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Article

Nicholas (Nick) G. Martin and the Extended Twin Model

Hermine H. Maes

Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

Abstract

The extended twin model is a unique design in the genetic epidemiology toolbox that allows to simultaneously estimate multiple causes of variation such as genetic and cultural transmission, genotype–environment covariance and assortative mating, among others. Nick Martin has played a key role in the conception of the model, the collection of substantially large data sets to test the model, the application of the model to a range of phenotypes, the publication of the results including cross-cultural comparisons, the evaluation of bias and power of the design and the further elaborations of the model, such as the children-of-twins design.

Keywords: Extended twin model; genetic transmission; cultural transmission; extended pedigrees

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I first met Nick at the very first 'Twin Methodology' workshop held in Leuven, Belgium, in 1987, and Since then I have had the pleasure of seeing him at almost every workshop (at 34 right now and counting). I was lucky enough to be able to attend the first workshop as it was held at my alma mater. Then I helped organize the next, and from then on, I was invited to help teach them. Nick and I have spent countless sessions teaching 'the ACE model 101' together to hundreds of workshop participants, with the same level of enthusiasm from Nick as at the first workshop. It was this enthusiasm for science and the desire to improve how investigators analyze their data that attracted me to pursue this line of research and led me to move to Richmond for a postdoc with Lindon Eaves.

Although Nick had already moved on from Richmond to Brisbane to start his own genetic epidemiology unit, his first major data collection project was clearly inspired by the work he had done with Lindon. They had conceived the extended twin (ET) model. Recognizing the limitations of the classical twin study, which typically partitions the variance in a trait in additive genetic (A), common (C) and unique (E) environmental sources, they sought to extend it to include other relatives such as the parents, siblings, spouses and children of twins (COTs). These extensions allow one to both evaluate the consistency of the estimates of the genetic and environmental contributions to the variance across a range of relationships and estimate additional sources of variance confounded with simpler study designs. The ET model (Eaves, Heath, Martin, Neale et al., 1999) provides a test for environmental or cultural transmission as well as genetic transmission, thus dividing the shared environment into sources shared with parents and those shared with siblings but not parents. In addition, dominance variance can now be simultaneously estimated with shared environmental variance. Further excess environmental sharing in twins compared to siblings can be quantified as 'special twin environment' or reflect potential age-specific effects of genes. Sex differences in all these sources of variance can equally be evaluated. Finally, relationship through marriage provide information about the extent of assortative mating.

Thus, from the theory of the causes of variation in human behavior, they developed a model system (Truett et al., 1994) for the analysis of family resemblance in extended kinships of twins, and collected data on health and lifestyle from a large sample of twins and their relatives and then fitted their model to the data and started the 'stealth' revolution. A path diagram of the model resembled a stealth bomber, a fitting name for a powerful model. Questionnaire data were collected on thousands of twins and their relatives both in Virginia (the Virginia 30,000) and in Australia (the Australia 25,000), allowing researchers to this day to explore the complexities of the causes of variation in complex traits ranging from social attitudes (Eaves, Heath, Martin, Maes et al., 1999), depressive symptoms (Kendler et al., 1994), panic and phobias (Kendler et al., 1995), body mass index (Bergin et al., 2012; Maes et al., 1997), church attendance (Kirk et al., 1999), alcohol use (Maes et al., 1999; Verhulst et al., 2018), neuroticism (Boomsma et al., 2018; Lake et al., 2000), smoking initiation (Maes et al., 2018; Maes et al., 2006), political attitudes (Hatemi et al., 2009), and so on. Many of these publications would not have happened had it not been for Nick's generosity of data, time, encouragement, travel assistance and hospitality, discussing results over wine and good food, often accompanied by excellent classical music.

Through these interactions, Nick inspired graduate students and postdocs to further explore the ET model. While the first iterations and applications of the ET model were written in Fortran, we developed code in Mx and later in OpenMx (Maes et al., 2009) that allowed fitting it to raw data, to continuous and categorical data, incorporating covariates and extending it to the multivariate case (Maes et al., 1999). Alternative mechanisms of intergenerational transmission and assortment — phenotypic cultural transmission and social homogamy — were coded (Keller et al., 2009). New programs were written to simulate

Author for correspondence: Hermine Maes, Email: hermine.maes@vcuhealth.org
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data to evaluate bias, precision and accuracy of the parameter estimates (Coventry & Keller, 2005; Keller et al., 2010) as well as power associated with different family structures (Medland & Keller, 2009). Additional relatives (Vinkhuyzen et al., 2012) and non-biologically related family members (Leve et al., 2018; Maes et al., 2007) were included. The utility of subsets of the data, such as COTs, to disentangle genetic from cultural transmission was explored (Docherty et al., 2015; Eaves et al., 2005) and expanded (Marceau et al., 2015; McAdams et al., 2018). Cross-cultural comparisons were undertaken to test the reproducibility and consistency of findings (Lake et al., 2000; Maes et al., 2018). Twin registries were expanded with data collected from other relatives (Boomsma et al., 2008; Kaprio et al., 1987; Ligthart et al., 2019), recognizing the added value, not just in terms of power but in capturing more of the nuances of how genetic and environmental factors act and interact in creating individual differences. The list of phenotypes to which these models has been applied continues to grow, with publications on brain structure (Posthuma et al., 2000), blood pressure (Kupper et al., 2005), parturition timing (Kistka et al., 2008), personality disorder (Distel et al., 2009), intelligence (Vinkhuyzen et al., 2012), political orientation (Kandler et al., 2012), proinflammatory state (Neijts et al., 2013), personality (Hahn et al., 2012; Kandler et al., 2019) and political affiliation (Hufer et al., 2019; Kornadt et al., 2018). On a personal note, Nick has been extremely supportive in my career — and deserves every spot as coauthor and contributor. Furthermore, he genuinely cares about moving the field of (behavior) genetics forward and has clearly put his stamp on developing models for ET kinships, collecting relevant data and fitting ET models to them, and through it all mentored and encouraged his academic extended family, while enjoying their company during 'just bring food' dinners, good wine and, if possible, listening to some lovely music. Thanks, Nick!

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