If constructs are indeed networks of causally related observables, individual differences are most likely to arise as differences in the strength of those relations: when Alice suffers from depressed mood, she fairly easily develops suicidal thoughts (i.e. strong relation between the observed symptoms 'depressed mood' and 'suicidal ideation'), whereas Bob does not ever contemplate suicide while feeling depressed (i.e. relatively weak relation). Furthermore, it is likely that the strength of such relations stands at least partly under genetic control. Now, it is not likely that each relation is influenced by the same set of genes for the sheer number of relations (k^2-k in a network containing k observables/symptoms) in any given network greatly diminishes this possibility and the relations probably differ in terms of the endophenotypes (and thus genes) involved (e.g. the more physiological homeostatic processes that are likely to govern relations between sleep and fatigue vis-à-vis the more cognitive processes that are probably involved in the relation between depressed mood and suicidal thoughts).

Hence, when trying to relate genetic polymorphisms to a sumscore, one only captures the genetic variance that is shared among those individual symptoms (including their relations); the different genetic polymorphisms that are responsible for individual differences in the strength of the *relations between* those symptoms are completely left unaccounted for. As such, the network approach may explain at least partly why current approaches cannot find the genetic culprits of mental disorders. By properly modeling their etiology, we increase our power to detect risk variants. It is, after all, the relations between symptoms that glue them together into a syndrome.

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Understanding Heritability by Explaining Heritability: Recent Developments in Behaviour Genetics Tell Us More

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Abstract: Johnson, Penke, and Spinath (2011) extensively discuss the limitations of heritability estimates obtained from twin studies in understanding the role of genes on behavioural traits. They plead for more advanced modeling and a focus on gene–environment interplay. We review the results from advanced modeling and molecular genetic research and argue that gene–environment interplay is not likely to be the main factor in explaining heritability. It is anticipated that future developments in these areas will provide an even more complete picture on the genetic and environmental mechanisms underlying behavioural traits.

Johnson et al. (2011) extensively discuss the limitations of heritability estimates obtained from twin studies in understanding the role of genes and environment on behavioural traits. They make three important points about heritability. First, heritability depends on how the trait under interest is measured. For example, measurement error and low item endorsement frequencies tend to lower heritability. Second, when heritability is based on the classical twin design, it can be biased if the assumptions of this design are violated. These assumptions include the absence of assortative mating, gene–environment interaction and correlation. Third, heritability tells us little about the underlying biology of a trait, because biology is only one of the factors that influence the magnitude of heritability estimates. They plead for more advanced modeling and a focus on gene–environment interaction and correlation ('interplay').

In this commentary, we introduce two types of advanced modeling that we feel remain underexposed: extended twin family designs and causal modeling. We further review some recent molecular genetic studies and theoretical developments that illustrate the progress in explaining the heritabilities of complex traits. We argue that the results from these approaches suggest that gene–environment interplay is not likely to be the main factor in explaining heritability.

EXTENDED TWIN FAMILY DESIGNS

Extended twin family designs test assumptions underlying the classical twin design and can address more complex questions about the influence of genetic and environmental factors than the classical twin design (Eaves et al., 1978; Keller et al., 2009). Twin-sibling studies on personality (e.g. neuroticism, extraversion, sensation seeking) and related traits converge on the finding that the heritabilities of these traits represent both additive and non-additive genetic influences (Keller

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et al., 2005; Stoel et al., 2006; Distel et al., 2009b). This has been confirmed by studies adding data from parents and other types of first-degree and second-degree relatives (Eaves et al., 1998; Eaves et al., 1999; Rettew et al., 2008; Distel et al., 2009a). These studies further show that the spouse correlation, an indicator for assortative mating, for personality traits is generally very low (0–0.2) and has an almost negligibly small impact on the estimates of heritability and the proportion of variance explained by environmental influences. There is typically no evidence for cultural transmission, a shared sibling or a shared twin environment. These findings are consistent with studies in adult twins reared apart or together (Bouchard et al., 1990), although in adolescent adoptees, some evidence for shared environment has been found (Buchanan et al., 2009). The absence of cultural transmission renders passive gene–environment correlation unlikely, although gene by environment interaction may still be present. Overall, the findings from extended twin family designs suggest that the initial heritability findings obtained with the classical twin design are less biased than Johnson et al. (2011) suggest, at least for personality and related behavioural traits.

CAUSAL MODELING

Twin family designs can be informative in testing for causal mechanisms among behavioural traits. Available methods include direction-of-causation modeling (Heath et al., 1993; Duffy & Martin, 1994), the children-of-twins design (D'Onofrio et al., 2003) and the co-twin control method (Kendler et al., 1993). These methods have been applied to test for causal effects of parenting, life events and lifestyle behaviours on mental health (Kendler et al., 1993; Kendler et al., 1999; Gillespie et al., 2003; Stubbe et al., 2006). A combination of the standard bivariate genetic model and the co-twin control design, has been applied to cross-sectional and longitudinal data on exercise behaviour and anxiety/depression, showing that the association can be best explained by common genetic factors rather than a causal effect (De Moor et al., 2008). These methods are also suitable to test causal hypotheses between personality and related behaviours. They show that twin (family) data are informative beyond establishing the heritability of a trait. They allow for genetic influences on behavioural traits to be mediated by other traits and hence give a more complete picture on the aetiology of behavioural traits. Future developments in this area are expected that may even better exploit the longitudinal nature of many twin (family) data and that incorporate data on measured genetic variants.

MOLECULAR GENETIC STUDIES

Recent molecular genetic studies show the progress in finding the genetic variants for complex traits. This holds not only for height, the example used by Johnson, Penke, and Spinath (2011), but also for psychiatric diseases and personality. The largest genome-wide association (GWA) study on height in 180 000 subjects identified 180 loci, explaining about 10% of the variance (Lango Allen & et al., 2010). These loci are enriched for genes in biological pathways involved in skeletal growth defects. Almost simultaneously with the Lango Allen paper, a study was published that showed that the proportion of variance captured by analysing all measured single-nucleotide polymorphisms (SNPs) on a common micro-array explained about 45% of the variance in height (Yang et al., 2010). Thus, common SNPs explain a large proportion of the heritability for human height.

One example to illustrate progress for psychiatric disorders is *CACNA1C*, which was identified as a gene for bipolar disorder, major depression and schizophrenia (Ferreira et al., 2008; Green et al., 2010) and which has also been shown to affect brain structure and activity (e.g. Wessa et al., 2010; Franke et al., 2010). Another example is the *PCLO* gene in relation to major depression (Sullivan et al., 2009; Hek et al., 2010) and bipolar disorder (Choi et al., 2010). For personality, the largest GWA study identified two loci for Openness to Experience and Conscientiousness in over 17 000 subjects (De Moor et al., 2010). The variants in these studies explain only very small portions of the heritabilities. This cannot simply be ascribed to the factors that Johnson, Penke, and Spinath (2011) mention, such as bias in heritability as a result of gene–environment interplay. Other reasons include imperfect genomic coverage of common variation by SNP chips, the high penalty that needs to be paid for multiple testing, small effect sizes of common variants and the possible influence of other types of variants (see also Manolio et al., 2009). The application of new technologies (e.g. sequencing) and methods (e.g. Yang et al., 2010) is expected to give more insight into the biological underpinnings of heritability estimates.

CONCLUSIONS

We discussed how extended twin family designs, causal modeling and molecular genetic studies have yielded knowledge that helps us better understand the nature of heritability. It is anticipated that future developments in these areas will provide an even more complete picture on the genetic mechanisms underlying personality and related behavioural traits.

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