Genoeconomics

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INTRODUCTION

Since Taubman (1976), twin studies have identified a significant degree of heritability for income, education, and many other economic phenotypes (e.g., Behrman et al., 1980, Behrman and Taubman, 1989). These studies estimate heritability by contrasting the correlation of economic phenotypes in monozygotic (identical) twin pairs and dizygotic (fraternal) twin pairs. Recent improvements in the technology of studying the human genome will enable social scientists to expand the study of heritability, by incorporating molecular information about variation in individual genes. This essay describes our hopes and concerns about the new research frontier of economic genomics, or genoeconomics.

The core theme of health economics is that individual behavior and social institutions influence health outcomes (Fuchs, 1974). The primary contribution of genoeconomics will likely be to identify the many ways in which individual behavior and social institutions moderate or amplify genetic differences.

Within genoeconomics, there will be at least three major types of conceptual contributions. First, economics can contribute a theoretical and empirical framework for understanding how market forces and behavioral responses mediate the influence of genetic factors. Second, incorporating genetics into economic analysis can help economists identify and measure important causal pathways (which may or may not be genetic). Finally, economics can aid in analyzing the policy issues raised by genetic information.

Smoking provides one example of economic analysis that can improve the study of how genetic variation influences phenotypic variation. Traditional heritability studies suggest at least some genetic component to lung cancer (Lichtenstein et al., 2000); molecular genetics identifies a locus of lung cancer susceptibility on chromosome 6q23-25 (Bailey-Wilson et al., 2004). The genetic susceptibility to lung cancer is undoubtedly amplified by cigarette smoking, an economic decision affected by advertising, social norms, cigarette prices, consumer income, and tax rates on cigarettes (Cutler and Glaeser, 2005). Economics can explain how social institutions – like the market for cigarettes -- interact with genes to jointly generate important health phenotypes like lung cancer. More generally, economic institutions may either reduce or amplify the inequalities produced by genetic variation. In some situations, social transfers partially offset genetic factors – for instance, when individuals with illness receive extra insurance-based resources to treat or manage their illness. On the other hand, social institutions sometimes heighten inequalities associated with genetic factors – for instance, when individuals with advantageous cognitive abilities receive *extra* "merit-based" resources in the form of academic scholarships and admission to college or post-graduate degree programs.

The second subfield uses genetic information to identify causal mechanisms. This subfield will recognize a central fact of empirical economics: the ubiquity of mutual causation – for instance, health influences wealth, and vice versa (Case, Lubotsky, and Paxson, 2002). Genetic measures can help to separate the causal effect in a particular direction. For example, a robust literature argues that height, even in adolescence, increases earnings (Persico et al., 2004). However, this literature is plagued by difficulty

in controlling for the fact that height also reflects better health and nutrition in wealthier families. If height-linked alleles were identified, then they could, in principle, be used to measure the causal impact of exogenous variation in height. More formally, such research would analyze allele variation across siblings to identify the causal effect of genetic predispositions for height (controlling for household background characteristics). To take another example, Ding et al. (2004) address the causal effect of health on educational outcomes, using genetic predictors of health to ameliorate confounding by third factors potentially correlated with both health and educational outcomes. More generally, cognition-linked alleles will contribute to our understanding of the cognitive factors that influence income, or the extent to which cognitive factors influence decision-making about savings and wealth. Genetic research will also identify biological mechanisms that interact with environmental factors to jointly influence behavior. We anticipate that crude concepts like "risk aversion" (unwillingness to take risks) and "patience" (willingness to delay gratification) that are central to economic analyses will be decomposed into much more useful subcomponents associated with particular neural mechanisms and their environmental and genetic antecedents (Plomin, Corley, Caspi, Fulker, and DeFries, 1998). Finally, ongoing research will eventually enable researchers to employ new genetic control variables, thereby improving the power of statistical procedures.

Much of the promise of genoeconomics is based in part on economists' long tradition of policy analysis. The economic approach is one in which governments are not seen as infallible custodians of the public good, but rather as separate actors that often have their own objectives (Stigler, 1971). Information economics may also play an

important role in the analysis of policy questions. Economists have identified competitive forces that cause individuals to reveal information that is privately beneficial but potentially socially harmful. Economists understand how the public release of certain genetic information can theoretically undermine insurance institutions and thereby inefficiently increase social inequality. Genoeconomics will also identify specific gene-environment interactions with policy implications. For example, imagine that particular genes turn out to be risk factors for poor educational outcomes, poor performance in the labor market, and consequently low levels of income. Imagine too that particular educational interventions are found that mitigate these disadvantages. Then gene-based policies could target disadvantaged groups with focused interventions. Such interventions will remain purely speculative until the necessary precursor research is implemented and ethical questions are resolved, but focused interventions nevertheless hold out considerable long-run potential.

Despite the promise of genoeconomics, there are clearly enormous pitfalls. Even under the best of circumstances—when a particular genetic pathway has been clearly established—there are concerns about informing individuals of their own risks, especially when there are few interventions to alleviate those risks or when the risks are very small. Providing information to parents about the genome of a fetus or child creates a different set of dilemmas, including the risk of selective abortion. This has been well-discussed with reference to a genetic endowment as straightforward as gender, where in many societies economic investment in a daughter is seen as less beneficial than economic investment in a son (e.g., Garg and Morduch, 1998). If the same issues arose in relation to more complex economic traits, this would generate a host of ethical and policy

questions. Documenting the power of the genome to society at large also creates risks as identifiable social and ethnic groups may face discrimination (or become beneficiaries of positive discrimination) on the basis of their presumed genetic endowments.

These problems are multiplied when genetic research is done carelessly. Historically, there have been many cases of false positives where early genetic claims have evaporated under subsequent attempts at replication. These false positives can create tremendous mischief. A failure to highlight the full extent of the interaction between genes and environment is likewise dangerous because the public may come to believe falsely in genetic determinism. The responsible path requires statistical care, attention to how genes and environment jointly determine outcomes, and extreme sensitivity to the ethical issues surrounding genetic knowledge.

Despite these dangers, we believe that there is potential for productive collaboration between economists, cognitive scientists, epidemiologists and genetic researchers. In the rest of this essay, we sketch one vision for this field. In Section II, we discuss methodological challenges that confront research in genoeconomics. In Section III, we outline a study that is currently underway, which uses a SNP panel to analyze associations between candidate cognitive genes and economic phenotypes. Section IV concludes.

II. METHODOLOGICAL CHALLENGES AND PITFALLS

Successful implementation of the research program described above will require careful attention to many methodological issues, some of which we outline in this

115 section. A critical issue is the choice of economic phenotypes to study. Proximal
116 behavioral phenotypes, such as impatience or risk-aversion, are probably more directly
117 related to genetic propensities than more distal economic phenotypes, such as wealth
118 accumulation or labor force participation.
119 Proximal phenotypes have typically been measured with personality tests. Some
120 personality systems are purely conceptually based (e.g., the five factor model) while
121 others are rooted in neurobiology (e.g., Cloninger's three dimensions tied to the
122 dopamine, serotonin, and norepinephrine systems; Cloninger, 1987; Cloninger et al.,
123 1993). Recently some personality attributes have been studied with neuroimaging (e.g.,
124 Hariri 2006).
125 Distal phenotypes -- for instance wealth accumulated over a lifetime – may also
126 strongly reflect genetic influences because they represent the cumulative effect of many
127 specific decisions, and may reflect the expression of genes over a long period of time.
128 Given the current state of knowledge (especially the relative lack of definitive findings
129 relating traditional personality traits to specific genetic polymorphisms; see Ebstein,
130 2006; Munafo et al., 2003), the wisest course is probably to measure both proximal and
131 distal phenotypes, and to investigate how the proximal phenotypes mediate the
132 relationship between genes and more distal phenotypes.
133 In the rest of this section, we focus on gene-environment interaction studies in the
134 context of quantitative genetic designs and modern association analysis. In that setting
135 we consider issues under three general headings: the non-independence of genes and
136 environments; the measurement of genetic variation; and problems searching for small,
137 complex effects.

Correlated Genes and Environments

Genes and environments are, for various reasons, often not independent factors. This has implications for statistical designs attempting to uncover genetic influences, environmental influences, and interactions of genes and environments.

Gene-environment interaction (GxE) can be conceptualized as the genetic control of *sensitivity* to different environments. In contrast, a correlation between genes and environment (GE correlation, rGE) can represent genetic control of *exposure* to different environments (Kendler, 1986; Plomin and Bergeman, 1991). For example, Jang et al. (2000) show that genetic influences on alcohol and drug misuse are correlated with various aspects of the family and school environment.

We might expect correlations between genes and environments to arise for a number of reasons. For example, individuals do, to some extent, implicitly select their own environments on the basis of innate, genetically-influenced characteristics.

One important form of gene-environment correlation arises due to population stratification. A stratified sample is one which contains individuals from two or more subpopulations which may differ in allele frequencies at many sites across the genome. This will induce a correlation in the sample between all allelic variants that differ in frequency between the subpopulations and any environmental factors, diseases, or other measures that also happen to differ (possibly for entirely non-genetic reasons) between the subpopulations. As such, population stratification is an important source of potential confounding in population-based genetic studies. For example, if cases and controls are

not matched for ethnic background, population stratification effects can lead to spurious association, or false-positive errors. To address concerns over possible hidden stratification effects, a series of family-based tests of association have been developed. Because related family members necessarily belong to the same population stratum, using relatives as controls automatically ensures protection against the effects of stratification (Spielman et al., 1993). Recently, a different approach—called genomic control, or structured association—has emerged, directly using DNA markers from across the genome to directly infer ancestry for individuals in the sample or to look for signs of stratification (Devlin & Roeder, 1999; Pritchard et al., 2000).

An association between an environment and an outcome may arise due to a third variable, namely common genetic inheritance (e.g., DiLalla and Gottesman 1991). For example, if a gene X is inherited, it might cause phenotypes Y and Z respectively in a parent and in a child. Researchers will observe a correlation between the parental phenotype Y and the child's phenotype Z. Researchers may mistakenly infer a causal relationship between Y and Z if they do not control for the real (unobserved) causal mechanism: gene X.

Measuring Genetic Variation

The typical "gene by environment" association study should really be called an "allele by environment" study because, very often, only a single variant within a gene is studied. In the context of standard candidate gene association studies, many researchers are realizing that failure to comprehensively measure all common variation in a gene or

region can lead to inconsistent results and makes the interpretation of negative results particularly troublesome. (If you have not adequately measured "G," then it is hard to evaluate its relationship to the phenotype.) With emerging genomic technologies, it will soon be easy to measure myriad single nucleotide polymorphisms or microsatellite markers, even if only one SNP is known to be functional.

The same issue applies to GxE analysis. The question will be how to adapt GxE methods to this new "gene-based" paradigm, in which the gene rather than the specific allele, genotype or haplotype becomes the central unit of analysis. In addition, if a researcher measures multiple genes (for example, all genes in a pathway, each with multiple markers), then new analytic approaches will be needed to simultaneously model the joint action of the pathway, as well as how the individual genes influence the phenotype or interact with the environment.

Naturally, more comprehensively measuring all common variation in a gene costs more both financially (more genotyping) and statistically (more tests are performed). How to best combine information from multiple markers in a given region is an ongoing issue in statistical genetics. One option is to simply test each variant individually and then adjust the significance levels to account for this multiple testing. Standard procedures such as the Bonferroni are typically too conservative because they assume the tests are independent. Instead, it is often better to use permutation procedures to control the family-wise error rate or to control the false discovery rate (FDR). A second option is to combine the single variants together, either in a multilocus test (such as Hotelling's T^2 or a set-based test using sum-statistics), or in a haplotype-based test. As mentioned above, this is currently a very active area of research (e.g., Brookes et al., 2006).

Unfortunately, all these approaches rely on the variation being common. Even for large samples, this means that variants with a population frequency of less than 1% are unlikely to be detected. If a gene is important for a given outcome but contains multiple, different rare variants, then many current approaches will fail.

Searching for Small Effects and Interactions

Increasingly, researchers are appreciating the central importance of large sample sizes in genetics to afford sufficient statistical power to detect small effects. For complex, multifactorial traits, many researchers expect the effects of individual variants to be as low as <1% of the total phenotypic variance for quantitative outcomes. For case/control designs, allelic odds ratios of 1.2 and lower are often considered. Such small effects require very large samples—typically thousands of individuals, if more than one variant is to be tested and proper controls for multiple testing are in place. The consequences of chronic low statistical power are sobering. If power is on average only marginally greater than the Type I error rate, then a large number of published studies may well be Type I errors. Average power around the 50% level yields a pattern of inconsistent replication. Unfortunately, a great deal of time and money has been spent on poorly designed experiments that, at best, stand little chance of doing what they are supposed to, and, at worst, are advancing Type I errors in the literature.

Although the individual effects of any one variant may be very small, it is of course a possibility that this is because they represent the marginal effect of an interaction, for example with some environmental factor. In other words, by looking only

230 at a single variant and essentially averaging over all other interacting environmental
231 factors, one would only see an attenuated signal and perhaps miss the link between the
232 gene, environment and outcome. This is one reason for explicitly considering GxE when
233 searching for genetic variants.
234 In humans, G×E has been found in monogenic diseases; in plant and animal
235 genetics, there is strong evidence for G×E in complex phenotypes. For example,
236 phenylketonuria is a Mendelian human disorder, but the gene only acts to produce the
237 severe symptoms of mental retardation in the presence of dietary phenylalanine.
238 Research in Drosophila melanogaster has found evidence for G×E in quantitative traits
239 including bristle number, longevity and wing shape (Mackay, 2001; Clare and Luckinbill,
240 1985). The detection of G×E in model organisms suggests that it will play an equally
241 important role in complex human phenotypes. Indeed, promising results are emerging
242 (e.g., Caspi et al., 2002, 2003; Mucci et al., 2001; MacDonald et al., 2002; Dick et al.,
243 2006). However, human studies suffer from a crucial methodological difference: the
244 inability to inexpensively experimentally manipulate genes and environments.
245 Epidemiological designs will therefore tend to be less powerful, as well as prone to
246 confounding. Despite these greater challenges, consideration of G×E in human
247 molecular genetic studies potentially offers a number of rewards, including increased
248 power to map genes, to identify high-risk individuals, and to elucidate biological
249 pathways.
250 Many commentators have noted the general difficulties faced in uncovering
251 interactions of any kind (e.g., Clayton and McKeigue, 2001; Cooper, 2003). Indeed,
252 general epidemiology has struggled for decades to adequately define and test interaction.

The central problem, as stated by Fisher and Mackenzie in 1923 when first describing the factorial design and analysis of variance (ANOVA), is that, in statistical terms, "interaction" is simply whatever is left over after the main effects are removed. It follows that the presence or absence of interaction can depend on how the main effects are defined. For dichotomous phenotypes, the presence of a measured interaction effect will depend on the modeling assumption that is used in the empirical analysis (see Campbell et al., 2005, for another example). For example, if the risk genotype G+ has (likelihood ratio) effect *g* and the risk environment E+ has (likelihood ratio) effect *e*, the question is how to specify the joint effect *in the absence of an interaction*. Assuming an additive model implies that the joint effect (without an interaction effect) is $g+e-1$ whereas a multiplicative model implies that the joint effect (without an interaction effect) is ge. Hence, the absence of an interaction effect in the additive model generically implies the existence of an interaction effect in the multiplicative model (and vice versa). Mathematically, as long as neither g nor e is equal to one, then, $g + e - 1 \neq ge$.

Analogously, for quantitative phenotypes, transformation of scale can induce or remove interaction effects. To see this, imagine a G×E study of amygdala morphology (i.e., measures of the anatomical size of the amygdala based on magnetic resonance images). For illustrative purposes, assume that the amygdala is a sphere with radius given by an additive sum of a gene effect -- 1mm -- and an environment effect -- also 1mm. Assume too that the radius exhibits no gene-environment interaction.

[INSERT FIGURE 1 HERE.]

FIGURE 1 Measurement of G×E depends on the modality of measurement

Radius (mm)		E-	E+
	G-	1	2
	G+	2	3

Area/π (mm^2)		E-	E+
	G-	1	4
	G+	4	9

Volume·3/(4π) (mm^3)		E-	E+
	G-	1	8
	G+	8	27

If the measured phenotype were cross-sectional area (a function of radius squared), however, gene and environment are no longer additive in their effects. There is now G×E, as G+ increases area by 3 units under E- and 5 units under E+. If the phenotype were based on volume, the apparent measurement of G×E is stronger. However, these interaction effects are purely "statistical" and not "biological": that is, G and E do not interact on any causal level. The interactions are effectively a consequence of misspecifying the main effects model (see Figure 1).

Consider now that a "downstream" phenotype is measured, such as some aspect of the serotonergic system that is influenced by the amygdala. There can be no guarantee that the effects of G and E should necessarily display an additive relationship at this level, considering the various neurochemical cascades and reciprocal feedback loops that are presumably involved in a system as complex as the human brain. Or the measured phenotype may be even further downstream—a clinical diagnosis based on behavioral symptoms, or a 25-item self-report questionnaire measure, log-transformed to

approximate normality. Finding G×E at these levels may well be strikingly irrelevant with respect to the presence of interaction at the causal level.

The point of this example is not to claim that the only appropriate causal level is the neurological one. Rather, for complex phenotypes, the level at which genes and environment operate (which need not be the same level) might often be quite distal compared to the level of measured phenotype. Consequently, the distinction between statistical and biological interaction always should be borne in mind. Purely statistical interactions are still useful if one's only goal is prediction, e.g., early diagnosis or identification of high risk individuals. But to help understand mechanisms and pathways, an interaction detected by statistical methods must have some causal, biological or behavioral counterpart to be of significant interest.

False negatives are also a major concern in the study of G×E. Tests of interaction generally suffer from relatively low power (Wahlsten, 1990). In this case, it is not clear that efforts to detect genes will benefit from more complex models that allow for potential G×E effects, even if G×E effects are large.

Nature is undoubtedly complex. How complex our statistical models need to be is less clear. Combining the definitional problems of interaction with the low power to detect G×E with the new avenues for multiple-testing abuses brought about by extra E variables, attempting to incorporate G×E could make an already difficult endeavor near impossible (Cooper, 2003). However, we see these obstacles as important but not insurmountable: with proper experimental design and better-developed statistical tools, GxE will be able to be robustly detected, with relevance to biology, public health, and eventually economics.

Although larger datasets—more individuals, more phenotypic measures, more genetic variants assayed—are desirable for many reasons (some of which have already been mentioned), they also pose a further methodological challenge for detecting GxE. A new wave of whole genome scale studies has already begun, in which as many as half a million single nucleotide polymorphisms (SNPs) are assayed. Issues of multiple testing and statistical power are already paramount in such studies. Efforts to detect G×E magnify these concerns.

III. THE AGES-REYKJAVIK STUDY COLLABORATION

Currently, the main obstacle to bringing genetic research into economics is the fact that few datasets combine economic measures with biosamples that can be genotyped. An exception is the Age, Gene/Environment Susceptibility-Reykjavik Study. In this section, we describe a project where we have begun using these data to explore associations between genes that are candidates for involvement in decision-making and economic phenotypes, and how these relationships are mediated by the environment. We believe our project illustrates one possible direction for research in economic genomics, as well as some of the benefits of multidisciplinary collaboration—including team members with training in economics, cognitive science, epidemiology, medicine, genetics, and statistics.

Administered by the Icelandic Heart Association, the original Reykjavik Study (RS) surveyed 30,795 men and women born between 1907 and 1935 who lived in Reykjavik as of 1967. While the majority of participants were surveyed once between

1967 and 1991, about 5,700 were surveyed twice and about 6,000 were surveyed six times over this period. The Older Persons Exam, which contained many components of the RS questionnaire as well as additional health measures, was administered between 1991 and 1997 to all living participants aged 70 and older as of 1991. The Laboratory of Epidemiology, Demography, and Biometry initiated the Age, Gene/Environment Susceptibility (AGES) Study in 2002 in collaboration with the Icelandic Heart Association to collect genotypic as well as additional phenotypic data from 5764 of the 11,549 surviving participants. Currently, 2,300 participants have been genotyped. Hereafter, we refer to the combined dataset as the "Icelandic data." For more detailed information about the Icelandic data, see Harris et al. (2007).

Although primarily used to study health, the Icelandic data already contain a number of measures of economic interest, summarized in Table 1. Distal economic phenotypes we plan to study include labor supply and wealth accumulation. For example, Figure 1 shows the percentage of respondents who have a second job. Figure 2 shows the distribution of working hours in the sample. Notice that there is a substantial amount of variation in these phenotypes. The RS questionnaire asks about attributes of participants' house or apartment, from which it is possible to construct a proxy measure of housing wealth. We are currently investigating the feasibility of collecting more extensive measures of wealth and income.

In addition to these distal phenotypes, we plan to study proximal phenotypes—such as impulsiveness, risk-aversion, and cognitive ability—that may be more closely related to underlying genetic propensities. A measure of general cognitive ability can be constructed from existing data on long-term memory, speed of processing, and working

memory. Various questionnaires ask about health-related decisions, such as smoking, drinking, eating habits, and conscientious health behaviors (e.g., getting regular check-ups). Each of these decisions reflects a tradeoff between the present and the future, and economic theory postulates that some individuals are more impulsive, or "impatient" in economics jargon. From these decisions, we will construct an index of impulsive behaviors.

We also plan to add standard experimental measures of impulsive and risk-averse preferences to the next wave of the AGES-Reykjavik study. These protocols ask participants to choose between immediate vs delayed monetary rewards or to choose between certain vs risky monetary rewards. These choices are played out with real monetary stakes. Such measures correlate with real-world impulsive and risky decisions across a range of contexts (e.g., for discounting: Fuchs, 1982; Bickel, Odum, and Madden, 1999; Petry and Casarella, 1999; Kirby, Petry, and Bickel, 1999; Kirby and Petry, 2004; Ashraf, Karlan, and Yin, 2004; Shapiro, 2005; for risk-aversion: Barsky et al., 1997; Dohmen et al., 2005; Kimball, Sahm, and Shapiro, 2006). These experimental measures yield similar distributions of responses whether they are administered to neurologically-healthy older adults or to college-age subjects (Kovalchik et al., 2003).

Existing research in economics implies that distal phenotypes, such as labor supply and wealth accumulation, will be related to proximal phenotypes that matter for decision-making such as impulsiveness, risk aversion, and cognitive ability (Barsky et al., 1997; Dohmen et al., 2005; Benjamin et al., 2006). These proximal phenotypes are more likely to be directly associated with underlying genetic propensities and to mediate the relationship between genetic polymorphisms and the distal phenotypes.

Three key empirical findings have motivated our choice of candidate genes for decision-making:

1. Research in the new field of neuroeconomics (Glimcher and Rustichini, 2004; Glimcher et al., 2005) has begun to explore the neuroscientific foundations of economic behavior.[2] McClure et al (2004) find that impulsive behavior, when measured with laboratory tasks, appears to be governed by the interaction between the brain's impatient "limbic system" (more accurately, mesolimbic dopaminergic reward-related regions) and a patient "cortical system" that includes elements of the prefrontal cortex and the parietal cortex. McClure et al. (2004) show that the limbic system is only active when individuals are confronted with choices between immediate and future rewards. By contrast, the cortical system is active for all decisions (whether or not immediate rewards are among the choices), and its activity increases on trials when subjects choose more delayed rewards.

2. Individual differences in the tendency to make impulsive, present-oriented decisions are associated with cognitive ability: high-ability individuals are less impulsive and more risk-neutral across a variety of decision-making domains, in both laboratory situations and real-world measures (Benjamin et al., 2006; see also Frederick, 2005), including financial choices, health behaviors, capital

[2] There is also a related, older literature that explores the relationship between personality and neuropharmacological interventions – for instance see Nelson and Cloninger (1997).

accumulation, and the like. Critically, this holds true even when controls for income are included.

3. Differences in cognitive ability, in turn, are mediated predominantly by structural and functional differences in prefrontal and parietal brain regions — the same network of cortical regions that functions to counter the impulsive tendencies of the limbic/reward system (Gray, Chabris, and Braver, 2003; Chabris, in press). General intelligence is also positively related to total brain volume (for a meta-analysis, see McDaniel, 2005).

These results lead us to the working hypothesis that prefrontal/parietal and limbic networks are the neural substrates of the psychological constructs of impulsiveness and cognitive ability (that are in turn related to economic decision-making). We therefore hypothesize that genes implicated in these traits and brain systems may be associated with economic behavior and outcomes in the Icelandic data. We have developed a list of these genes and their known or likely functional SNPs. Table 2 lists these genes. A SNP panel will be created for use with Illumina technology to rapidly genotype all 2300 subjects who have provided DNA in the Icelandic data. These SNPs will include both functional alleles and SNPs to tag haplotypes of the genes, based on the HapMap.

To select genes for this SNP panel, we focused on specific phenotypes and biological pathways of relevance to the model sketched above. First, we selected genes in two critical neurotransmission pathways, the serotonin and dopamine systems, because both of these pathways have been associated with impulsive behavior. (It is true that

these systems are not *exclusively* involved in impulsiveness, or decision-making in general — all genetic or neurobiological systems, including the putative "language gene" FOXP2, are involved in multiple cognitive and behavioral domains — but these provide a useful starting points given the current state of knowledge about the neurobiology of decision-making.) Serotonin function has been associated with several aspects of impulsivity, including reward sensitivity and inhibitory cognitive control (e.g., Cools et al., 2005; Walderhaug et al., 2002), as well as prefrontal cortex activity (Rubia et al., 2005), while several dopamine-related genes have been associated with attention-deficit hyperactivity disorder (ADHD; see Faraone et al., 2005 for a meta-analysis of association studies) and with limbic/reward system functioning. Second, we selected genes that have been associated or implicated in phenotypes related to cognitive ability: general intelligence (i.e., IQ; Plomin, 1999; Plomin et al., in press); memory (e.g., de Quervain and Papassotiropoulos, 2006); schizophrenia, which involves neurocognitive dysfunction (Hallmayer et al., 2005); Alzheimer's Disease; and brain size, which is positively related to general cognitive ability (for a meta-analysis, see McDaniel, 2005; for candidate genes, see Gilbert et al., 2005; Woods et al., 2005). Finally, we added several genes associated with specific cognitive abilities such as memory and attention, or that are linked to cognition via other mechanisms (Goldberg & Weinberger, 2004). Naturally, there is overlap among these categories; for example, COMT (catechol-O-methyltransferase) is part of the dopamine pathway, and it also has a common SNP that is associated with measures of executive function and frontal lobe activation (Egan et al., 2001); HTR2A (serotonin receptor 2A) is a serotonin receptor gene that has been associated with long-term memory ability (de Quervain et al., 2003); and while HTT

(serotonin transporter) is a part of the serotonin system, it has also been associated with ADHD and cognitive ability. Table 2 is therefore not meant to be an exhaustive or final list of possible candidate genes for economic behavior, but rather our estimate of the best starting points for study, given the literature published through the end of 2006.

In addition to the considerable behavioral and medical phenotypes, the Icelandic data includes several measures of cognitive ability: speed of processing, working memory, and long-term memory, as well as educational achievement, the mini-mental state exam, and a clinical dementia evaluation. An index of general cognitive ability (*g*) can be inferred from a principal components analysis of the individual cognitive tests; indeed, working memory and processing speed are prominent components of *g* (Chabris, 2007). Each subject in the AGES follow-up also received structural magnetic resonance imaging (MRI) of the brain with evaluations of atrophy, infarcts, white matter lesions, and high-resolution T1-weighted images for voxel-based morphometric analysis.

We plan to examine direct associations between the genes in our SNP panel and the distal economic outcomes measured in the Icelandic data – for instance, labor force participation and housing wealth. We will also investigate whether these associations are mediated by proximal variables like cognitive ability, brain morphology, and impatience.

To implement these analyses, we will construct composite phenotypic measures. Such composites will reduce measurement error, increase power, and reduce the number of statistical tests. Moreover, rather than simply testing each SNP genotype individually, we will construct composite "SNP sets" that index the "load" of sets of SNPs that individually may have small effects but collectively explain more variance in an outcome measure (for examples of this methodology, see Harlaar et al., 2005, for general cognitive

ability; de Quervain and Papassotiropoulos, 2006, for memory; and Comings et al., 2002, for pathological gambling behavior).

IV. CONCLUSIONS

This essay reviews our hopes and concerns about the joint study of genetic variation and variation in economic phenotypes. The new field of genoeconomics will study the ways in which genetic variation interacts with social institutions and individual behavior to jointly influence economic outcomes.

Genetic research and economic research will have three major points of contact. First, economics can contribute a theoretical and empirical framework for understanding how individual behavior and economic markets mediate the influence of genetic factors. Second, incorporating (exogenous) genetic variation into empirical analysis can help economists identify and measure causal pathways and mechanisms that produce individual differences. Finally, economics can aid in analyzing the policy issues raised by the existence of genetic knowledge and its potential societal diffusion.

Despite the promise of genoeconomics, there are numerous pitfalls. Ethical issues crop up at every juncture, both during the research process and once the research results are disseminated. The problems are even greater when genetic research is done carelessly or reported misleadingly. Historically, there have been many cases of false positives in which preliminary genetic claims have subsequently collapsed as a result of unsuccessful replications. Communication about research results must also highlight the fact that genes alone do not determine outcomes. A highly complex set of gene effects,

environment effects, and gene-environment interactions jointly cause phenotypic variation.

The way forward requires statistical care, attention to how the environment mediates genes, and sensitivity to the ethical issues surrounding genetic knowledge. We believe that there is potential for productive collaboration between economists, cognitive scientists, epidemiologists, and genetic researchers. Indeed, we end the paper by summarizing a study that is currently underway, which uses a SNP panel to analyze associations between candidate cognitive genes and economic phenotypes.

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977 **Figure Captions**

978 FIGURE 1: Percentage of respondents in the Icelandic data who have a second job, by

979 gender and age. Source: Author's calculations.

980 FIGURE 2: Distribution of working hours in the Icelandic data, by gender and age.

981 Source: Author's calculations.

TABLE 1 Measured Phenotypes in the Icelandic Data

Measured phenotypes	Reykjavik Study 1967–1991	Older Persons Exam 1991–1996	AGES-Reykjavik 2002–2006
Distal economic phenotypes			
Number of jobs and hours worked (labor supply)	X	X	
Attributes of house/apartment (housing wealth)	X	X	
Occupational history (human capital accumulation)	X	X	X
Years of education (human capital accumulation)	X	X	X
Social networks (social capital accumulation)		X	X
Proximal decision-making phenotypes			
Smoking frequency (impulsivity)	X	X	X
Drinking frequency (impulsivity)		X	X
Exercise frequency (impulsivity)	X	X	X
Eating habits (impulsivity)		X	X
Health conscientiousness (impulsivity)	X	X	
Long-term memory (general cognitive ability)			X
Speed of processing (general cognitive ability)		X	X
Working memory (general cognitive ability)			X
MRI of the brain (general cognitive ability)			X

NOTES: This table displays phenotypic data already collected. For the next wave of the AGES-Reykjavik study, we plan to add additional distal phenotypes (wealth and income) and proximal phenotypes (experimental measures of impulsivity and risk-aversion). The cognitive SNP panel will be administered to participants in the AGES-Reykjavik study. In addition to the AGES-Reykjavik questionnaire, participants in the AGES-Reykjavik study have answered the Reykjavik study questionnaire once, twice, or six times during 1967–1991. The Older Persons Exam was administered to those aged 70 and older as of 1991.

TABLE 2. Genes that are candidates for inclusion in a panel of SNPs for association studies with cognitive, neural, and economic phenotypes, with notes on possible mechanisms mediating genetic influences on these phenotypes (or other reasons for including the gene). Both known or suspected functional SNPs in these genes, as well as tagging SNPs from the HapMap, would be used. Names and genomic positions are taken from OMIM or the UCSC Genome Browser. Genes marked with an asterisk (*) have known or probable functional alleles that are *not* SNPs. Citations given for each gene are meant to be representative of the suggestive evidence in the literature (through 2006), not exhaustive lists of relevant publications on the gene.

Gene	Position	Description and references
Dopamine (DA) System		
TH	11p15.5	Tyrosine hydroxylase
DDC	7p12.2	Dopa decarboxylase
VMAT1	8p21.3	Vesicular monoamine transporter 1
VMAT2	10q25.3	Vesicular monoamine transporter 2
DRD1	5q35.1	Dopamine receptor 1 ADHD (Bobb et al., 2005)
DRD2	11q23	Dopamine receptor 2 Neural activation during working memory (Jacobsen et al., 2006) DRD2 binding in striatum (Hirvonen et al., 2004)
DRD3	3q13.3	Dopamine receptor 3
DRD4*	11p15.5	Dopamine receptor 4 ADHD (Faraone et al., 2005)
DRD5	4p16.1	Dopamine receptor 5 ADHD (Faraone et al., 2005)
CALCYON	10q26.3	Calcyon (DRD1 interacting protein) ADHD (Laurin et al., 2005)
DAT1*	5p15.3	Dopamine transporter ADHD (Faraone et al., 2005)
COMT	22q11.2	Catechol-o-methyltransferase Frontal lobe, executive function (Egan et al., 2001; Meyer-Lindberg et al., 2006)
MAOA*	Xp11.23	Monoamine oxidase A NEO personality traits (Rosenberg et al., 2006); aggression GxE interaction (Caspi et al., 2002)
MAOB	Xp11.23	Monoamine oxidase B

DBH	9q34.2	Dopamine beta hydroxylase ADHD (Faraone et al., 2005)
Serotonin (5-HT) System		
TPH1	11p15.3	Tryptophan hydroxylase 1
TPH2	12q21.1	Tryptophan hydroxylase 2
HTR1A		Serotonin receptor 1A
HTR1B	6q14.1	Serotonin receptor 1B ADHD (Faraone et al., 2005)
HTR2A	13q14.2	Serotonin receptor 2A Explicit memory (de Quervain et al., 2003; Papassotiropoulos et al., 2005; Reynolds et al., 2006)
HTR3A	11q23.1	Serotonin receptor 3A Amygdala & frontal lobe function (Iidaka et al., 2005)
HTT*	17q11.1	Serotonin transporter Amygdala function (Hariri et al., 2003) ADHD (Faraone et al., 2005) Cognitive aging (Payton et al., 2005) Under selection in CEU and ASN populations (Voight et al., 2006)
Genes Reported to be Associated with General Cognitive Ability (reviewed by Payton, 2006; Plomin et al., in press)		
CBS	21q22.3	Cystathionine beta-synthase IQ (Barbaux et al., 2000)
CCKAR	4p15.2	Cholecystokinin A receptor IQ (Shimokata et al., 2005)
CHRM2	7q33	Muscarinic cholinergic receptor 2 IQ (Comings et al., 2003; Gosso et al., 2006) Performance IQ (Dick, Aliev, Kramer et al., 2006)
CTSD	11p15.5	Cathepsin D Mental retardation & microcephaly caused by mutation (Siintola et al., 2006) IQ (Payton et al., 2003, 2006)
IGF2R	6q25.3	Insulin-like growth factor 2 receptor IQ (Chorney et al., 1998; Jirtle, 2005)
KLOTHO	13q13.1	Klotho IQ (Deary et al., 2005b)
MSX1	4p16.2	Muscle segment homeobox, drosophila, homolog of, 1 IQ (Fisher et al., 1999)

NCSTN	1q23.2	Nicastrin IQ (Deary et al., 2005a) AD (Bertram et al., 2007)
PLXNB3	Xq28	Plexin B3 Vocabulary, white matter (Rujescu et al., 2006)
PRNP	20p13	Prion protein IQ (Rujescu et al., 2003; Kachiwala et al., 2005) Brain structure (Rujescu et al., 2002) Long-term memory (Papassotiropoulos et al., 2005b) AD (Bertram et al., 2007)
RECQL2	8p12	RECQ protein-like 2 Cognitive composite in LSADT (Bendixen et al., 2004)
SSADH	6p22.2	Succinate semi-aldehyde dehydrogenase IQ (Plomin et al., 2004) IQ linkage peak on chr6 is near this gene (Posthuma et al., 2005) Recent positive selection (Blasi et al., 2006)

Candidate Genes Near Linkage Peaks in Studies of IQ
(Posthuma et al., 2005; Luciano et al., 2006; Hallmayer et al., 2005; Dick, Aliev, Beirut et al., 2006)

NR4A2	2q24.1	Nuclear receptor subfamily 4, group A, member 2
SLC25A12	2q31.1	Solute carrier family 25, member 12
SCN1A	2q24.3	Sodium channel, neuronal type 1, alpha subunit
SCN2A	2q24.3	Sodium channel, neuronal type 2, alpha subunit
TBR1	2q24.2	T-box, brain, 1
SCN3A	2q24.3	Sodium channel, neuronal type 3, alpha subunit
KCNH7	2q24.2	Potassium channel, voltage-gated, subfamily H, member 7
GAD1	2q31.1	Gluatamate decarboxylase 1
HOXD1	2q31.1	Homeobox D1
CHN1	2q31.1	Chimerin 1
RAPGEF4	2q31.1	RAP guanine nucleotide exchange factor
NOSTRIN	2q24.3	Nitric oxide synthase trafficker
BBS5	2q31.1	BBS5 gene
DLX1	2q31.1	Distal-less homeobox 1
DLX2	2q31.1	Distal-less homeobox 2

KIF13A	6p22.3	Kinesin family member 13A
NQO2	6p25.2	NAD(P)H dehydrogenase, quinone 2
RANBP9	6p23	RAN-binding protein 9
PNR	6q23.2	Trace amine-associated receptor 5 (“putative neurotransmitter receptor”)
NRN1	6p25.1	Neuritin 1
S100B	21q22.3	S100 calcium-binding protein, beta

Genes Associated with Memory Ability

de Quervain & Papassotiropoulos, 2006

ADCY8	8q24.2	Adenylate cyclase 8
CAMK2G	10q22	Calcium/calmodulin-dependent protein kinase 2 gamma
GRIN2A	16p13	Ionotropic glutamate receptor, NMDA subunit 2A
GRIN2B	12p12	Ionotropic glutamate receptor, NMDA subunit 2B
GRM3	7q21.1	Metabotropic glutamate receptor 3 Frontal & hippocampal function (Egan et al., 2004)
PRKCA	17q22–23.2	Protein kinase C, alpha
PRKACG	9q13	Protein kinase, cAMP-dependent, catalytic, gamma

Papassotiropoulos et al., 2006

KIBRA	5q35.1	Kidney and brain expressed protein
CLSTN2	3q23	Calsyntenin 2

Kravitz et al., 2006

ESR1	6q25.1	Estrogen receptor 1 AD (Bertram et al., 2007)
HSD17B1	17q21.31	Hydroxysteroid (17-beta) dehydrogenase 1

Genes Associated with Schizophrenia (SZ)
(reviewed by Norton et al., 2006; Owen et al., 2005)

AKT1	14q32.3	V-AKT murine thymoma viral oncogene homolog 1
DAOA	13q34	D-amino acid oxidase activator
DISC1	1q42.1	Disrupted in schizophrenia 1 Hippocampal structure and function (Callicott et al., 2005) Cognitive aging in women (Thomson et al., 2005)

		Cognitive performance in SZ (Burdick et al., 2005; reviewed by Porteous et al., 2006)
DTNBP1	6p22.3	Dystrobrevin-binding protein 1 *g* in SZ & controls (Burdick et al., 2006) IQ (Posthuma et al., 2005): linkage peak on chr6 contains this gene PFC function (Fallgatter et al., 2006) Under selection in Europeans (Voight et al., 2006)
NRG1	8p22	Neuregulin 1 Premorbid IQ in high-risk SZ subjects (Hall et al., 2006)
RGS4	1q23.3	Regulator of G-protein signaling 4 Talkowski et al. (2006)

Genes Associated with Alzheimer's Disease (AD)
(reviewd by Bertram et al., 2007; Bertram & Tanzi, 2004)

ACE	17q23	Angiotensin I-converting enzyme
APOE	19q13.2	Apolipoprotein E Risk factor for AD, general cognitive function (Small et al., 2004)
BACE1	11q23.3	Beta-site amyloid beta A4 precursor protein-cleaving enzyme 1 Interacts w/ APOE (Bertram & Tanzi, 2004) Modulates myelination in mice (Hu et al., 2006)
CHRNB2	1q21	Cholinergic receptor, neural nicotinic, beta polypeptide 2
CST3	20p11.2	Cystatin 3
GAPDHS	19q13.1	Clyceraldehyde-3 phosphate dehydrogenase, spermatogenic
IDE	10q23.33	Insulin-degrading enzyme 2 Interacts w/ APOE (Bertram & Tanzi, 2004)
MTHFR	1p36.3	Methylenetetrahydrofolate reductase
PSEN1	14q24.3	Presenilin 1
TF	3q21	Transferrin
TFAM	10q21	Transcription factor A, mitochondrial
TNF	6p21.3	Tumor necrosis factor

Genes Associated with Brain/Head Size
(except for VDR, all have mutations causing microcephaly)

ASPM	1q31.3	Abnormal spindle-like, microcephaly-associated Under selection in humans (Mekel-Bobrov et al., 2005) Small effect on IQ subtests (Luciano et al., 2006) No significant effect on normal-range brain size (Woods et al., 2006)

CDK5RAP2	9q33.2	CDK5 regulatory subunit associated protein 2 Brain size (Woods et al., 2005; Evans et al., 2006) Reverse association w/ verbal IQ (Luciano et al., 2006)
CENPJ	13q12.12	Centromeric protein J Brain size; under selection in CEU sample (Voight et al., 2006; cf. Evans et al., 2006)
MCPH1	8p23.1	Microcephalin Under selection in humans (Evans et al., 2005) No significant effects on IQ subtests (Luciano et al., 2006), normal-range brain size (Woods et al., 2006)
VDR	12q13.11	Vitaimin D receptor Head size (Handoko et al., 2006), not associated with schizophrenia
Genes Associated with Miscellaneous Brain and Cognitive Functions		
BDNF	11p14.1	Brain-derived neurotrophic factor Memory, hippocampus (Egan et al., 2003; Dempster et al., 2005) Age-related cognitive decline (Harris et al., 2006) Not associated with working memory performance (Hansell et al., 2006)
CHRNA4	20q13.2	Neuronal nicotinic cholinergic receptor alpha polypeptide 4 Attentional function (Greenwood et al., 2005; Parasuraman et al., 2005)
CHRNA7	15q13.3	Neuronal nicotinic cholinergic receptor alpha polypeptide 7 Schizophrenia and auditory processing (Leonard et al., 2002)
NET1	16q12.2	Norepinephrine transporter ADHD (Bobb et al., 2005)
OXTR	3p26.2	Oxytocin receptor Trust; autism (Wu et al., 2005; Ylisaukko-Oja et al., 2005)
PAX6	11p13	Paired box gene 6 Development of executive function networks (Ellison-Wright et al., 2004)
SNAP25	20p12.2	Synaptosomal-associated protein, 25-KD ADHD (Faraone et al., 2005) Performance IQ (Gosso et al., 2006)
FADS2	11q12–q13	Fatty-acid desaturase 2 ADHD (Brookes et al., 2006)
NOS1	12q24	Neuronal nitric oxide synthase PFC function, schizophrenia (Reif et al., 2006)
CETP	16q21	Cholesterol ester transfer protein Better MMSE performance in centenarians (Barzilai et al., 2006)

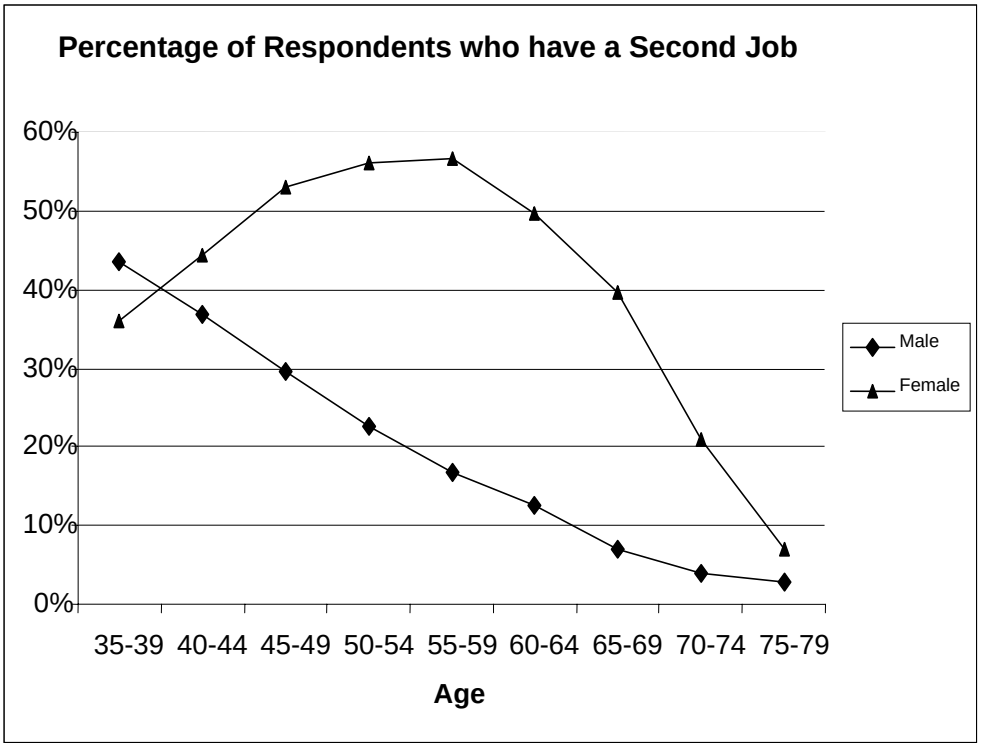
Percentage of Respondents who have a Second Job
60%
50%
40%
30%
20%
10%
0%
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
Age
Male
Female

FIGURE 1

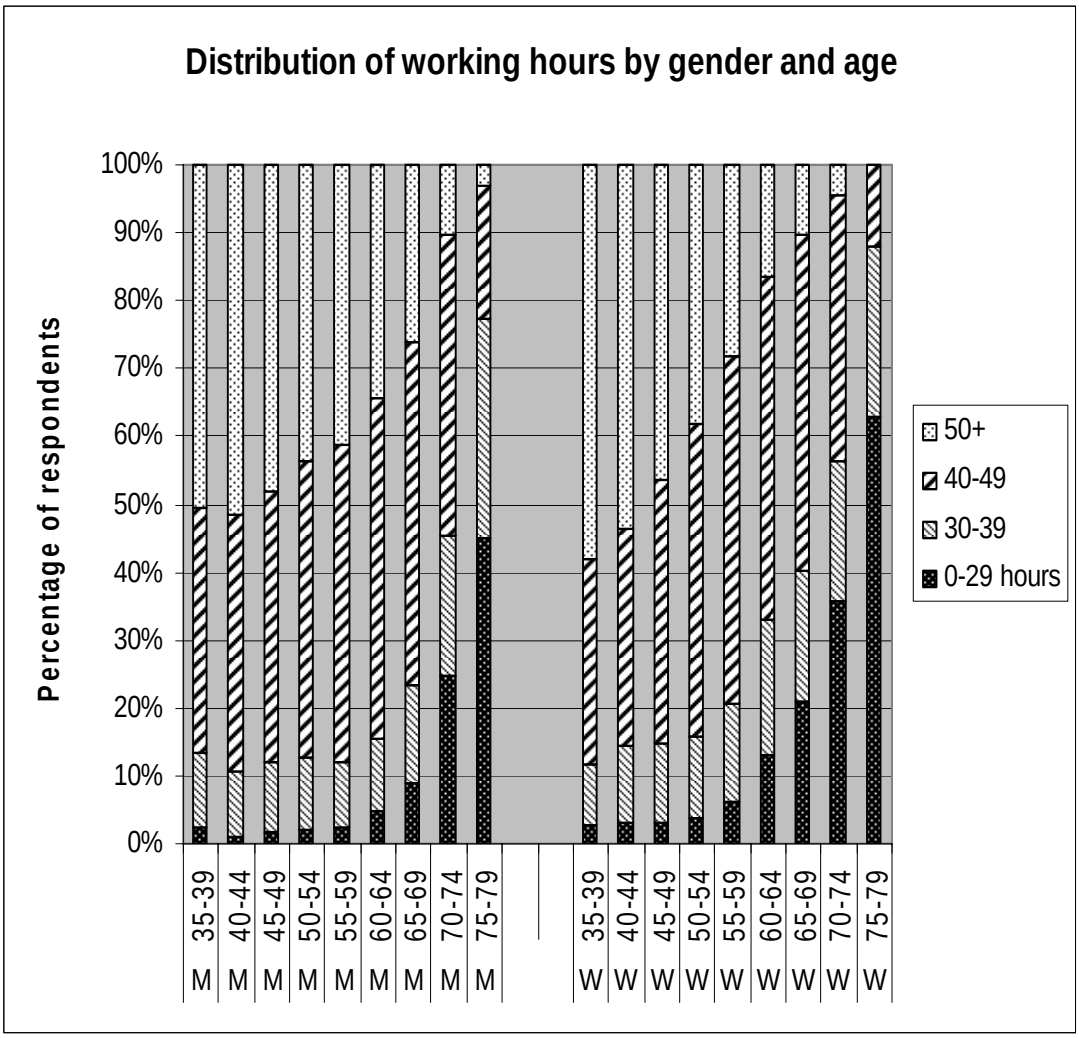
Distribution of working hours by gender and age
Percentage of respondents
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
50+
40-49
30-39
0-29 hours
35-39 M
40-44 M
45-49 M
50-54 M
55-59 M
60-64 M
65-69 M
70-74 M
75-79 M
35-39 W
40-44 W
45-49 W
50-54 W
55-59 W
60-64 W
65-69 W
70-74 W
75-79 W

FIGURE 2