

When it runs in the family: putting susceptibility genes in perspective

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Using the genetics of late onset Alzheimer's disease (LOAD) as illustrative, this paper argues for a reflexive critique of the involved science, specifically in connection with estimations of increased risk. Following a review of social science commentary on genetic testing and screening in general, current scientific understanding about the molecular and population genetics of LOAD is then presented. The results of open-ended interviews conducted with first-degree relatives of individuals diagnosed with LOAD at two study sites follow. It is shown that the majority of people interviewed embrace the idea of complexity in connection with Alzheimer's disease causation and that many draw on a concept of "blended inheritance" with respect to the disease that "runs" in their family. It is argued that knowledge about risk obtained from genetic testing for LOAD rarely usurps other forms of understanding, but is nested by interviewees into previously held ideas about who in the family is most at risk for the disease.

1. Introduction

More than a decade ago the sociologist Brian Wynne (1993) roundly criticized a commonly held assumption that the major stumbling block to the rational implementation of science and technology in society is a deficit in knowledge on the part of the public. Although arguments about a lack in public knowledge are not new (see Irwin and Wynne, 1996), in recent times resort to the "deficit model" has become especially noticeable in efforts to counter widespread public concern about several tragic events, including nuclear "accidents" and "mad cow" disease. Currently, it is being applied in the United Kingdom to explain resistance on the part of the public to arguments in favor of the introduction of genetically modified organisms into agricultural practices. The deficit model assumes that public concern about practices and events in which technology is implicated is in effect driven by ignorance. Countering this assumption, Wynne insists that the situation is more complex; that the production of scientific knowledge is inevitably socially negotiated, and a "reflexive problematization of science" is crucial in advance of discussions about public knowledge and trust. In making an argument for reflexivity, Wynne aligns himself with the position set out two decades ago by Bruno Latour, Michel Callon, and others (Callon and

Latour, 1981; Latour, 1983). However, Wynne notes that when dealing with public responses to technology, something more is needed than recognition of the social construction of scientific knowledge.

Bruno Latour recently voiced similar concerns, and has openly recanted on the position he took when he published *We Have Never Been Modern* (1993). He insists that the fashionable debunking of “facts” set in motion over the past 20 years, in which he himself was complicit, has left us in “darkness,” and that we have not been aiming at the right target. “Reality is not defined by matters of fact,” he now asserts. “Matters of fact are not all that is given in experience. Matters of fact are only very partial and, I would argue, very polemical, very political renderings of matters of concern” (2004: 232). What is now urgently needed, Latour insists, is to add “reality to matters of fact”—thus making things more complicated (see also Hacking, 1999).

One way to take up “matters of concern” is to undertake a reflexive critique of the production of scientific knowledge and its implementation in practice while at the same time assessing public responses to specific technologies—exactly the kind of research that Wynne and colleagues have done so effectively for many years (Irwin and Wynne, 1996). Similarly, medical anthropologists and sociologists have put considerable energy into documenting individual and community responses to new biomedical technologies as they become available in local settings. These researchers make explicit the broader medical, social, and political embedding of such technologies world-wide, including government limits frequently put on their implementation when technologies are perceived as a threat to moral order—particularly prevalent in connection with stem cell research, the new reproductive technologies, and organ transplant technology. Matters of concern are at the heart of this type of research and what counts as “facts” is systematically problematized and contextualized (see, for example, Inhorn, 2003; Ginsburg and Rapp, 1995; Greenhalgh, 2003; Lock, 1993, 2002; Lock, Young and Cambrosio, 2000; Rapp, 1999, 2003; Young, 1995).

Some years ago, Sally McIntyre (1995) identified four assumptions embedded in the UK Medical Research Council’s attempt to promote an increased public understanding of genetic screening: ignorance and denial on the part of a poorly informed public; lay people’s lack of appreciation for the hereditary components of many common diseases; a public that cannot understand the mathematics of probability; and a mass media that willfully misrepresents science. While agreeing with the importance of a foundational knowledge of molecular genetics common to the public and professionals, McIntyre argued that investigation of the lives of individuals affected by these disorders could lead to a more “scientific” understanding of the public. Such an approach, she argued, would call into question a one-sided assumption that the public must simply understand the facts of science in order to make decisions. McIntyre emphasized instead the importance of focusing on the application of knowledge in practice, including the contingencies that arise in everyday life. Our paper represents an effort to respond to this challenge made all the more difficult by revelations about the complexity of molecular genomics that were not fully appreciated when McIntyre wrote her article.

Our object of inquiry is late onset Alzheimer’s disease (LOAD). Emerging knowledge in molecular genomics has radically transformed professional understanding of this devastating disease; even so, there is no prevention for it, nor treatment that is more than minimally effective. Pressure is mounting from research communities working on dementia and related disorders to have DNA samples in very large numbers at their disposal in the hope of overcoming, by means of intensive basic science investigation, the impasse posed by LOAD and other dementias. In research settings in major medical centers, with informed consent, bloods are routinely taken from patients diagnosed as having incipient Alzheimer’s

disease (AD), or else as being in the early stages of late onset AD, in order that DNA typing and other tests can be carried out. These samples are anonymized, and the results are not returned to patients or their primary physicians, but the assumption is that this practice is likely to change in the not too distant future, particularly if research in pharmacogenetics demonstrates that a specific medication is more effective with patients of a particular genotype as compared to the population at large.

Currently, the official guidelines of professional and health policymaking institutions and organizations involved with Alzheimer's disease, and those of the Alzheimer societies of the United States, Canada, and the United Kingdom, state that genetic testing should not be routinely performed in connection with LOAD (see, for example, American Geriatrics Society, 2001; Alzheimer's Society, 2003). This recommendation is easily justified because it is argued that knowledge about the genotype of a patient has absolutely no effect on clinical care. Even so, several private companies offer testing, and an "Early Alert Alzheimer's Home Screening Test" kit is marketed directly to consumers (Kier and Molinari, 2003). Furthermore, a National Institutes of Health (NIH) approved randomized controlled trial that goes under the name of REVEAL (Risk Evaluation and Education for Alzheimer's disease) is in progress. Families where one or more members have been affected by LOAD are subjects for this research. One of several justifications for the REVEAL project is to assess how people respond to being informed that they have a gene that clinicians believe puts them at increased risk for Alzheimer's disease.

We will first review a selection of the social science literature on genetic testing and screening. Virtually all of this research has been carried out in connection with single gene disorders—the so-called Mendelian disorders. We argue that further research is urgently called for in connection with complex, late onset diseases, given that it is now universally recognized that genetics are implicated in all such conditions. A critical review of the literature pertaining to the genetics of Alzheimer's disease follows. This review makes evident the confusion involved when calculating and then transmitting information about risk associated with susceptibility genes to patients and families. Problems arise in part because the information is probabilistic, but also because the key piece of information—how exactly, and under what circumstances the gene in question puts individuals at risk—is not known. In addition to genotype, age, gender, ethnicity, education, head trauma, and comorbidities are the principal implicated variables, along with other factors that are *apparently* less robust, making for enormous complexity. The effects of the macro-environment and life-long exposure to toxins and other stressors are under-researched. Findings from ethnographic research consisting of interviews with first-degree relatives of Alzheimer patients in Canada and the United States follow the review. The majority of respondents believe that the disease "runs in their family," but even so, give multi-causal explanations for LOAD. Few take a deterministic position about the contribution of genes to the disease.

In conclusion we argue that, as health care systems in numerous countries move inexorably towards the routinization of genotyping, and genetic testing is integrated more systematically into public health programs and clinical practice, a reflexive approach to the production of knowledge in connection with susceptibility genes¹ and the creation of risk estimates is required in which, above all, a sensibility to the provisional nature of the evidence is made explicit. Given the complexity involved, the size and composition of the "normal" population on the basis of which individual risk is calculated, presents a major challenge. For example, the assumption that a "Caucasian" population provides an adequate baseline, as has so often been the case in the past in connection with medically related research more generally, is inappropriate; recognition of the significance of genetic diversity

is important. Second, it is questionable to what extent meaningful risk estimates can be made, in large part due to the paucity of knowledge to date about the interaction among genes, the cellular environment, and with the macro-environment external to the body. Third, translation of risk estimates in connection with susceptibility genes into everyday language presents enormous difficulties.

It is no doubt the case that the public has a knowledge deficit about molecular genetics, but then so too do numerous medical experts; this is knowledge that is changing exceedingly rapidly and often in surprising ways. Furthermore, those individuals who come from families where LOAD is frequently diagnosed already have informal knowledge at their disposal about bloodlines and inheritance patterns that predict who in their family is marked for the disease. The findings presented in this paper suggest that this informal knowledge carries a great deal of weight, more so, it seems, than do cumulative risk estimates about possible futures.

2. Genetic testing and screening: social science commentary

Edward Yoxen (1982) suggested over two decades ago that newfound abilities to detect “pre-symptomatically ill” individuals would ensure that virtually all of us would be subject to increased medical surveillance in the near future. Among the technologies that Yoxen had in mind were genetic testing and screening. The relentless pace of technological development in connection with molecular biology and the hype and public acclaim that accompany much of it, have caused concern among many critical commentators (see for example, Duster, 1990). It has been suggested that social scientists and bioethicists, may collude in the hype by “over-sensationalizing” the potential of such technologies to transform society at large (Franklin, 1995: 178). This is certainly the situation at times, but it is becoming increasingly clear, however, that Yoxen’s statement about medical surveillance was not hyperbolic.

Lippman created the concept of “geneticization” to characterize her concern about the introduction of molecular genetics into the clinic “in which differences between individuals are reduced to their DNA codes” (1992: 1470). She argued that an indirect reinforcement of racism, social inequalities, and discrimination of various kinds is likely to result from a newly rekindled conflation of social realities and an essentialized biology grounded in small differences in DNA sequences among individuals (for evidence of this see, for example, Draper, 1991; Duster, 1990; Parens and Asch, 1999; Paul and Spencer, 1994). Lippman further argued that we might well be witnessing an incipient neo-eugenics, a consequence of the voluntary termination of pregnancies on the basis of results obtained from fetal genetic testing. Other writers have made similar comments, noting that what in the early twentieth century was enforced by the state through involuntary sterilization programs is now carried out under the rubric of individual choice (see, for example, Kitcher, 1996).

Increasingly nuanced investigations of the way that people respond to and are affected by the introduction of molecular genetics into the clinic and public health screening programs are being carried out (Kerr et al., 1998; Michie et al., 1995). This shift in emphasis that parallels other research in connection with the public understanding of science more generally, shows clearly how individuals and families are profoundly affected by genetic testing (Hallowell, 1999; Novas and Rose, 2000), and in families where lethal childhood diseases are common, parents frequently become politicized in order to advance research that may help overcome the particular disease that affects their family (Heath et al., 2004; Rapp, 2003).

In contrast, other studies have documented the way in which individuals actively interpret available knowledge about molecular genetics, and how they frequently exhibit resistance to using genetic explanations alone to account for the illnesses that “run” in their families (Condit, 1999; Lock, Lloyd, and Prest, in press). Furthermore, when genetic information is incorporated into accounts about illness causation, such information supplements previously held notions of kinship, heredity, and health. For example, Cox and McKellin (1999: 130), writing about Huntington disease, have shown that lay understandings of heredity conflict with theories of Mendelian genetics because scientific explanations prove to be inadequate for families dealing with the lived experience of genetic risk. They argue, on the basis of empirical findings: “theories of Mendelian inheritance frame risk in static, objective terms. They abstract risk from the messiness of human contingency and biography” (1999: 140). Their findings show graphically how at certain junctures in an individual’s life cycle—notably when making decisions about reproduction—knowledge obtained from genetic testing is recognized as useful but, in general, factors such as social proximity to an affected family member and the family’s inter-subjective construction of risk are the most significant forms of knowledge that inform everyday life. Kerr suggests that it is reasonable to assume that lay people are their own authority when it comes to appreciating and understanding how exactly genetics may shape their lives (Kerr et al., 1998).

To date, almost all social science research into the social ramifications of the new genetics has concentrated on the impact of transmitting information about mutant genes with a highly predictable (but not fully so) mode of Mendelian transmission. This commentary is exceedingly rich, and has set a high standard for future research. However, the focus of attention today, for political and economic reasons, if no other, is primarily on complex disease that accounts for 98 percent of the disease burden in the “developed” world. Increasingly, too, in the so-called “developing” world, complex diseases are of major concern (where, because population sizes are very large, the actual numbers of people affected are greater than in those countries that “modernized” earlier). Creation and transmission of knowledge about susceptibility genes associated with complex diseases poses a challenge that far exceeds what we have been confronted with to date. For one thing, molecular biology and associated clinical practices are riddled with competing discourses that must be analyzed in their own terms as part of a reflexive approach (Lock, 2005).

It is now recognized among involved researchers that there is no simple correspondence between genotype and phenotype and, for complex traits, “usually a weak (and often variable) correlation between genotype and phenotype” (Nijhout, 2001: 129). The philosopher of biology, Lenny Moss, notes that as a developmental resource a gene is “ontologically on the same plane as any number of other biomolecules” (2004: 47). And biologist Steven Rose argues: “the functioning cell, as a unit, constrains the properties of its individual components. The whole has primacy over its parts” (1997: 169). The contents of human cells—DNA, RNA, enzymes, proteins, and other key molecules including important regulatory ions, mutually interact throughout the life course of individuals, in a dynamic molecular mix. This interaction is influenced by micro-environments—intra and extra cellular—and by macro-environments external to the body. Disruptions in this complex cell machinery, often stimulated by toxins and stressors of various kinds, as well as by the process of aging, result in temporary fluctuations or else outright pathology, and eventually death of the organism.

The presence of one or more susceptibility genes in an individual’s genome (as is likely the case for all of us) puts one at increased risk for a specific disease or diseases. The complex biological pathways that sustain function within a normal range are, under certain

conditions, more vulnerable to disruption than is the case in the population at large. Susceptibility genes associated with complex diseases can be tested for relatively easily today but, as noted above, making even rough estimates of exactly how and under what circumstances such genes place individuals at increased risk is exceptionally difficult to calculate (many would say impossible (Moss, 2004)), and is further complicated by the need to transmit this unstable, elusive information to involved families.

In the case of Mendelian diseases, a grasp of the relevant scientific knowledge means that individuals understand how transmission of autosomal dominant and recessive genes is accomplished and, further, in the professional jargon, that such genes have high penetrance—in other words having either one or two copies of such a gene leads to reliably predictable outcomes for individuals and their relatives (although, because the phenotype is variable, age of onset and severity often cannot be predicted). Knowledge about the presence of one or two copies of a specific mutational gene, together with information about average age of onset of the disease, can then be drawn on to make crucial family decisions, most often in connection with reproduction.

The situation is quite different with susceptibility genes because estimates of risk are based on calculations of probability that frequently have low explanatory power. Adding to the complexity, professional understanding about the molecular genetics of complex disease is for the most part “knowledge-in-flux,” with the result that the variables on which estimates of probability are made are subject to revision. We are not dealing with “matters of fact,” but with information that is both provisional and probabilistic, and that must, of course, be translated into estimates presumed relevant for individual cases.

The question with which we are confronted is the following: if professional explanations about genetic risk in connection with Mendelian diseases do not always result in the types of understanding and behaviors that have been hoped for when members of the public are given professional genetic counseling (Hill, 1994; Rapp, 1999), what might be the situation in connection with the genetics of complex diseases? In order to address this problem, we refer to “blended inheritance,” a concept that describes an idea prevalent among many people about a mixing or blending of entities from both parents, assumed to be passed on from generation to generation in clusters. Phenotypic resemblances shared among certain family members—physical features, personality types, and so on—indicate that these individuals also are equally prone for disorders that “run in their family.” This type of lay understanding is more common than one that draws on a Mendelian explanation in which genes are associated with the expression of specific phenotypes (Richards, 1996: 222). Ideas about blended inheritance stem from a long tradition of such reasoning evident as early as classical times (Turney, 1995: 12). Martin Richards (1996) suggests that today the notion of blended inheritance not only conflicts with professional genetic explanations about single gene disorders, but also works to reduce acceptance of those same explanations, in both the classroom and the clinic.

On the basis of ethnographic findings to be presented below, we argue that the idea of blended inheritance is drawn on by families, not only in connection with diseases transmitted in a Mendelian mode but, not surprisingly, when accounting for who is at risk for complex diseases. For example, when a disease such as AD occurs in a family, there is a consistent tendency to identify a family member who in some way resembles the afflicted person as the individual most likely to be at risk for developing the disorder, whether individual genotypes are known or not. These findings are particularly significant given a decade of social theorizing about discourses of “geneticization” (Hedgecoe, 2001; Lippman, 1992), and highlight the need to pay attention to the specific effects of named diseases, notably the age of onset and the form that the pathology takes (for example, is the disease

lethal in early life or does it only confer disability later in life?). And in addition to acknowledge that, as Kerr et al. (1998) have already noted, people will in effect act as their own authority about the interpretation of genomic information.

3. Genetics of Alzheimer's disease

Research is proving that genes are shape-shifters without peer, the products of both evolutionary and recent human history, of toxic environments and, at times, of serendipitous mutations as a result of faulty replication. The ApoE gene is no exception. Until recently, LOAD was described in the medical literature as "sporadic," because familial inheritance patterns did not appear to be at issue. However, 10 years ago the "discovery" of a susceptibility gene, apolipoproteinE, radically disrupted this perception. This gene, present in all mammals, located on chromosome 19 in humans is, along with other genes, essential for lipid metabolism. One particular allelic variation of the ApoE gene was shown by linkage studies carried out in the laboratory of Alan Roses to be associated with late onset Alzheimer's disease (Strittmatter et al., 1993). This finding has since been verified in over 100 laboratories. ApoE, already implicated in heart disease before its association with Alzheimer's was recognized, is a polymorphic protein with three alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, that are distributed unequally (clinically) around the world. It is the ApoE $\epsilon 4$ variation that places individuals at increased risk, not only for contracting AD, but also for an earlier age of onset of the disease by as much as 7 to 9 years. The homozygous $\epsilon 4/\epsilon 4$ creates the greatest vulnerability, particularly in those individuals who have had a head injury (Mayeux et al., 1995).

Despite broad based consensus about these findings, it is at the same time agreed that the allele alone determines nothing with respect to the incidence of AD. All that can be inferred is that the ApoE $\epsilon 4$ genotype confers a greater degree of susceptibility but that it is neither necessary nor sufficient to cause the disease. It is generally agreed that about 30–50 percent of the population risk for AD can be attributed to genetic factors (Farrer et al., 1991; Silverman et al., 1994). In about 50 percent of diagnosed cases the patient does not have this particular genotype. Furthermore, research suggests that about 50 percent of people who have the genotype do not exhibit dementia (Tilley et al., 1998). Recently a good number of other genes, proteins, and enzymes have been implicated in the disease process, and further "candidate genes" are currently being analyzed.

John Hardy, the chief of the genetics laboratory of the United States National Institute of Aging, stated during a presentation at the 2002 biannual AD conference held in Stockholm: "genetics underpins our understanding of this disease,"² and he added, "findings from genetics are the baseline for research into AD." But while Hardy's presentation, and others like it that focused on genetics, received a great deal of attention at Stockholm, they did not incite enormous excitement for the reason that, including the ApoE $\epsilon 4$ discovery 10 years earlier, no findings that derive from knowledge about the genetics of AD have as yet resulted in clear advances in the prevention or treatment of the disease, although inevitably, such a hope persists.

Population genetics must be relied upon to establish what characteristics place specific groups of people at increased risk for AD, with the limitations inherent to any such research, in that findings cannot be applied directly in the clinic to individual cases. Since 1993 a large number of population based studies, most of which are confined to so-called Caucasian subjects, have been published about the relationship of the ApoE gene to AD incidence and prevalence (Growdon, 1998; Roses, 1998; Saunders, 2000; Silverman et al., 2003). But this

literature leaves room for confusion. For example, estimates of the number of individuals diagnosed with AD who carry the $\epsilon 4$ allele have a very wide confidence interval ranging from 30 to 90 percent (Liddell et al., 2001; Ritchie and Dupuy, 1999) and many studies do not specify whether these numbers refer to those who are hetero- or homozygous for the allele.³ In addition to retrospective studies of individuals who already have AD, other research attempts to estimate the number of people with ApoE $\epsilon 4$ alleles who will eventually develop AD. There is also considerable variation among the estimates derived from these prospective studies (Holmes, 2002; Farlow, 1997).

In contrast, there is better agreement that individuals with ApoE $\epsilon 4$ alleles have an increased relative risk of developing AD. The literature suggests that a person with one $\epsilon 4$ allele has 3 times the chance, and a person with two $\epsilon 4$ alleles has between 8 and 30 times the chance of developing AD compared to someone with no $\epsilon 4$ alleles (Holmes, 2002; Swartz et al., 1999). However, the baseline on which these probabilities are estimated is not always provided, and without this information relative risk estimates are misleading, although they still have the power to create anxiety.

For those individuals with two ApoE $\epsilon 3$ alleles (about 75 percent of the population in Europe and North America), risk for AD is estimated as “average,” and most estimates are that about a quarter will develop AD once over the age of 80. Relatively few people carry ApoE $\epsilon 2$, and this allele is proportionally more frequent among “non-Caucasian” populations. Those who inherit two copies of this gene are thought to be at relatively low risk of contracting AD, since this allele appears to be protective, in contrast to the ApoE $\epsilon 4$ allele.

One of the principal causes of confusion about genetic risk for AD is inherent to research designs. Holmes (2002) and Ritchie and Dupuy (1999) suggest that many studies do not represent the population at large, because they are based on clinical samples. When general population samples are made use of, the relationship between ApoE $\epsilon 4$ and AD appears to be significantly weaker than is commonly suggested (Blacker and Tanzi, 2000).

The emphasis on ApoE $\epsilon 4$ and the genetics of AD in the research literature obscures the fact that many other risk factors have been associated with LOAD. Further, ApoE $\epsilon 4$ has been shown to work in unexpected ways in certain locations. For instance, among Pygmies, and other populations whose subsistence economy was until relatively recently predominantly that of hunting and gathering, ApoE $\epsilon 4$ apparently protects against LOAD, suggesting strongly that genetic pleiotropy is implicated (Gerber and Crews, 1999). This finding holds when controlled for age (Corbo and Scacchi, 1999). Low rates of LOAD have been reported for parts of Nigeria, and the presence of an ApoE $\epsilon 4$ allele does not appear to be implicated when it does occur. On the other hand, ApoE $\epsilon 4$ is significantly associated with LOAD among African Americans, although less so than in populations of whites (Farrer, 2000). It is argued that risk reducing factors (in Africa) *and* risk enhancing factors (in North America) must be implicated, including other genes, their protein products, diet, and environment, but researchers also acknowledge limitations to the research methodologies used to date. Clearly, as a result of both methodological inconsistencies and the complexity involved, the contribution of ApoE $\epsilon 4$ to LOAD is far from being fully understood (for further elaboration of these findings see Lock, 2005).

The majority of clinicians consider individual risk assessments for late onset AD made on the basis of genetics alone to have little explanatory power, and to be of no use in clinical care except at times to confirm a diagnosis, although it is acknowledged that this situation may change in the future (Farlow, 1997; Liddell et al., 2001; McConnell et al., 1998; St. George-Hyslop, 2000; Tilley et al., 1998). Although gene hunting continues to be central in dementia research, over the past two or three years attention has shifted to a search for biomarkers thought to be signs of incipient Alzheimer’s disease before the condition is

manifest clinically. This type of research currently causes more excitement than does gene hunting (DeKosky and Marek, 2003; Walsh et al., 2002), although it is important to note that the ApoE gene is routinely made use of as a variable, along with age, gender, and education when doing this kind of research. The search for biomarkers is regarded as important not only as an aid to early diagnosis, but also by pharmaceutical companies as essential for drug development (Lipp, 2005).

Reflexivity is evident among researchers and clinicians in that there is questioning by some as to what exactly *is* Alzheimer's disease. Debates about taxonomies take place ceaselessly, and it is not only genetic research that incites these arguments (Burns and Zaudig, 2002; Petersen et al., 2001). Research findings in connection with biomarkers, brain-imaging technologies, and autopsies create uncertainties and destabilization. Given that some individuals exhibit advanced signs of behavioral changes but, at autopsy, show few of the characteristic lesions of LOAD, and that the reverse situation—very few behavioral changes but many lesions at autopsy—is also the case at times, clearly questions arise about the ontological status of this disease and, more profoundly, about the relationship among mind, body and person (Swartz et al., 1999). Two geneticists of neurodegenerative disorders recently summarized the current situation as follows: “First, and most importantly, the heritability of AD is high . . . this had been demonstrated in various studies . . . while the genetic association *per se* [of ApoE ϵ 4 with AD] has been extremely well established over the past decade, there is no consensus as to *how* this association translates pathophysiologically” (Bertram and Tanzi, 2004: 135–7). Evidently genetics do not determine things, but genes can make one vulnerable under circumstances that remain mysterious. The writers of the current guidelines apparently believe that knowledge-in-flux should not be routinely transmitted to patients and families, but there are signs that this position may not last much longer.

4. Family understandings of Alzheimer's disease: methodology

The ethnographic findings that follow are derived from two data sets resulting from interviews with individuals who have one or more family member diagnosed with LOAD. One data set consists of 40 interviews carried out between 2002 and 2003 in Montréal, Québec. Potential respondents were contacted through memory clinics and gerontology units that specialize in neurological assessments, where their relatives were being followed. The average age of the sample is 50 years, and 58 percent are female, no doubt reflecting the fact that women are for the most part caregivers of ailing parents, and are often present in the clinic in this capacity. Following informed consent, participants took part in semi-structured interviews averaging 45 minutes in length, at a time and location of their choice.

The second data set consists of participants in an NIH approved randomized controlled trial known as REVEAL (Risk Evaluation and Education for Alzheimer's disease). Subjects for this trial were recruited either through systematic ascertainment from American AD research registries kept at Boston, Case Western Reserve, and Cornell Universities, or through self-referral at each site (Cupples et al., 2004). The 160 REVEAL participants, as do the Montréal sample, come from families where LOAD has been diagnosed in one or more first-degree relative, and upon recruitment they were randomized into intervention and control groups. Virtually all the sample self-identifies as “white.” The REVEAL participants are highly motivated by what we term “corporeal citizenship,” in that they are eager to assist with medical research. They first attended an education session about Alzheimer's disease in the form of a Power Point presentation, with emphasis on theories about causation, including

genetic susceptibility, after which they were asked to return to the research site at a later date for a blood draw. People in the intervention arm were informed a few weeks later about their ApoE status.⁴ People assigned to be controls were not given this information. Reactions of REVEAL subjects who were informed of their ApoE status were systematically monitored by means of three follow up structured interviews conducted by genetic counselors over the course of 12 months, and then compared with the reactions of individuals in the control group whose blood has been stored but not tested. A subset of the sample, 55 individuals, volunteered to return after the completion of the basic REVEAL study to undergo semi-structured, open-ended interviews carried out between 2002 and 2003 by anthropologists.⁵ Eighty-seven percent of this subset are women, with an average age of 50 years. Data from these interviews, obtained from people in both the intervention and control arms, are compared with findings from the Montréal study.

The concerns of the Montréal group about the genetics of AD, if they have them, are not discussed in the clinical setting, because these people are present in the clinic as caregivers, and are not identified patients. The Montréal respondents must rely on information made available by advocacy groups and the media, and on what acquaintances tell them, as opposed to the REVEAL participants who are systematically exposed to genetic counseling.

5. Multiple explanations and uncertainty about causation

Participants in the Montréal project are of diverse ethnic and socioeconomic backgrounds. They range in age from 28 to 70 years. A few have professional expertise that they have drawn on in dealing with their encounter with AD, but the majority have learned about the disease and how to cope with it from first hand experience in their daily life, family physicians, the media, advocacy groups, and elsewhere. It is not surprising, therefore, that individuals hold a wide range of theories about AD causation.

For example, Katherine (age 62, one affected relative) holds a number of theories about what might have caused her mother's AD:

... I can only hypothesize really ... Because if I look at the issues of diet, she basically had an okay diet ... maybe too many carbs., that's why she may have the sugar problem. I don't know if there is any correlation between the diabetes [and AD] ... I don't know if they are working on that at all ... I often personally think of environmental factors, I think of the pollutants in the air, and I am very neurotic about things like that in general, so I would just write that off as another example of living in a highly industrialized city, where there's a lot of pollutants. She didn't live near high-tension wires, but close to the Metropolitan [highway] for most of her life ... I don't know about her early childhood, what may or may not have been a factor. On her own personal level until she remarried, it was high stress, I don't know if that contributes or not.

The most influential source of information for Robert (age 45, one affected relative) appears to be television, specifically the program *The Nature of Things*, from which he learned that the after effects of surgery could lead to memory problems. Other sources include pamphlets made available at the hospital and comments made by nursing staff and physicians. Robert holds at least three theories of causation responsible for his father's AD: the heart surgery his father underwent, exposure to aluminum, and his father's work environment (that regularly exposed him to a variety of chemicals).

Katherine's and Robert's multi-causal accounts are representative of the majority of the Montréal participants whose narratives are shaped by the life histories of their relatives ("he

had head trauma,” “she was depressed”), in addition to a number of written and oral sources (“I heard something about aluminum being involved,” “lack of exercise is a problem”). When participants were asked what possible causes could account for their family member’s AD, more than two-thirds responded with ideas derived from several sources, including the media and the Internet, their own family history, their work experience, and information gleaned from physicians and medical staff. Only nine of the 40 interviewees held a single theory of causation, six of whom maintained that “genetics” or “heredity” was the sole cause of the disease (specific references to genes, or to genetic “triggers” were classified as a genetic theory of causation; responses were classified as “hereditary” when references were made to the disease being “in” the family, bloodline, or due to inheritance). It is of note that five of the six people who gave priority to either heredity or genetics had more than one family member diagnosed with the disease.

On average, interviewees hold more than two theories about AD causation. Those most commonly cited are as follows: heredity (32 percent), diet (28 percent), genetics (23 percent), environment (18 percent), a lack of “mental activity” (18 percent), genetics (18 percent), aluminum, stress, depression, and age (each 15 percent respectively), followed by very many other less frequently cited causes. Four people stated that they do not know what causes AD; two of these individuals noted that the scientific community had not yet definitively identified the cause(s). This multiplicity of theories and uncertainty about AD causation testifies in part to the diversity of sources from which people access information and the range of experiences drawn on in order to account for it. However, research has shown that neither clinicians, the media, nor advocacy groups give priority to genetics when accounting for the occurrence of AD (Lock et al., in press), making it unlikely that the public would emphasize above all else the contribution of genetics. Nevertheless, it is clear that many individuals whose relatives are directly affected believe that the disease “runs in their family.”

6. Genes and heredity in Alzheimer’s disease causation

Despite a diversity of responses about causality, a consistent pattern emerges when people discuss how AD is transmitted in families; individuals move back and forth between ideas about “genetics” and “inheritance” in predictable ways. The word “genetic” may be used spontaneously to initiate a discussion, which then turns, almost without exception, to oblique or nebulous references to heritable substances and discussion of a vague process whereby AD is passed on “in the family.” For example, John, aged 40, with three affected relatives, described his family’s response to his mother’s diagnosis in the following way: “[W]hen we heard that she [his mother] had Alzheimer’s, the first thing that came to mind was that her mother had it, and her brother, and so that’s what we’re blaming it on . . . It’s genetic, but then you never know, do you?” He later went on to say, “Knowing that it’s hereditary, from my grandmother, to my mother, and now her brother too—it’s all the same blood . . . it’s not like saying it was somebody else, it was all in the same blood.”

Very few participants were confident about explaining the effects of genes in the transmission of AD. For example, Katherine makes frequent reference to a “genetic component” that resulted in her mother’s AD, and she supports this theory by pointing to her mother’s sister’s loss of memory:

between my mother and my aunt, somewhere there must be some gene . . . I do believe that there has to be a genetic component, because my mother’s sister has memory loss and she is much younger than my mother, although that is related to stroke and

depression. So I don't know if one would say that it is in the same package or not, I have no idea.

When asked to elaborate on the genetics of AD, Katherine notes that she has not seen or read anything in the media about a "genetic component" of the disease and cannot advance any further explanation about what specific gene might be involved, how it is transmitted, or how it could cause Alzheimer's disease.

Even though some interviewees name "genetics" as one cause of AD, they have little to say about what exactly this might signify: "If you ask me what exactly is a DNA marker or a gene sequence I'd say it's one of those things in your body, it's small, and scientists play around with it. I don't really know what it means at all" (Tom, 51 years, one affected relative).

Obviously no discussion about genotypes or specific alleles is required for meaningful everyday conversation (not one of the 40 people interviewed mentioned the ApoE gene). Marilyn, a 52 year old, with three affected relatives, is one of the few participants that named genetics as the single cause of AD, but even so, she is far from specific about it. She states,

[G]enetics are, according to me, mostly responsible for the disease . . . Sometimes people say to me, "You are going to heat something in an aluminum pan, you're going to 'catch' Alzheimer's!" I think that it's mostly genetics that make you have this disease, I might be wrong, I don't know, but I think that it is the family baggage rather than an aluminum pan or living in a certain area or whatever.

When Marilyn was asked if she thought that specific genes are implicated, she replied that she did not know.

Although "genetics" may be referred to, this explanation may then be abruptly discarded because this information is not regarded as useful. As Raymond noted:

I know that there are some people who are concerned about whether it's genetic. I think there is some stuff they'd written about it, that it can be passed down, I think I was reading about it but I didn't flash on it too much 'cause it really didn't have much relevance to me, in the sense that . . . I mean if it's passed down to me, I'm not changing what I'm doing anyway. (53 years, one affected relative)

Moreover, when "genetics" is brought up during family exchanges it can cause anxiety or anger. It may well be that holding multiple theories of causation is one way to assuage family stress. Eva, the youngest participant in the study (28 years), with five family members affected with LOAD, sheds some light on this possibility. She claims:

A lot of people just think it's bad genes, you know, that it's just bad genetics. "She comes from a bad gene family." It made me question the quality of my own family genetics. But I think I've realized that it's not necessarily your genes, it does play a factor, yes, but . . .

Eva went on to assert that the environment must be implicated in the disease, a position that perhaps lessens her anxiety about the future (see also Richards, 1996).

Although "genetics" appears to be the topic of discussion in the above quotes, the manner in which this is discussed indicates that AD causation and risk for AD are very often being conceptualized in terms of "blended inheritance." Consequently, families frequently pick out the relative among them who phenotypically (physically, intellectually, or emotionally) resembles the diagnosed person as being the one who is most likely to develop the disease in the future. A supposed shared genotype is conflated with phenotypic expression of

complex traits. As noted above, it has been shown that concerns about developing autosomal dominant diseases are often based on this conflation (Cox and McKellin, 1999), and our data show that this is apparently even more applicable when families are confronted with complex disorders. For instance, when Robert is asked if he has ever thought that genetics might be involved in his father's illness, he replies, "I worry about it because genetically I'm pretty much a carbon copy of him . . . [I] have the same physique, same mannerisms, I'm obviously his son, it's very apparent." He clarifies: ". . . my sisters take after my mother. And my brother, after my uncle actually . . . So I'm not so worried about them."

Conflation works to assign the burden of anxiety to one or more unfortunate family member. When Katherine is asked if she worries about AD, she says: "Worry is a big word; does it ever cross my mind? Yes. Do I worry about it? My brother worries, and my mother worries more about my brother than me. She thinks his personality is more likely to be similar to hers than mine." Katherine makes it clear that she thinks she is not at risk for Alzheimer's disease because of her own medical history. She already suffers from Crohn's disease, and contends, because of this, that she is less likely to be vulnerable to AD; exhibiting a surprising optimism she argues: ". . . there's Crohn's in my father's family and I somehow think: Okay, if I picked up that gene, how likely is it that I have the AD gene too? Can I have them both? I hope not."

Katherine is not the only participant who holds such a calculus about her own risk for AD. For instance, Marilyn too frames her understanding in terms of generalized ideas about heredity, but with a different outcome:

My fears are pretty important, because my mother often said to me, "Look at me, I am 77 and I am in good shape, you can hold onto that." And that's right, except that I have a 50% chance of getting the disease because my father suffered from the disease. So I have worries about the fact that I could potentially have the disease. This worry doesn't prevent me from functioning or anything, I just think about it. It is just something that could happen because my father had it and because other members of the family had this disease . . .

While Sara, aged 50, with three affected relatives notes: "On my dad's side they all lived to be 100 years old, so I hope I get those genes." Moreover, as Samuel exemplifies, genetics can be used to elucidate rather vague suppositions: "In terms of my mother I just assume it's very similar to her sister, it started at the same time, so there is a genetic aspect to it" (age 51, with two affected family members).

Seven interviewees had heard that genetic testing for AD could be made available; three of them have two or more affected family members and, of the seven, two named heredity as the sole cause of AD. Interest in taking this test was variable; Anna, aged 47, with four affected relatives, stated that she had already been tested. When asked what gene she had been tested for she laughed, "I don't know. It's one among the others!" On the other hand, a 58-year-old woman with two affected family members adamantly rejected the possibility of predictive testing: "If I took the test and the results were not to my liking I would go straight to the Jacques Cartier bridge and jump . . . I don't think I want to know."

Given the emphasis attributed to multiple factors involved in the development of AD in the above accounts, and especially considering uncertainty on the part of most participants about the role of genes in AD causation, it is of interest to compare these findings with responses from participants in the REVEAL project, in which current information about the ApoE gene was systematically disseminated to them.

7. Interpretation of risk estimates

All participants in the REVEAL study have participated in a “genetic” educational session and received individual genetic counseling. During counseling, they were provided with “personalized risk assessments” for LOAD (based on age, family history, gender and in addition, for those people in the experimental arm of the project, on DNA typing). By the time open-ended interviews were carried out, more than 12 months after being told of their estimated risk, participants had transformed the estimates they had been given into accounts that “fit” with their experience of being related to someone with Alzheimer’s disease; personal assessments of their own family history, and the accumulated knowledge about the disease that they had gathered from a variety of sources. In other words, risk estimates provided in the REVEAL study rarely displace “lay knowledge” that participants bring with them to the project. Rather, this “scientific” information is nested into preexisting knowledge. This may in part account for the relatively small number of REVEAL participants (27 percent) who are able to recall accurately the risk estimates that they were given—particularly noteworthy when 91 percent of the informants stated that “wanting to know” their genotype was a major motivation for participation in the REVEAL study.⁶ Even though most could not recall their risk estimates accurately, nearly half made it clear that they had retained the gist of the information—usually they were able to recall if they have a “good” or “bad” gene. But 20 percent came away from the trial either very confused or entirely wrong about the risk estimates they had been given.

Carolyn, a psychiatric nurse aged 52, states that she is less interested in finding out about her own genotype than that of her sister, who also took part in REVEAL. Carolyn is married and has no children, whereas her sister has two, and Carolyn perceives an enormous difference in the significance of testing for the two of them:

If Alzheimer’s happens to me, it happens to me. But I would be much more concerned if I had children . . . I would want to know every single thing out there. She does have two kids, you know . . . So when my sister learned that the testing was in Boston, I really came along for her, not so much for myself . . . , it’s good knowledge to have for myself, but I wanted to be there for her . . . To do it together as sisters.

Carolyn and her sister were both in the randomized group that received their ApoE status. Carolyn learned that she has a 3/3 genotype, whereas her sister is 3/4 and so carries a single copy of the $\epsilon 4$ allele. Carolyn’s experience as a caregiver contributed to her response to her sister’s results: “In all honesty, I try not to think about it, because when I think about it I think of my sister’s risk factors and—I went through it with my dad. I really don’t want to think about going through it with her, you know.”

When asked specifically about her reaction to her own results, Carolyn responded: “I didn’t think one way or the other when I found out my risk factor . . . I guess I don’t recall an awful lot.” And yet she also justifies her participation in REVEAL as having a desire to know about her genotype: “Knowledge is power. I really believe that. I mean, I don’t think you can necessarily change your destiny, but certainly to go through life with your eyes only half open doesn’t help you at all.” To the question of what kinds of actions such power might motivate, Carolyn remains unsure: “I think [REVEAL] provides useful information . . . Just don’t ask me how I would use it . . . I honestly don’t know.”

As noted above, 75 percent of the participants when interviewed had forgotten or mixed up their risk estimates:

Is it the 3/4 that’s the least likely to get it? I don’t even remember. But it was good news. Whatever it was. (66-year-old female, ApoE $\epsilon 3/3$)

I would come in—from one meeting to the next, I would come in and I couldn't remember what my risk was. And to this day, I'm not 100 percent sure. But I know that it's elevated. (54-year-old female, control)

I don't remember much . . . to be truthful, not much. I'm sure I have [my risk estimate] somewhere, but I don't remember where. (45-year-old female, control)

The inability to recall risk assessments may be considered a knowledge deficit, but participants take away other information that they readily recall. Individuals seemed particularly receptive to what they were taught about the fallibility of genetic risk estimates and the uncertainty about how and under what circumstances genetics contribute to the disease. Participants applied this knowledge to their own life situation and contextualized the information within their previously held beliefs about patterns of inheritance, expression of traits, and AD causation. Although 71 percent of the REVEAL participants cited genetics as one of the causes of AD, much higher than the Montréal informants at 18 percent, only two of the REVEAL informants believe that genetics is the sole cause of AD, testimony, perhaps, to the success of the REVEAL education component.

Laura, like Carolyn's sister, discovered during testing for REVEAL that she carries the ApoE $\epsilon 4$ allele. Unlike Carolyn's sister, however, who has a 3/4 status, Laura is a 4/4. A 55 year old from New York city, Laura had already undergone genetic testing for breast cancer prior to participating in REVEAL—her family has a history of breast cancer and psychiatric disorder. In addition, Laura's mother and one of her mother's cousins were diagnosed with LOAD and have since deceased, and she suspects the disease is present on her father's side of the family as well. Laura has been in therapy for depression for many years and her therapist was her major support while her mother was sick. Laura thinks of herself as someone who "wants to know" about her physical condition.

Even before the ApoE test, Laura perceived herself to be at risk for Alzheimer's disease because of its prevalence in her family. Further, her experiences of genetic testing for cancer and of living with depression have increased her concern. Laura creates her own probability estimates when speaking about her family as a whole: "I have a family where everyone's depressed. I mean, that has been the story of my life. And it's sort of like, you know, if there were 10 depressional genes, I know I would have each one." She goes on: "I guess I thought [prior to REVEAL] I might have a 90 percent chance of having it [AD] . . . So, in a way it's funny. Fifty, fifty, so you just say, well let's just chance it. We'll flip the coin."⁷

Although Laura, like Carolyn, appreciated the experience of participating in REVEAL, she remembers few of the specific details:

You know what, having been to, like, these little workshops, I'm still totally confused. I know I have two of them, whatever these bad things are, or something. And I've got one on my mother's side and on my father's side. So, I do know that by the time I'm, like, 70 I have a 50 percent chance of having it, which doesn't seem so bad except that most people have a 10 percent chance and reach 70. It's not too good.

When asked to explain more about the "bad things" she replied: "I don't know. I don't know what gene it is . . . It's not the BRCA [a gene associated with breast cancer]."

Laura is especially concerned about her risk for AD because she is convinced that she is suffering from memory loss. This, together with her family history, more than the information she was given about her ApoE status in the REVEAL study, makes the idea of genetic causation real to her:

I can say that I've always felt all my life that I've had some memory issues . . . so, I have this little question, whether it's something that you actually have in some way

even when you are very young . . . Do people wind up getting Alzheimer's who were aware of some memory problem when they were younger, and the connection hasn't been researched yet?

Participants often make use of the information provided in the REVEAL study to minimally modify their previous knowledge. Jennifer notes that the experience and education gained from participating in REVEAL reinforced the position she already held, but caused her to reflect a little further: "I don't know what caused it [AD in her parent]. I don't think anybody really knows what causes it. The study helped me think that maybe it's the genes" (73 years, one affected relative, ϵ 3/3).

Other participants found that the information provided by REVEAL apparently conflicted with their personal understanding of risk, as well as with their family histories. For example, Rebecca argues:

According to that [AD test], I don't have the risk, okay? I really don't have a whole lot . . . So, technically I should feel better. But I don't believe it. Technically, I should feel better. And if I had all the confidence in the world in that test, I would say, "Oh maybe it's not going to happen." But if I had a gene test come out and say, "Yes, definitively, this is you, you're going to get it, okay?" . . . it wouldn't make any difference because I already thought I did anyway . . . (48 years, four affected relatives, ϵ 3/3)

Rebecca was later asked if she remembered what genes are associated with AD, to which she replied: "I don't even remember what the names are because it meant so little to me. I'm sorry but it just meant so little to me, I couldn't quote off the top of my head with it."

When the REVEAL interviewees discussed theories of causation, as with the Montréal sample, multi-causal explanations were common. Although genetics is cited much more often than any other cause (71 percent), followed by environment (33 percent), diet (29 percent), and aluminum (22 percent), and then numerous other causes including depression, stress, hereditary (four responses only), lack of mental or physical activity, and age, even a brief discussion shows how beliefs about genetics are embedded in a complex narrative account. Laura's creation of risk estimates above is just one example of a strategy of incorporating the information she was taught by the REVEAL genetic counselors into a more complex account.

When asked what caused her father's illness, Carolyn responded, "I can't pinpoint any one thing" but when pushed she said she thought genetics might be involved: "It might be a warning sign. I mean, I really don't know . . . In all honesty, I try not to think about it."

Carolyn expresses her perception of her own risk for AD in the language of blended inheritance:

You inherit certain characteristics from your parents . . . I figure I've already got my share of the load. I have a serious problem with depression; I have rheumatoid arthritis . . . What I got from my dad was his sharp wit and disposition, which is not always nice. So I figure I've already got my full load.

Many other participants echo this logic:

Do I think I have a higher than normal chance? Yes. Heredity. And also I am so much like my mother. And I would say to her, "mother, I hope I'm not like you in this regard," you know . . . I know that she had Alzheimer's. Fact. Therefore, there's a very high likelihood that one or more of her children will have a predisposition toward it. And I would say I'm the front-runner because of so many other characteristics that are very much like my mother's. (Jean, 52 year old, control)

I found out my results. I have—don't even know what—don't even remember because it meant so little to me . . . My risk before 85 was just minimally more than others'. After 85, like 15 percent more. To me, that made no sense . . . I really believe I don't have much chance of missing it just by the genealogy. I mean . . . when I look at both sides of my family, my mother's family is all—there's nothing else, just Alzheimer's. My father's side, there's no Alzheimer's. It's heart trouble and high cholesterol and high triglycerides. Well, I take after my mother. (Louise, 48 year old, $\epsilon 3/3$)

I've showed you the picture of me and my dad. We look like clones, practically, physically. And nobody's really said—I don't know whether the information is out there because I haven't read it—whether or not that makes a difference, a person's physical appearance. But I have a suspicion that it does. (Zoe, 56 year old, control)

One participant comments about her brother:

My brother is very worried. My brother is not very sophisticated scientifically, and he tends to feel that he has inherited a lot of my mother's qualities. He has her hair color and her blue eyes and many of her behavioral traits as well. I don't mean to belittle my brother. (Nina, 50 year old, $\epsilon 3/3$)

However, many participants do not confine AD causation to the passing along of traits in families. The following comment, made by Carolyn, is very typical: "I believe there are certain factors that come at us from the outside that we can do nothing about; I think we can take care of our bodies just to a point, you know."

Laura, who has many more relatives with AD than does Carolyn, puts more emphasis on genetics as contributory to AD, but she too is not certain that this is the whole story:

I don't know what else does it besides genetics. Maybe depression played a part. She [her mother] was always a very, like, non-perky person. But, also, I think having a psychotic daughter was like a constant, you know, "Oh my God, how did I do this?" And, then, my father died when I was young. And she had all this responsibility. Just, maybe, depression played a part, but I think it's probably genetic.

As with the examples from Montréal discussed above, most REVEAL participants acknowledge a range of possible causes, and an awareness that there might be a number of "triggers" or "factors" that could come into play. When one participant was asked in what way she thinks genetics is involved in the causation of AD, she replied: "I think it plays a part, but I don't think it's the end all. I'm sure that a lot of the diet, and the health, and the exercise that we do today will prolong life and mental acuity" (Lilian, 74 year old, one affected relative, $\epsilon 3/3$).

Another participant noted: ". . . It's kind of a Russian roulette kind of thing. Everything's got to be working against you, whatever those factors may be. And I don't even know what. Maybe aluminum in your teeth? You hear some of those things. I don't know" (Hesta, 52 year old, one affected relative, control).

In the quantitative part of the REVEAL study, people were asked to respond to scales designed in order to establish if anxiety was heightened by genotype disclosure. Interviewees who were told that they do not have the $\epsilon 4$ allele expressed considerable relief, and assumed that their anxiety would have been heightened if they had been informed that they have the "bad" allele (there is, of course, a potential danger that these participants now assume that they will not get LOAD). However, participants who were told that they have either one or two $\epsilon 4$ alleles ($n = 17$), usually responded pragmatically, pointing out the limitations of testing for susceptibility genes that they had learned as part of the REVEAL

educational component, and many also noted that, regardless of testing, there is not much one can do to prevent AD.

The qualitative interviews show clearly, regardless of ApoE status, life experience, and family history, that REVEAL participants do not confine their accounts of disease causation to “genetics,” but frequently combine their prior understanding about LOAD with the information they recall from participation in the trial. In fact, the education sessions that REVEAL participants were required to attend in all probability worked to reinforce the concept of blended inheritance already in the minds of many participants prior to the study, because emphasis was given in the sessions to the way in which the ApoE $\epsilon 4$ allele does not determine disease occurrence but only puts certain individuals at increased risk. Despite sessions with genetic counselors, participants discussed “genes” and “alleles” in the same breath as inheritance of a parent’s personality or physical constitution. The results of genetic testing did not apparently elevate anxiety in most cases, in part because genetic or “science based” explanations do not displace common sense explanations, and in part because those people who already believed they are at 100 percent risk for LOAD were reassured that this is not the case.

8. Conclusions

It is clear that the public, even those most directly affected by AD in their families, are not in possession of “foundational” knowledge about susceptibility genes. However, many people come away from the REVEAL project with feelings of relief because they learn that they are not at such high risk for LOAD as they had presupposed, and furthermore have the satisfaction of knowing that they assisted in the creation of scientific knowledge in connection with this devastating disease that affects their immediate family. Moreover, some make changes to their health insurance arrangements as a result of testing. Are the REVEAL investigators correct then, when they claim that it is paternalistic to withhold information about genotyping from people who are at risk for AD? Given the current “needs” of the research community that requires routine DNA typing of patients diagnosed with AD, and also the intense monitoring, including DNA typing, of healthy people who attend memory clinics to try to detect the biomarkers associated with incipient dementia long before the behavioral changes of AD are diagnosable, it is a foregone conclusion that many of us will be genotyped before long. It may well be the case too, that the market for direct to consumer ApoE testing will expand. Given these developments REVEAL is a timely project and consideration of the implicated “matters of concern” an urgent matter. Of course in daily life, rather than as part of a controlled trial designed to assess psychological responses to testing, people will be able to refuse information about their own genome, even if they agree to participate in research. Experience with late onset diseases, such as Huntington disease, suggests that most people will not want to know what their genetic status is. Matters such as these are ethical problems involving questions of privacy and informed consent.

More fundamental is the question of the science itself, and professional and public understanding of it. Clearly, most participants in the REVEAL project, although they understood that the “bad” allele does not *cause* LOAD, nevertheless did not grasp the specifics of the ApoE gene. Perhaps this is not a major shortcoming of the project. More to the point is the question of the reliability of the standardized risk estimates and, moreover, what exactly they represent. Inevitably the contributions made by familial and social environments, politics, ethnicity, poverty, and the physical environment to the occurrence of

dementias are set to one side, while the focus of attention remains squarely on the molecularized body, family history, and gender. Most informants who participated in REVEAL, as do the Montréal sample, believe that these larger facets of daily life contribute greatly to the incidence of the disease, and they do not recognize susceptibility genes as determinants of disease; this is exactly what they were taught as part of the REVEAL education program, but the present two site findings suggest that the majority may well have held such views before they entered the trial.

On the other hand, the REVEAL project is focused on DNA typing and it cannot avoid heightening the sensitivity of participants to the importance that the scientific world attributes to genetics. Participants are taught that many people who are homozygous for ApoE $\epsilon 4$ will not get AD, but this message could be made much stronger—in one population based study, for example, 85 percent of elderly individuals homozygous for ApoE $\epsilon 4$ showed no signs of dementia (Hyman et al., 1996). This study and others like it make it clear that many unknowns are involved when making predictions about ApoE. For example, when more than one person in a family has LOAD, it should not be assumed that these cases are inevitably associated with the presence of ApoE $\epsilon 4$ alleles. Research is beginning to show that what apparently “runs” in families, is by no means always predicted by ApoE genotyping (and the case of Rebecca above is possibly an example of this). People in the Montréal sample resorted less frequently than did the subjects of the REVEAL trial to accounts based on blended inheritance; they mentioned diet and environment more frequently than REVEAL participants, and their use of a language of genetics was more diffuse than that of REVEAL participants. This suggests that a form of geneticization has taken place among REVEAL participants who came away with a heightened sensitivity about AD as an inherited disease, that many then attempt to buffer by means of multi-causal explanations and resort to the concept of blended inheritance. But perhaps this response to what they have learnt is not inappropriate.

As indicated above, it is now well established that, in addition to the 2 percent of the DNA that codes for proteins that has been the focus of attention until recently in genomic research, non-coding DNA, RNA, proteins, and other basic molecules all contribute to expressed phenotypes. The molecularized body is undergoing a radical reconceptualization, yet again, and emerging knowledge about the action of genes (with the exception of some rare mutational genes) is, more often than not, contextualized in cells and tissues, having the effect of scaling genes down to size. The task that lies ahead in connection with public understanding of genomics is to undo the former dogma—the former “facts”—of molecular genetics that most of us learned a little about in school, namely that the genotype determines the phenotype, and in its place to create a narrative of complexity in which it is recognized that risk estimates for late onset disease based on genotyping⁸ modified by a few other involved variables may have little or no useful meaning at all. At the same time, it is appropriate to try to wean people away from ideas about blended inheritance. This form of knowledge can be stigmatizing to some family members and cause unnecessary anxiety. But this is a challenge, because it is so deeply ingrained and apparently provides an account that makes intuitive sense, whereas probability estimates about what may happen in old age do not.

A radical transformation in public understanding, including that of health care professionals whose specialty is not genetics, can only come about through extensive revision of formal education on the subject of genetics from high school on into university, exposure of science reporters and the media at large to the complexity associated with molecular genetics, changes in the training of genetic counselors, wider recognition of the significance

of findings from population and epidemiological genetics, and above all a recontextualization of genes in their proper place—as part of a complex, dynamic apparatus in which genes do not call the shots.

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Notes

- 1 Numerous genes come in more than one form known as polymorphic variations that are widely distributed throughout human populations. Such polymorphic genes can place the people who have them at increased risk for specific diseases such as cancer or heart disease. However, having the polymorphism is neither necessary nor sufficient to cause the disease and it is assumed that other, as yet unknown genes, their protein products, other molecular materials, and/or environmental factors must also be implicated.
- 2 At this same conference, an epidemiologist clarified the way in which genes are believed to be implicated from before birth in what will happen to individuals in old age. Genes influence the building of “cognitive capacity” this epidemiologist argued, starting in the intra-uterine environment and playing a large role throughout infancy and childhood and into early adult life. When interviewed by the lead author AD experts frequently made claims that people with high IQs and with extensive education are at considerably less risk for AD than are others. The conference presentation made it clear that what is assumed in such statements is that genetic predisposition influences the laying down of the neurological networks required for brain functioning. As a result, in the brains of biologically predisposed individuals fewer synapses will be created; such people are likely to have lower IQs and will complete less schooling. It is assumed that the plaques, tangles, and cell death associated with AD will do proportionally more damage in a short space of time to such people.
- 3 The term heterozygous refers to people who carry only one ApoE ϵ 4 allele. Someone who is homozygous for ApoE ϵ 4 has two of these alleles.
- 4 In order to carry out the “risk disclosure” portion of the study all subjects are shown a “risk curve.” These curves were developed by first drawing on gender- and age-specific incidence curves of first-degree relatives of persons with AD that had already been calculated from a meta analysis of studies involving very large samples of Caucasian subjects (Green et al., 1997). In addition, the curves were further sub-divided by incorporating ApoE genotype-specific odds ratio estimates for gender and age, reported in a second meta analysis of 50 studies world-wide (Farrer et al., 1997). This gives a total of 12 curves based on the six possible combinations of ApoE alleles for both males and females. Risk curves for the control group were based on gender, age, and family history alone. On the basis of their genotyping, the researchers show the appropriate risk curve to each trial participant and then discuss with them their estimated increased risk for AD as they age. Creating these risk curves entails exceedingly complex mathematical formulations (Cupples et al., 2004). No other variables, such as ethnicity or education are factored in, nor are such variables discussed informally during time with genetic counselors. To date virtually everyone enrolled in the trial has been white, but the second part of the REVEAL project, due to start in 2005, will include at one of its sites, individuals recruited through Howard University who will be African American. The risk estimates to be used with these volunteers are currently being estimated (Green et al., 2002).
- 5 The first author and two research assistants were responsible for developing and carrying out these interviews. In the collection of both data sets interviews were tape recorded and then transcribed verbatim. The software NVivo was used to systematize emergent themes.
- 6 Two major motivations for participating in the REVEAL study were cited by interviewees: the desire to know, as indicated above, as well as the desire to help further research on AD (74%).
- 7 The REVEAL study estimates of increased risk for LOAD for white women with a double ApoE ϵ 4 by age 75 is just over 50%.
- 8 This claim does not apply to genetic testing for genes inherited in the Mendelian fashion, although even in these cases outcomes cannot always be predicted with certainty.

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