THE VALIDITY OF GENES RELATED TO NEUROTRANSMITTERS AS INSTRUMENTAL VARIABLES

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Health economics has a tradition of evaluating the models of instrumental variables (IV) used in our field. For example, French and Popovici (2011) assess the instruments used in 60 recent studies measuring the effect of substance use (alcohol, illicit drugs, and tobacco) on various outcomes. Rashad and Kaestner (2004) evaluate the instruments used by Sen (2002) and Rees and colleagues (2001) to identify the effect of alcohol on risky sex among adolescents. Terza *et al.* (2008) review the health economics literature that applies linear IV methods in inherently nonlinear regression settings.

In this editorial we discuss the IVs used in Fletcher and Lehrer (2009a), hereafter FL, to estimate the effect of health conditions on educational attainment. We focus on FL because it is novel, well-written, and careful in many ways; it won the 2009 Victor R. Fuchs award for 'the best research paper with the potential to spawn new research in an underdeveloped area of health economics or health policy'. The use of genes as IVs (and in other empirical capacities) is likely to become more widespread as large social science datasets continue to add data from genetic assays. Therefore, consideration of this method is timely and likely to be useful in the future. Our comments should not be interpreted as exclusively about FL, but also apply to other papers in this emerging area of empirical health economics (e.g. Ding *et al.*, 2009; Fletcher and Lehrer, 2009b), including our own (Norton and Han, 2008).

FL estimate IV models using data from the third wave of the National Longitudinal Survey of Adolescent Health (Add Health) to test whether overweight (based on self-reported weight and height), depression (based on the 20-item Center for Epidemiologic Studies-Depression Scale), and attention deficit and hyperactivity disorder or ADHD (based on 18 retrospective questions) affect years of schooling completed when respondents were on average 22 years old. FL argue persuasively that these measures of physical and mental health are endogenous to educational attainment. For example, poor grades in school may contribute to depression (reverse causality) and unobserved factors, such as rate of time preference, may contribute to both poor health and worse educational outcomes. As a result, simple regression would result in biased estimates of the effect of health on educational attainment.

FL address the endogeneity of health by using genes as IVs. The specific IVs they use, listed in column 1 of Table I, are genes related to the neurotransmitters dopamine and serotonin. Fletcher and Lehrer (2009b) note that geneticists have linked these specific genes to overweight, depression, and ADHD, and that these correlations make sense in light of the fact that neurotransmitters affect mood, attention, and are associated with feelings of pleasure and reward, and thus serve as positive reinforcement for certain decisions. For example, people who are genetically predisposed to low levels

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Table I. Genes related to neurotransmitters that are used as instruments in Fletcher and Lehrer (2009a)

Name of gene	Perceived function	Linked to which conditions that threaten validity?
SLC6A3 locus (DAT1)	Regulates reuptake of dopamine	Alcoholism (Muramatsu and Higuchi, 1995)
		Affinity for delinquent peers (Beaver *et al.*, 2008)
		Generalized anxiety, social phobia, obsessive-compulsive disorder, and Tourette's (Rowe *et al.*, 1998)
		Externalizing behavior problems such as aggressive and delinquent behavior (Young *et al.*, 2002)
		Drug use, delinquency, and other risky behaviors (Guo *et al.*, 2010)
		Bipolar disorder (Serretti and Mandelli, 2008)
Dopamine receptor D2 locus (DRD2)	Regulates density of D2 dopamine receptors on neurons in the brain	Schizophrenia (Arinami *et al.*, 1997)
		Alcoholism (Samochowiec *et al.*, 2006)
		Bipolar disorder (Zhan *et al.*, 2010)
		Impulsive self-damaging behaviors (Nemoda *et al.*, 2010)
Dopamine D4 receptor (DRD4)	Codes D4 dopamine receptors, which may vary in the affinity with which they bind with dopamine	Schizophrenia and heroin addiction (Lai *et al.*, 2010)
		Addictions of many kinds (McGeary, 2009)
		Personality traits such as novelty seeking and impulsivity (Munafò *et al.*, 2008)
		Borderline personality disorder (Nemoda *et al.*, 2010)
		Bipolar disorder (Serretti and Mandelli, 2008)
Serotonin transporter (5HTT)	Regulates reuptake of serotonin	Aggression and violence (Craig, 2007)
		Obsessive compulsive disorder (Wendland *et al.*, 2008)
		Anxiety (Lesch *et al.*, 1996)
		Suicide and suicidal behavior (Anguelova *et al.*, 2003)
		Bipolar disorder (Cho *et al.*, 2005)
Monoamine oxidase A (MAOA)	Regulates the degradation of dopamine, serotonine, and nenorepinephrine	Aggression and violence (Craig, 2007)
		Autism severity (Cohen *et al.*, 2011)
		Moderates children's sensitivity to environmental insults (Caspi *et al.*, 2002)

Note: The articles cited in the final column also represent the sources for the perceived functions of the genes.

of dopamine and serotonin may be at greater risk of 'self-medicating' by overeating. The specific genes used as instruments by FL affect levels of neurotransmitters in the brain in a variety of ways; e.g. by regulating the amounts released, the number of receptors that the neurotransmitters can bind to, and the rate of reuptake (see column 2 of Table I for more information on the perceived function of each gene).

The problem with using genes that relate to neurotransmitters as instruments in this context is that they may be associated with too many things to satisfy the exclusion restriction. This is particularly relevant when studying outcomes such as educational attainment, because it requires the unattractive identifying assumption that *genes that affect brain chemistry do not affect educational attainment*, except through obesity, depression, and ADHD.

A search of the genetics literature (via the biomedical and life science journal search indexes PubMed Central and Medline as well as the website http://www.wikigenes.org) yields many studies that link these specific genes to conditions that are likely to be unobserved determinants of educational attainment. The final column of Table I lists, for each gene, selected conditions to which the gene has been linked (with citations to the relevant genetics literature) that threaten its validity as an instrument in this context. The conditions associated with those genes include: generalized anxiety, social phobia, obsessive–compulsive disorder, aggression, delinquency, self-damaging behaviors, schizophrenia, bipolar disorder, novelty seeking and impulsivity, borderline personality disorder, suicidal behavior, autism severity, affinity for antisocial peers, and a wide range of addictive behaviors including alcoholism and drug addiction. These conditions and behaviors are not controlled for in the IV models

of FL; moreover, it would likely be impossible to control for them because many are not observed in the Add Health data (or other large secondary datasets that economists commonly use). As a result, genes for neurotransmitters are likely correlated with residual educational attainment in the second stage of IV models, resulting in biased IV estimates. FL conduct overidentification tests, but this relies upon assuming that one or more genes are valid instruments. The findings cited in Table I imply that genes associated with neurotransmitters may be associated with too many relevant conditions to be valid instruments in this context.

For this reason, the use of genes related to neurotransmitters as instruments has been criticized by researchers outside of economics. Conley (2009, pp. 242–243) writes: 'Does DRD4 only affect school performance through the pathway of diagnosed ADHD? Of course not. ADHD is a complicated syndrome that involves lots of measurement error and thus most likely reflects a whole host of other unmeasured traits. And even if ADHD were measured perfectly by the researchers, there may be other effects of the genes in question on educational outcomes through any number of mechanisms, thereby violating the exclusion restriction necessary for unbiased IV estimation.'

RECOMMENDED BEST PRACTICES

The standards for empirical work in economics are continually rising; for example, recent IV papers contain much more information about power and tests of overidentification than those written during the 1980s. Part of the reason for evaluating recent IV papers is to recommend best practices in order for the field to continue to advance and improve (see, e.g. French and Popvici, 2011; Terza *et al.*, 2008).

The general advice of Angrist and Krueger (2001) and Angrist and Pischke (2009) can be adapted to this specific case. We highlight a few of the many considerations that should be addressed in such analyses. Studies should include a clear description of how the set of instruments was chosen (i.e. which genes and which alleles of those genes). For example, FL report selecting their instruments through stepwise regression, which is an *ad hoc* method that results in overestimation of the instruments' power in the first stage. There should also be a clear description of the mechanisms by which each genetic instrument is expected to affect the endogenous regressor, with citations to the relevant genetics literature. Authors should provide the results of the first-stage regressions, so readers can determine whether the coefficients on the instruments have the expected sign given the findings in the genetics literature and thus whether the hypothesized mechanisms are plausible. In addition, papers should include a summary of the process and results of the literature search that was done to investigate whether the specific genes used as instruments are linked to any conditions that are likely to be correlated with the error term in the second stage, and would thus raise concerns about the validity of the instruments and bias in the IV estimates. Adhering to these practices when using genes as instruments will better communicate to readers the strengths and weaknesses of the IV approach. These recommendations are not directed solely at FL but are intended for the entire emerging literature that uses genes as instruments.

There may in some instances be a biological mechanism that serves as the identifying assumption, explaining both a link between the genetic instruments and the endogenous regressor and justifying the exclusion restriction. An ideal instrument would be a gene that acts as a switch, turning on or off one characteristic (that affects the endogenous regressor) while affecting no other characteristics (that would affect the second-stage error term). However, Conley (2009) is skeptical; he notes that humans have only 21 000 genes to code for the vast number of individual characteristics and thus genes tend not to act as individual, isolated switches but instead act in concert with many other genes to affect a large number of characteristics. Although it is too early to say, it is possible that what we conclude about genes for neurotransmitters – that they may affect too many things to be valid instruments in most contexts – may be true of many other genes as well.

However, we remain optimistic that genes can be useful in economics research. For example, it may be possible to use genes related to neurotransmitters to test for peer effects in risky behaviors (Cawley *et al.*, 2010). Specifically, if one had data on randomly assigned roommates (as in, e.g. Sacerdote, 2001; Duncan *et al.*, 2005) including their genetic assays, one could regress the risky behaviors of one roommate directly on the other roommate's genes related to neurotransmitters. The fact that genes related to neurotransmitters affect many things is not a problem in this context, because the genes of one person can affect a different person's behavior only through peer effects. In this context, randomized assignment of peers is necessary because assortative matching of peers based on those genes may result in a spurious correlation between the behavior of the respondent and the genes of his chosen peers.

As science progresses, behavioral geneticists will learn more about which genes affect which aspects of health and through what mechanisms; this will provide economists with more information about which genes might be powerful and valid instruments in a given context. In the meantime, economists should proceed with caution when using genes, particularly those related to neurotransmitters, as instruments.

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