal effects and sex-linkage in humans. *Heredity, 46,* 227–38.

Heath, A. C., & Eaves, L. J. (1985). Resolving the effects of phenotype and social background on mate selection. *Behavior Genetics, 15,* 15–30.

Heath, A. C., Kendler, K. S., Eaves, L. J., & Markell, D. (1985). The resolution of biological and cultural inheritance: The informativeness of different relationships. *Behavior Genetics*, *15,* 439–465.

Heston, L. L. (1966). Psychiatric disorders in foster home reared children of schizophrenic mothers. *British Journal of Psychiatry*, *112,* 819–825.

Jencks, C. (1972). *Inequality: A reassessment of the effects of family and schooling in America.* New York: Basic Books.

Jensen, A. (1969). How much can we boost IQ and scholastic achievement? *Harvard Educational Review, 39,* 1–123.

Jinks, J. L., & Fulker, D. W. (1970). Comparison of the biometrical genetical, MAVA and classical approaches to the analysis of human behavior. *Psychological Bulletin, 73,* 311–349.

Keller, M. C., Medland, S. E., Duncan, L. E., Hatemi, P. K., Neale, M. C., Maes, H. H. M., & Eaves, L. J. (2009). Modeling extended twin family data I: Description of the Cascade model. *Twin Research and Human Genetics, 12,* 8–18.

Keller, M. C., Medland, S. E., & Duncan, L. E. (in prep.). Evaluating the bias and accuracy of the Cascade model via simulation.

Kendler, K. S., Walters, E. E., Truett, K. R., Heath, A. C., Neale, M. C., Martin, N. G., & Eaves, L. J. (1994). Sources of individual differences in depressive symptoms: Analysis of two samples of twins and their families. *American Journal of Psychiatry, 151,* 1605–14.

Kirk, K. M., Maes, H. H., Neale, M. C., Heath, A. C., Martin, N. G. & Eaves, L. J. (1999). Frequency of church attendance in Australia and the United States: Models of family resemblance. *Twin Research, 2,* 99–107.

Kruglyak, L., & Lander, E. S. (1995). Complete multipoint sib-pair analysis of qualitative and quantitative traits. *American Journal of Human Genetics, 57,* 439–454.

Lakatos, I., & Musgrave, A. (Eds.). (1970). *Criticism and the Growth of Knowledge.* Cambridge: Cambridge University Press.

Lake, R. I., Eaves, L. J., Maes, H. H., Heath, A. C., & Martin, N. G. (2002). Further evidence against the environmental transmission of individual differences in neuroticism from a collaborative study of 45,850 twins and relatives on two continents. *Behavior Genetics, 30*, 223–33.

Loehlin, J. C. (1965). Some methodological problems in Cattell's Multiple Abstract Variance Analysis. *Psychological Review, 72,* 156–161.

Martin, N. G., Eaves, L. J., Kearsey, M. J. & Davis, P. (1978). The power of the classical twin study. *Heredity, 40,* 97–116.

Maes, H. H., Neale, M. C., & Eaves, L. J. (1997). Genetic and environmental factors in relative body weight and human adiposity, *Behavior Genetics, 27*, 325–251.

Maes, H. H., Neale, M. C., Martin, N. G., Heath, A. C. & Eaves, L. J. (1999). Religious attendance and frequency

https://doi.org/10.1375/twin.12.1.1 Published online by Cambridge University Press

of alcohol use, same genes or same environments: A bivariate extended twin kinship model. *Twin Research, 2,* 169–179.

Maes, H. H., Neale, M. C., Kendler, K. S., Martin, N. G., Heath, A. C., & Eaves, L. J. (2006). Genetic and cultural transmission of smoking initiation: An extended twin kinship model. *Behavior Genetics, 36,* 795–808.

Medland, S. E., & Keller, M. C. (2009). Modeling Extended Twin Family Data II: Power associated with different family structures. *Twin Research and Human Genetics, 12,* 19–25.

Mendel, G. (1958). Experiments in plant hybridization. In E. W. Sinnott, L. C. Dunn, & T. Dobzhansky (Eds. & Trans.), *Principles of genetics* (pp. 419–443). New York: McGraw Hill.

Morton, N. E. (1973). Analysis of family resemblance. I. Introduction. *American Journal of Human Genetics, 26,* 318–330.

Rao, D. C., Morton, N. E., & Yee, S. (1974). Analysis of family resemblance II. A linear model for family correlation. *American Journal of Human Genetics, 26,* 331–359.

Rao, D. C., Morton, N. E., Elston, R. C., & Yee, S. (1977). Causal analysis of academic performance. *Behavior Genetics, 7,* 147–159.

Rice, J., Cloninger, C. R., & Reich, T. (1978). Multifactorial inheritance with cultural transmission and assortative mating. I. Description and basic properties of unitary models. *American Journal of Human Genetics, 30,* 618–643.

Shields, J. (1962). *Monozygotic twins.* Oxford: Oxford University Press.

Sing, C. F. & Skolnick, M. (Eds.). (1979). *Genetic analysis of common diseases: Applications to predictive factors in coronary disease.* New York: Alan R Liss.

Sklar, P., Smoller, J. W., Fan, J., Ferreira, M. A., Perlis, R. H., Chambert, K., Nimgaonkar, V. L., McQueen, M. B., Faraone, S. V., Kirby, A., de Bakker, P. I., Ogdie, M. N., Thase, M. E., Sachs, G. S., Todd-Brown, K., Gabriel, S. B., Sougnez, C., Gates, C., Blumenstiel, B., Defelice, M., Ardlie, K. G., Franklin, J., Muir, W. J., McGhee, K. A., MacIntyre, D. J., McLean, A., VanBeck, M., McQuillin, A., Bass, N. J., Robinson, M., Lawrence, J., Anjorin, A., Curtis, D., Scolnick, E. M., Daly, M. J., Blackwood, D. H., Gurling, H. M., & Purcell, S. M. (2008). Whole-genome association study of bipolar disorder. *Molecular Psychiatry, 13,* 558–569.

Tambs, K., Eaves, L. J., Mom, T., Neale, M. C., Naess, S., & Lund-Larsen, P. G. (1993). Age-specific genetic effects for blood pressure. *Hypertension, 22,* 789–95.

Truett, K. R., Eaves, L. J., Walters, E. E., Heath, A. C., Hewitt, J. K., Meyer, J. M., Silberg, J. L, Neale, M. C., Martin, N. G., & Kendler, K. S. (1994). A model system for the analysis of family resemblance in extended kinships of twins. *Behavior Genetics, 24,* 35–49.

Van Erdewegh, P. (1982). *Statistical selection in multivariate systems with applications in quantitative genetics.* PhD thesis, Washington University, St Louis.

Wright, S. (1921). Correlation and causation. *Journal of Agricultural Research, 20,* 557–585.

Young, P. A., Eaves, L. J. & Eysenck, H. J. (1980). Intergenerational stability and change in the causes of variation in personality. *Journal of Personality and Individual Differences, 1,* 5–55.

https://doi.org/10.1375/twin.12.1.1 Published online by Cambridge University Press