A Genome-Wide Analysis of Liberal and Conservative Political Attitudes

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The assumption that the transmission of social behaviors and political preferences is purely cultural has been challenged repeatedly over the last 40 years by the combined evidence of large studies of adult twins and their relatives, adoption studies, and twins reared apart. Variance components and path modeling analyses using data from extended families quantified the overall genetic influence on political attitudes, but few studies have attempted to localize the parts of the genome which accounted for the heritability estimates found for political preferences. Here, we present the first genome-wide analysis of Conservative-Liberal attitudes from a sample of 13,000 respondents whose DNA was collected in conjunction with a 50-item sociopolitical attitude questionnaire. Several significant linkage peaks were identified and potential candidate genes discussed.

There is marked family resemblance for political attitudes (Alwin, Cohen, and Newcomb 1991; Jennings and Niemi 1982). The dominant paradigm in the social and political sciences has asserted that this resemblance is due almost entirely to social learning, social background, or environmental influences (Campbell et al. 1960; Converse 1964; Jennings and Niemi 1968). Indeed, social and political behaviors have been used to illustrate elegant mathematical theories of cultural inheritance (Cavalli-Sforza and Feldman 1981). However, over the last 40 years, a series of very large studies of twins, families, and adoptions have given strong support to the alternative view that a significant component of family resemblance on political attitudes is genetically influenced (Eaves, Eysenck, and Martin 1989; Eaves et al. 1999; Martin et al. 1986). More recently, political scientists have also adopted a "partially genetic" approach (Alford, Funk, and Hibbing 2005; Fowler, Baker, and Dawes 2008; Hatemi et al. 2009) and using longitudinal and extended pedigree studies further elaborated on the genetic influence for political attitudes (Eaves and Hatemi 2008; Hatemi et al. 2010).[1]

Familial modeling is most valuable for clarifying modes of transmission and identifying the potential for genetic and environmental sources of influence,

[1]All appendices are located online at http://www.journals.cambridge.org/JOP.

The Journal of Politics, Vol. 73, No. 1, January 2011, Pp. 271–285 doi:10.1017/S0022381610001015

ISSN 0022-3816

but it does not identify the specific biological systems relevant to political preference formation. Identifying these systems is necessary for understanding the pathways, if any, from genes to complex political behaviors and preferences, such as attitude positions or ideology. For example, identifying genes that influence the development of neurological functions and release of hormones, which in turn influence cognition and interpretation of environmental stimuli, could indicate whether the genetic basis of political preferences share common biological influences with cognition (Gazanniga 2004), reactions to threat (Oxley et al. 2008), morality (Lakoff 2002), disgust (Rozin, Haidt and Fincher 2009), emotion reading (Dolan 2002), risk taking (McClure et al. 2004), reproductive differences (Skuse 2005), fear (Hatemi and McDermott 2009), aggression (McDermott et al. 2009), pursuit of power (Madsen 1986), or rational action (Sanfey et al. 2003), to name just a few possibilities.

However, no studies have yet attempted to identify specific genes that contribute to the genetic influence on political preferences utilizing genome-wide methods. This is not to say there has been no attempt to link specific genes to political behavior. There are two basic approaches to identifying genes for complex traits. The first exploits a priori information that suggests a certain gene might be expected to be associated with a specific trait. This "candidate gene" approach has recently been undertaken for political traits and several genetic markers have been implicated using allelic[2] association methods, including monoamine oxidase and serotonin for voting participation (Fowler and Dawes 2008), serotonin for certain attitude positions (Hatemi et al. 2008), and dopamine for ideology (Dawes and Fowler 2009). However, these candidate gene studies were undertaken because those genes were previously found to be associated with traits similar to political attitudes. This is important because in most studies of complex human traits, candidate gene studies not supported by genome wide methods have typically been unrewarding and not replicated. For example, in possibly the most celebrated of allelic gene-environment interaction studies, Caspi et al. (2003) reported that 5-HTTPLR (serotonin) moderates the effects of stressful life events on depression. However, a recent meta-analysis provided evidence that Caspi's results do not withstand empirical validation (see Risch et al.2009).

As a result, geneticists have tended to pay more attention to a second approach; to search systematically across the genome for genes that demonstrate significant association with the trait in question while taking into account all other identified genetic markers. There are over 20,000 identified genes in the human genome, many of which we know little about. Genome-wide methods allow researchers to search for individual genetic markers or chromosomal regions that influence a trait, regardless of their function, and offer a much more robust test than candidate gene studies which are biased by the choice of genes included. Thus, genome-wide analyses can implicate specific genes or regions of genes that we *did not* suspect were influencing a trait of interest and thus reveal novel pathways to the formation of political orientations.

Although there is a growing volume of evidence confirming Fisher's (1918) conjecture that human physical and behavioral traits reflect the cumulative small effects of a very large number of individual genetic loci (e.g., Benyamin et al. 2008), so far, there has been no systematic empirical attempt to begin such analysis for individual differences in political preferences using sample sizes that come near those required to detect the relatively small effects of individual quantitative trait loci (QTL)[3] likely to account for the genetic components of complex traits. Here, on over 13,000 individuals, we present the results from the first genome-wide analysis on Conservative-Liberal orientations which identifies several significant genetic focal points. In doing so we begin the initial step of locating genes which may account for the source of heritability found from twin and kinship studies.

The structure and nature of this article is somewhat different from that of traditional hypothesis testing models. Genome-wide approaches are not absent theory, but they are data driven. They are used to identify genetic markers for future hypothesis testing using candidate gene and marker approaches or hormonal assays, and "genome-wide linkage," the approach we use here, is one such method. Genome-wide linkage is an exploratory method which identifies a particular region of the genome where shared ancestry between relatives correlates significantly with their similarity for the trait of interest. The approach gives researchers a rationale for searching for individual genetic loci within that region. The findings from this process allow for better informed hypothesis testing, a place to look for replication and a means to combine the linkage results with other methods for future analyses (see Fulker et al. 1999; Roeder et al. 2006). This article illustrates the application of genome-wide

[2]An allele is a different form of a gene at a particular locus. For example, Dawes and Fowler (2009) found that individuals with the A2 allele of the D2 dopamine receptor gene were significantly more likely to identify as a partisan than those with the A1 allele.

[3]QTL is a region of DNA that is associated with a particular measurable trait.

linkage to family data on social and political attitudes. It provides an initial suggestion of specific genomic regions that might contain loci contributing to individual genetic differences in these socially significant aspects of human behavior.

Material and Methods

The human genome consists of approximately 3.2 billion nucleotides, organized into well over 20,000 functional genes plus a tremendous amount of material outside of the protein-coding regions. To discover a single "gene" that is related to a given behavior is virtually impossible without first acquiring some sense of a promising place to look. One cannot simply go through the entire genome one gene at a time and test for the association of allelic differences and differences in ideology and have any belief in the results. Such an approach is both impractical as well as statistically inappropriate. Genome-wide linkage constitutes one method of narrowing down the regions in which there is likely to reside a gene or genes relevant to the phenotype[4] of interest and identifies regions of markers suitable for candidate marker association analyses. The phrase "genome-wide linkage" might suggest to nongeneticists something quite different from what it actually is. It does not indicate a gene by gene scan of the entire genome in search of individual loci that vary in ways predictive of a behavioral variation of interest. Instead it refers to an attempt to narrow the search to a specific stretch of territory on a specific chromosome, across all chromosomes that could potentially contain individual genes that vary with the behavior of interest (for more on the rationale behind linkage see Appendix A).

The mapping of the human genome has identified a tremendous number of genetic markers. However, it is not necessary for the marker itself to shape a trait, only that it be polymorphic (come in different alleles) and that its location be known. Much of the human genome is identical for all people, but sections do vary from person to person. These "polymorphic" portions are important in explaining human variation. Polymorphisms can result either because of variations in a single nucleotide (these are called SNPs or single nucleotide polymorphisms) or because a DNA section has a different length in one person than in another. The latter is usually due to a short DNA sequence repeating a different number of times and leading to a short version of the gene in some people and a long version in others (very short repeat sequences are often called microsatellites). Regardless of their nature, these polymorphisms make it possible to search the genome for regions where the phenotype seems to be inherited (cosegregate) with one of the genetic markers.

[4]A phenotype can be any observable characteristic of an organism, such as physical parts, metabolism, reflexes, or behaviors.

Sample and Measures

All participants were relatives of Caucasian ancestry. Participants completed a Health and Lifestyle Questionnaire (HLQ) between 1988 and 1990 and gave blood samples for DNA extraction and genotyping. Conservatism-Liberalism was assessed by a 50-item scale of contemporary socially and politically relevant Australian attitudes designed to be similar to the Wilson-Patterson (1968) inventory. The inventory presented participants with a short stimulus word or phrase and asked them to respond positive, negative, or neutral to each (the specific attitudes and question format are presented in Appendix B). Confirmatory factor analysis of these items on this population has shown that a uni-dimensional model fits the data, but three to five correlated subfactors may also be extracted (Martin et al. 1986; Verhulst, Hatemi, and Martin 2010). The present analysis focuses on the first general factor of Conservatism-Liberalism which is normally distributed (Appendix C) and widely used in the extant literature (Bouchard et al. 1990).

Complete Conservatism-Liberalism scores were available on 20,725 individuals from 8,139 families, which included parents, siblings, spouses, and offspring. However, the number of participants for which we have genotypic data is less. Complete phenotypic *and* genotypic data were available for 13,201 people from 2,774 families (for family structure see Table 1).

Genotyping was performed using standard methods at one of five genotyping centers: Gemini P/L, Sequana Therapeutics Inc., Leiden University Medical Centre, Center for Mammalian Genetics, Mammalian Genotyping Service of the Marshfield Clinic Research Foundation, and the Australian Genome Research Facility. Descriptions of genotyping and the subsequent merging and data cleaning to remove Mendelian errors,[5] unlikely genotypes,[6] and consistency

[5]A Mendelian error occurs when an allele in an individual could not have been received from the biological parents by Mendelian inheritance, or the structure of the inheritance as defined by the parental genes is incorrect. This can happen if one or both parents of an individual are not actually the parent indicated or result from laboratory error.

[6]Inclusion of unlikely genotypes may give a false positive result.

TABLE 1 Family Structure for Persons with Genome-Wide Linkage Data

No. of families	2,774
No. of individuals	13,201
Pair counts	
No. of sib pairs	7,433
No. of half sibs	111
Cousins	14
Parent-child	14,962
Grandparent-grandchild	524
Avuncular	251
Proportion of families with	
2 sibs	58.5%
3 sibs	4.4%
$\geq$ 4 sibs	11.0%

of pedigree and marker relationships is described in detail elsewhere (see Wray et al. 2008). All family members' DNA samples were submitted to the same genotyping facility.

Map positions of all 2,171 microsatellite markers were estimated in Kosambi cM[7] by locally weighted linear regression from the National Center for Biotechnology Information (NCBI) build 35.1 physical map positions and published Decode and Marshfield genetic map positions (Duffy et al. 2007). Individuals were required to have genotypes on more than 280 markers resulting in a minimum average distance of 8.2 cM between genotyped markers of sib pairs in order to be included in the sample, so as to reduce the chance of spurious findings. Thirty-eight percent of parents were genotyped.

Statistical Method

In order to detect which chromosomal regions may be responsible for variation in our Conservatism-Liberalism factor we conducted variance components genome-wide linkage analysis with age and sex as covariates in MERLIN 1.1.2 (Abecasis et al. 2002) using a 10cM grid with maximum likelihood estimated allele frequencies. This commonly used method tests for cosegregation of chromosomal regions and the phenotypic trait of interest (Conservatism-Liberalism). The significance of each individual marker is assessed by comparing the difference in the $\log_{10}$ likelihood between a model that includes the marker and one in which the marker's effect is fixed to zero. The logarithm of odds (LOD) score is used as a guide to assess the weight of evidence in favor of linkage at each location throughout the genome and is the statistical test for determining significant linkage. LOD scores greater than 3.0 are significant (Lander and Kruglyak 1995) and the likelihood of observing a significant genetic polymorphism which is not linked to the trait is less than 1 in 1000. However, linkage analysis has limited power to detect genes of small effects. When many genes contribute to trait variation, as is almost certainly the case with political temperament, then even very large linkage studies may not have sufficient statistical power to detect the effects of most genetic loci (Carey 2003). Thus, it is conventional in genetic studies to report LOD scores above 2.5 as "suggestive" and pursue replication in future studies (e.g., Bakker et al. 2003).

[7]Kosambi is a mapping function to measure distance between genetic markers, expressed in centimorgans (cM).

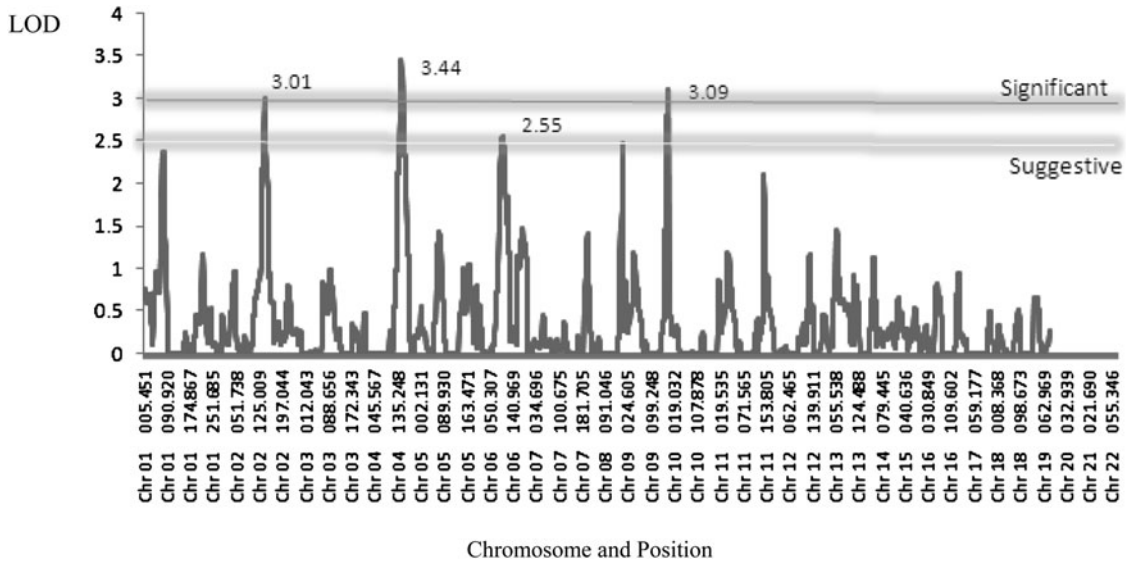
Results

Figure 1 plots the LOD scores by location for the genome-wide variance component linkage analysis of the Conservatism-Liberalism attitude factor, adjusted for age and sex. Three of the peaks reach genome-wide significance (LOD >3) as defined by Lander and Kruglyak (1995) and one peak reaches "suggestive" linkage (LOD >2.5).

Geneticists use several standardized ways of describing a gene's location on a given chromosome. Here we use one such method, the location and sequence of base pairs for each human chromosome. This sequence provides a specific molecular "address" of a gene and pinpoints the location in terms of the base pairs. It describes the gene's precise position on a chromosome and indicates the size of the gene. Significant LOD score peaks were found on: chromosome 4 between 137,000K and 178,000K base pairs (bp) with the peak at 142,000K bp (LOD score of 3.44); chromosome 9 between 135,000K and 165,000K bp with the peak at 150,000K bp (LOD score of 3.09); and chromosome 2 between 130,000K and 155,000K bp with the peak at 142,000K bp (LOD score of 3.01). One suggestive LOD peak was found on chromosome 6 between 78,000K and 98,000K bp with the peak at 93,000K bp (LOD score of 2.55). These four most significant QTLs accounted for an estimated 12.9%, 12.9%, 12.7% and 9.4% of the total phenotypic variation on the Conservatism-Liberalism attitude factor.

However, these effects may be biased upwards as a result of capitalizing on chance deviations, and as is commonly the case, their sum is greater than the

FIGURE 1 Results of Genome Wide Linkage on Conservative-Liberal Political Attitudes



heritability of the trait obtained through analysis of the correlations between relatives. Thus, we simulated empirical significance levels for these pedigrees, phenotypes and configurations of markers using gene-dropping simulations (for more detail, see Appendix D). Using this more conservative approach, *the simulation based* one-tailed genome-wide significance level was estimated to be 0.05 for LOD scores of 3.47, instead of 3. We include this simulated significance value as an added statistical measure of caution, but not to replace the standard significance criteria, as we do not want to wrongfully dismiss a true linkage signal. Indeed, by convention, a LOD score greater than 3.0 is considered evidence for linkage and is used in future studies to test markers in the regions identified. By the simulated criteria, only the region identified on chromosome 4 was significant at the .05 level, making this region the most likely to be replicated if the linkage signal is not specific to our population.

As we identified four regions of interest, and one that meets the strictest criteria, our findings are consistent with what might be expected if the genetic component of variation in Conservatism-Liberalism resembles any other polygenic human trait, for which the genetic resemblance between relatives can only be resolved reliably into the effects of a large number of genes with small effects that typically cannot be identified by linkage. This makes our findings all the more intriguing. That is, the expectation that we should find no significant linkage peaks for such a complex human trait as political orientation is not supported. Rather, we find the opposite, which is somewhat remarkable, because for many biometric traits, more commonly viewed as being genetically influenced, such as height, LOD peaks are most often well below 3, as most genetic influences are the cumulative effect of a very large number of genes with very small effects, and linkage signals seldom have the power to identify such small effects. Here we found regions of interest which contain many genetic loci, but only a few loci in those regions have been previously identified as having some relationship with human social behavior. While the findings offer reasons for optimism, the relatively modest LOD scores are consistent with what we know about genetics at this point in time and what we should expect for such a complex human trait.

Looking Within the Linkage Regions to Identify Potential Candidate Genes

Linkage signal regions are large and can include many genes. Linkage does not identify a specific genetic marker, but regions on a chromosome. Any link between ''genes'' and political attitudes or behaviors would entail a long and complex developmental trajectory involving networks of individual pathways which include, but are not limited to: epigenetic mechanisms, development, products of metabolism and brain function, as well as the behavior of the whole organism in creating, selecting and being affected by salient environments. Elaborating on linkage results remains an imperfect science.

Significant linkage signals give us an empirically supported reason to look within a specific location for genetic loci. From this point, researchers can then further explore the genes closest to the linkage peak or identify genetic markers within the significant region which have some known functional reason to influence the trait of interest, based either on some previously known biological function, or on a previously identified significant allelic association.

Using data from the National Center for Biotechnology Information (NCBI) human genome database,[8] we provide all the known genetic variants surrounding each of the linkage peaks within a 95% confidence interval (CI) of the LOD score. These are located in Appendices E-H because the number of markers on each chromosomal region makes it impractical to present them in tables within the text. We reviewed every gene within the CI's of our observed linkage peaks to identify which, if any, have previously been implicated in cognitive functioning or social behaviors. These genes, specifically ones directly located at the LOD peaks, are then potential candidate genes accounting for the linkage signals found for Conservative–Liberal orientations. We discuss these markers with their location and distance from the LOD peak in more detail below. We further elaborate on the identified genetic markers as to their potential influence on political attitudes.

Genes within the 95% Confidence Interval of the LOD Peak on Chromosome 4

This being said, of the 60 known genetic markers within the 95% CI of the LOD peak (142,000K) on Chromosome 4, only one, which was also located a minimal distance from the peak, has previously been associated with human social behavior (see online Appendix E). NARG1, an N-methyl-D-aspartate (NMDA) receptor is located at 140,442K bp and has a significant LOD score of 3.38. NMDA is part of the ionotropic family of glutamate receptors. Glutamate is the principal excitatory neurotransmitter in the brain and is directly involved in a wide array of cognitive functions such as memory and learning (Jamain et al. 2002). The gene NARG1 is understood to encode an N-acetyltransferase protein thought to be important for vascular, hematopoietic, and neuronal growth and development (Sugiura, Patel, and Corriveau 2001). It is expressed at high levels in the testis and ocular endothelial cells, but also found in the largest connective pathway in the human brain (corpus callosum). NMDA receptors have been found to play an important role in a wide range of physiological, behavioral, and cognitive processes in mammals and contribute to synaptic transmission at sites throughout the brain and spinal cord. Both human and animal studies have identified NMDA being related to cognitive-behavioral performance, working memory, counting behavior, social learning, fear conditioning, spatial learning, motor performance, and social interaction, to include prosocial, antisocial, and aggressive behaviors (Duncan et al. 2004; Gewirtz and Davis 1997).

Genes within the 90% Confidence Interval of the LOD peak on Chromosome 9

On chromosome 9, there are no known genetic markers within the 95% confidence intervals of the LOD peak (3.09) at 150,000K bp. This is not surprising as there are no markers identified after 141,000K bp on chromosome 9. If we extend the CI to 90%, the range includes 120 known genetic markers (see online Appendix F). However, this range moves out of the significant LOD criteria of 3. In this *suggestive* range (90% CI), at 140,000K bp (LOD 2.78) is GRIN1, a glutamate receptor which encodes a protein that is a critical subunit of NMDA (Mundo et al. 2003). This location also includes DBH (dopamine beta-hydroxyla, LOD 2.28), which encodes a protein that converts dopamine to norepinephrine. DBH has been positively associated with attention-deficit hyperactivity disorder (Nyman et al. 2007) and substance dependence (Freire et al. 2006), while norepinephrine is primarily an emergency hormone and has numerous behavioral implications, most notably "fight or flight" response. Another marker of interest is LHX3 (139,000K bp, LOD 2.76), which is expressed at all stages of early development with essential roles in pituitary and motor neuron development (Sobrier et al. 2004).

Curiously, there are also a large number of genes related to olfaction in this region (LOD range 2.16-2.78), including: OBP2B (136,000K bp), LCN1, LCN9, and OLFM1 (137,000K bp), LCN6, 10, 12, 15 and OBP2A (138,000K bp), and LCNL1, LCN8 and PTGDS (139,000K bp). The majority are lipocalins, which are a group of proteins that are suspected to play a role in reproduction, odor transport, taste reception, and are linked to olfaction and pheromone receptors (Lacazette et al. 1997; Rajab et al. 2008). The two odorant binding proteins OBP2B and OBP2A also belong to the lipocalin superfamily and are believed to participate in odor detection by transporting, deactivating, and/or

[8]See http://genome.ucsc.edu/cgi-bin/hgGateway

selecting odorant molecules through the nasal mucus to olfactory receptors (Lacazette, Gachon, and Pitiot 2000).

Genes within the 95% Confidence Interval of the LOD Peak on Chromosome 2

On chromosome 2 there are 84 genetic markers in the 95% CI range (see Appendix G). Of these, only two have been previously implicated in human social and cognitive behaviors. The gene KYNU, located at 143,000K bp, is directly on the significant LOD peak (3.01). KYNU is part of the kynurenine and glutamate pathways and is significantly expressed in one of the few cell types to produce QUIN, which is an NMDA antagonist (Guillemin et al. 2007). In addition, GPR39 (133,000K bp, LOD 2.18) is 9,000K bp from the LOD peak. This gene is part of the G protein-coupled receptors (GPCRs) which belong to the metabotropic family of glutamate receptors and activate intracellular messenger systems (Zhang et al. 2008). GPR39 is believed to be important for the functions of numerous metabolic organs (Dong et al. 2009) and modulates a wide array of physiological roles, including visual sense, the sense of smell (through olfactory, pheromones and vomeronasal receptors), food intake, gastric mobility, regulation of immune system activity, and autonomic nervous system transmission (e.g., blood pressure and heart rate, see Egerod et al. 2007), as well as behavioral and mood regulation (receptors in the brain bind several different neurotransmitters, including serotonin and dopamine, see Tang et al. 2008).

Genes within the 95% Confidence Interval of the LOD Peak on Chromosome 6

Finally, on Chromosome 6 there are over 250 genes located within the 95% CI of the suggestive LOD peak of 2.55 (93,000K bp, see online Appendix H). Such a large amount of identified genes is not unexpected, as chromosome 6 constitutes about 6% of the human genome and better than 96% of the protein-coding genes on chromosome 6 have been identified, to include 1,500 genes and 600 pseudogenes. We found only eight genes in this suggestive region that were previously implicated in human behavior and cognition. Most interesting in this group are the neurotransmitters HTR1E (87,000K bp, LOD 2.36) and HTR1B (78,000K bp, LOD 1.88). These are two of several different receptors for 5- hydroxytryptamine (serotonin), a biogenic hormone that exerts a wide variety of physiological functions through a multiplicity of receptors (Heath and Hen 1995; Zifa and Fillion 1992). The serotonin system modulates affective, cognitive, and behavioral processes, presynaptic inhibition, and influences vascular effects, such as pulmonary vasoconstriction (Dickel et al. 2007). The highest concentrations in the brain are found in the frontal cortex, where it is believed to regulate the release of dopamine, and in the basal ganglia. Previous studies have found serotonin receptors important in a wide array of psychological and behavioral traits, including: executive control, impulsivity, compulsive behaviors, mood, anger, aggression, fear, cooperation, learning, memory, body temperature, sleep, sexuality, appetite, metabolism, personality traits, suicide, alcoholism, depression, anxiety, addiction, posttraumatic stress, and autism, among others (Davidge et al. 2004; Gillihan et al. 2007; Hu et al. 2006; Jensen et al. 2009; Lesch et al. 1996; Lopez-Leon et al. 2008; Sibille et al. 2007; Strug et al. 2008).

There are several other genes of interest in the 95% CI region. Mannosidase, endo-alpha (MANEA), located at 96,000K bp (LOD 2.43), encodes the enzyme a-endomannosidase that metabolizes carbohydrates and has been associated with cocaine dependence (Farrer et al. 2009). Three other G protein-coupled receptors (see discussion above), GPR63, GPR6, GPRC6A, were also within the 95% CI (LOD 2.43). The region also included GRIK2 (101,000K bp), another glutamate receptor. One final marker of interest is DDO (D-aspartate Oxidase, 110,000K bp), which encodes a protein that catalyzes the oxidative breakdown of NMDA.

Linking Genes to Political Orientation

Because the influence of specific genes on political ideology and the processes by which genes could be indirectly influencing ideology are relatively unknown, it is useful to discuss the markers identified above and to consider hypotheses based on what we know of previous relationships between political ideology and biological systems. It is here that we believe genetics research may prove its best use for political science. It is highly unlikely that there is any reason for certain genes to directly influence political preferences. Identifying which biological processes are related, however indirectly, to political orientations, is one plausible avenue to better understand how and why individual differences are accounted for, to any substantial degree, by genetic variance. Genome-wide analyses offer an empirically driven reverse engineering approach. Narrowing down the genome, identifying specific markers, and building

testable hypotheses on what biological systems those genetic markers influence may prove to be a very powerful method for a better understanding of the ''nature'' of political behavior.

The results point toward NMDA and glutamate related receptors as being worthy of further examination. Indeed, in every significant or suggestive chromosomal region these receptors were implicated. Specifically, NARG1 and KYNU were both located on or very near the significant LOD peaks for their respective chromosomes. NMDA has been explored at length for cognitive performance and childhood development. Thought organization, information processing, capacity for abstract thought, learning, and performance are related to blockage of NMDA (e.g., Anis et al. 1983). Of particular interest to political ideology is the relationship between NMDA and performance on the Wisconsin Card Sorting Test (WCST). The WCST is a neuropsychological test of the ability to display flexibility in the face of changing schedules of reinforcement (Krystal et al. 1998). By definition Conservatism and Liberalism have much to do with flexibility of opinion in the face of a changing world (Wilson 1973). Much research regarding NMDA and behavior has focused on performance tasks, but we know very little about its relationship to social tasks and preference structures. Thus, the results of our linkage scan provide a strong reason to explore the glutamate and NMDA system more thoroughly for its relationship between information processing and political ideology.

It makes sense to also include the ''suggestive'' serotonin receptors on chromosome 6 in this discussion with NMDA and political orientations, as both NMDA and serotonin have been significantly associated with a similar array of traits relevant to human social behaviors. Indeed, in various neurochemical studies, functional relationships between serotonin and NMDA have been reported (Madden and Morrison 2006; Shishido et al. 2000; Yuen et al. 2005) as they are both critically involved in the regulation of cognition and emotion (Canli and Lesch 2007; Hariri and Holmes 2006). Among the more intriguing relationships are the role both NMDA and serotonin have as regulators of fear, stress, and anxiety (Dai et al. 2008; Hariri et al. 2002; Young et al. 2007). Recently, there has been renewed interest in the influence of threat, fear and anxiety on ideological positions (Lupia and Menning 2009). For example, Oxley et al. (2008) found physiological differences in threat reaction between those with more conservative positions on outgroups (e.g., attitudes on immigration), while Hatemi and McDermott (2009) found that individual differences in fear dispositions were a significant predictor of political attitudes, and that the relationship between social fear and outgroup attitudes was largely of function of shared genetic influence (also see Jost et al. 2008). Furthermore, certain political dispositions and behaviors, such as political participation (Fowler and Dawes 2008) and power seeking (Madsen 1986) have been found to be significantly related to serotonin receptor length and whole blood levels of serotonin respectively. Based on the combination of our findings with those in the extant literature, the NMDA receptor NARG1, as well as KYNU and the serotonin loci HTR1E and HTR1B, are promising genes for allelic relationships with political attitudes, particularly those that are influenced by fear or anxiety. Future explorations would benefit by also including associated downstream neurobiological pathways, to include hormone regulation.

The remaining genes located in the linkage regions that relate in some way to human social behavior do not present as clear a path toward political influence nor are they as empirically supported. They are much less explored for social behavior, though there are some interesting connections worth mentioning. For example, the gene DBH, found on chromosome 9, is part of the dopamine pathway, and glutamate, by activating NMDA receptors, in part regulates dopamine release. The dopamine system has been implicated in a wide variety of personality and political behaviors, such as partisanship (Dawes and Fowler 2009), liberalism when combined with number of friends (Settle et al. 2010), attachment (Fisher et al. 2002) cognition, attention, working memory, planning, visual processing, novelty seeking, and reward dependence (Backman et al. 2000; Cropley et al. 2006; Noble et al. 1998; Reeves et al. 2005). However, DBH is on the tail end of the 90% confidence interval, and research on DBH has largely focused on ADHD and clinical traits, unlike better known dopamine receptors such as DRD4 and D2, which have been explored for a wide array of social behaviors and dispositions. Yet, DBH and D2 have been found to have the same effect on substance use behaviors (Freire et al. 2006). Therefore, we consider DBH a potential candidate gene for political orientation, but remain cautious to its relevance, as it has yet to be explored for any nonclinical human social behaviors as far as we know.

We are also intrigued by the large number of receptors related to olfaction located within the 90% CI on chromosome 9. Olfactory receptors constitute the basis for the sense of smell and the transfer of odor is aided by odorant-binding proteins, which are

members of the lipocalin family. Two areas of research link olfaction and political preferences. First, mate selection has been linked to pheromone, lipocalin, and olfactory receptor activity in humans and mammals (Brennan 2004; Havlicek and Roberts 2009; Ziegler, Dohr, and Uchanska-Ziegler 2002). LCN6, identified in our linkage scan, is believed to be one of the genetic markers which influence fertility and reproduction in humans (Hamil et al. 2003). This is of interest because mate selection has also been linked to political attitudes (Alford et al. 2010; Eaves et al. 2010).[9] Indeed spousal concordance for politics is among the highest of all social traits in the United States and Australia. If olfactory receptors account for some variation on political preferences, it may do so through intended optimal breeding and rearing strategies such as spousal selection.

Secondly, there is a relationship between disgust, political preferences, and sense of smell (Miller 1997). Rozin, Haidt, and McCauley (2000) suggested that humans have a ''core disgust'' system which involves the rejection of foul tastes and smells, and this system has been shown to differ by political orientation. Individuals with more conservative political positions intimated a higher predisposition to feel disgust (Inbar, Pizzaro, and Bloom 2009). One possibility in which political preferences vary by disgust sensitivity might just be through neural structures linked to taste or smell. However, as noted, the results on chromosome 9 are particularly tentative, and we can only speculate on the complexities of a relationship between the olfactory markers identified with spousal concordance on political preferences or disgust sensitivity and political ideology.

Considerations and Limitations

Because individual genetic effects for complex traits are likely to be smaller than the resolving power of linkage studies the alternative strategy of genome-wide association scans (GWAS) is becoming more widely used. GWAS studies compare the DNA of people on a polymorphism by polymorphism basis, rather than a region approach such as linkage. GWAS can take advantage of high-throughput genotyping techniques to screen entire genomes for large samples of unrelated individuals in an attempt to identify specific genes which may be responsible for the trait of interest. This approach offers a more powerful alternative to identify genes with small effects.[10]

Although linkage is becoming less common in comparison to the more frequent use of GWAS, it is nonetheless an important part of genetics research. The discovery of the BRACA1 and BRACA2 breast cancer susceptibility genes is owed to linkage (Rowell et al. 1994). Not only does linkage avoid problems of population stratification,[11] linkage information can also be incorporated into weighted false discovery rate estimates which are used to correct for the problem of multiple testing encountered in GWAS studies (Roeder et al. 2006).

The value of linkage is underscored by the finding that *true* linkage signals will tend to occur among the most significant allelic associations.[12] For example, the polymorphism (among 116,204 genotyped SNPs) which Klein and colleagues (2005) found to be significantly associated with age-related macular degeneration (AMD) is in the same region on chromosome 1 that has been consistently observed in most linkage studies of AMD.[13]

An important contribution of the present study is that it provides an initial unbiased foray into exploring the genetic etiology of Conservatism-Liberalism by identifying chromosomal regions of genetic markers not previously known to be associated with political preferences. In addition, future studies may use the findings here as means to test the specific Quantitative Trait Loci (QTL). Over time the cumulative knowledge gained from future studies will either result in a generally accepted finding that the

[9]Numerous animal studies also find that olfactory activity is directly related to mate selection. For example, mate selection in mice is strongly influenced by the immune system's exigencies which are detected by certain pheromone activity in the opposite sex (Kavaliers et al. 2006).

[10]Several large scale genotyping efforts are underway by this team and others, and future GWAS studies will benefit from the findings presented here. Replication and multiple approaches are the standard in genetics research.

[11]Population stratification refers to the potential for a false positive signal due to differences in allele frequencies in the population based on differences in ancestry.

[12]Linkage will find a gene that has a significant influence on a trait, but does not depend on characterizing the allele. Rather, it identifies the physical proximity to the gene of interest, regardless of any correlation between alleles of the genes involved. GWAS detects genes of small effects with greater power, but success and interpretation is dependent on characterizing the actual alleles affecting the trait or those closely correlated with them. Linkage typically requires characterizing a relatively small number (say a few hundred) of genetic polymorphisms or variants across the genome, but can only pick up genes of larger effects. GWAS can detect genes with far smaller effects, but requires characterizing a million or more variants.

[13]See also the association between IRF6 and cleft lip, which has been consistently replicated across populations (Blanton et al. 2005; Ghassibe et al. 2005; Srichomthong, Siriwan, and Shotelersuk 2005).

regions identified here are generalizable or specific to this sample.

Many large-scale genetic analyses of clinical and behavioral phenotypes ignore potential sources of heterogeneity that may further reduce power to identify specific genes in a single analysis of the entire sample. The current study is no exception. Among such effects are interaction of gene expression with sex, age, and environmental exposure. Statistical genetic analyses of extended kinships of twins and their relatives suggest that the same genes appear to influence most political attitudes in men and women (Hatemi, Medland, and Eaves 2009), but that a significant nonadditive genetic effect may reflect the interaction between genes and age or secular change. So far, few studies have addressed gene by environment (GxE) interaction for political preferences. However there are reports of GxE interaction for other aspects of social behaviors such as religiosity (Boomsma et al. 1999).

Discussion

Almost four decades of behavior-genetic research has provided a serious challenge to purely environmental theories of political attitudes and behaviors. Notwithstanding their inherent importance as quintessentially ''human'' traits and as salient factors in cohesion and friction between and within societies, social, religious, and political attitudes have largely been ignored in the mainstream of modern genetic research. In part, this may be due to biologist's tacit acceptance of the theory, implicit in social and political science, that a universal ''Promethean genotype'' (Lumsden and Wilson 1983) has led to the evolutionary emancipation of human social behavior from biology. Part may reflect the medical orientation of genetic research and funding. Part may be concern about how to interpret the societal implications, if any, of a more complex model involving genetic as well as social factors and an aversion to endorsing crude genetic determinism. Partially genetic models of human behavior are no more or less ''deterministic'' than purely environmental theories. Rather, the philosophical issues of reductionism and determinism have to be addressed for any purely scientific understanding of human differences, regardless of what combination of genetic or environmental influence is found.

In numerous studies, involving different time periods and populations, it has been reported that genes contribute significantly to the variation in liberal and conservative political attitudes (Hatemi et al. 2010; Martin et al. 1986). However, any pathway from DNA to social behavior is certain to be convoluted, involving networks of genes, genetic expression, multiple intervening neurobiological processes, development, and a multitude of environmental contingencies. As such, rarely are results from small or even modest sized genome-wide analyses, whether linkage or GWAS, replicated. Our sample size is not small; three regions reach standard statistical significance, and one reaches significance by simulated criteria. However, it would be naïve to imply that any one gene, or even a particular pathway of genes, explain any substantial amount of genetic variation. That is, our data are consistent with this cautious perspective that turns out to be the case for a variety of human traits that have been studied far more extensively. Traits more heritable than political preferences, such as stature (heritability ~0.80), are typically resolved into very large numbers of genes of very small individual effects (Visscher 2008), most of which could not be identified individually through linkage.

Although the current sample is the largest used so far in any attempt to identify specific genetic influences on social and political attitudes, and the only sample implicating individual QTLs contributing to individual differences in political attitudes, it still has low power to detect genes which have very small effects that typically account for the vast majority of genetic variation in complex behaviors (Fulker and Cherny 1996). Nevertheless, our largest chromosome-region effects explain ~13% of the total variance, implying that the gene accounting for this QTL is substantially correlated ($\sqrt{0.13} = 0.36$) with Conservatism-Liberalism. However, we recognize the larger estimates of QTL effects in genome scans are typically biased upwards and our simulations show that estimates of 8% are not unusual even if there were no true linkage.

The fact that so little is known about the biology of political ideology may reflect the prevailing focus of political science on environmental theories and covariates and biologists' preference for studying variables that have more direct clinical significance and their desire to avoid the controversy that has sometimes accompanied attempts to study genetic influences on socially important behaviors and functions. However, within the behavioral sciences, there is a growing body of empirical data concerning the biological, physiological, endocrinological, and neural bases of personal temperaments, including personality, social and antisocial behaviors, psychiatric disorders, parenting, affiliative behavior, and aggressive behaviors.

Do political temperaments spring from the same biological sources as other personal temperaments and psychological traits, or is political thought distinct from other components of our behavior? Which biological systems are connected to which political belief structures? While, at all costs, we want to avoid claiming too much for early findings, our data give preliminary support to the hypothesis that whatever relationship exists between politics and genetics, it may be those genetic loci that influence flexibility in information processing and cognition. There is also some evidence, though weak, that the biological systems which influence political attitudes may be the ones related to those which regulate fear and anxiety (Hatemi and McDermott 2009; Oxley et al. 2008) or even possibly mate selection and disgust (Eaves et al. 2010; Navarrete and Fessler 2006). Whether or not it is a function of fear and loathing, betrothing and sexual desire, success of offspring, or other factors, eventually we may better understand the genetic variance behind political dispositions through locating genes by genome-wide analyses and working through the biological mechanisms that those genes are known to influence. We contend the pursuit of such knowledge is best approached using a variety of neurobiological, cultural, and environmental methods.

Taking care to avoid overstatement in advance of replication, the finding that glutamate and NMDA receptors are located on every significant or suggestive chromosomal region related to Conservative-Liberal attitudes provides reason to explore a previously uncharted pathway to how ideologies are formed. Future studies, directly exploring glutamate and NMDA's role in information processing, attitude formation and constraint, particularly during critical neurological development in childhood, which corresponds to the same critical period of social learning and cultural assimilation of values, may offer a better understanding of political ideology. Indeed, NMDA's function in learning and memory during development is of primary interest for future study.

To find a significant linkage region that may implicate certain genetic markers is not to say that a particular gene determines a particular behavior. Nor do our results advocate that genes have some greater effects than that of the environment. This is certainly not the case. Rather, we are starting from two opposite ends of a very complex process: DNA, somewhere near the very basic matter of what living organisms are made of on one end; and an expressed complex behavior (political ideology) on the other. Behavior is the final end product of all that goes in and out of what it is to be human, interacting in a complex and changing environment during one's lifecycle (e.g., puberty, menopause, etc.). We have barely begun to understand what goes on in between those two spaces, which makes this area of research exciting, while also inspiring caution. The understanding that we cannot yet accurately map how genes influence brain processes and biological mechanisms which in turn interact with our upbringing, social life, personal experience, the weather, diet, etc, to somehow be expressed in part as a Conservative-Liberal orientation, is the exact reason that genome-wide analyses are valuable and necessary for political science. Human behavior emerges from the interaction and interplay of genes, socialization and environmental stimuli, working through ontogenetic neurobiological processes embedded in an evolutionary framework (Dobzhansky 1973). So far as the data suggest, a theory and method which includes genetic influences, no matter how large or small, accounts for portions of Conservative-Liberal orientations that environment-only models do not.

Acknowledgments

We thank the participants, without whom this study would not be possible. We also thank Goncalo Abecasis for free access to the Merlin software package. Data and materials necessary to reproduce the numerical results in the paper can be made available by contacting peter.hatemi@qimr.edu.au. Data collection was funded by NHMRC grants to NGM and NIAAA grants to ACH. Data analysis was supported in part by NIH grant MH20030-09. SEM was supported by the Australian NHMRC Sidney Sax Fellowship (443036).

Manuscript submitted 5 June 2009
Manuscript accepted for publication 11 February 2010

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