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Postgenomics, uncertain futures, and the familiarization of susceptibility genes

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Abstract

This paper draws on empirical findings from interview studies in the USA and Canada to interrogate the idea that expanding practices of genetic testing are likely to transform kin and family relations in fundamental ways. We argue that in connection with common adult onset disorders in which susceptibility genes with low predictive power are implicated it is unlikely that family relationships will be radically altered as a result of learning about either individual or family genotypes. Rather, pre-existing family dynamics and ideas about family susceptibilities for disease may be reinforced. The case of the ApoE gene and its relationship to Alzheimer's disease is used as an illustrative example. We found that "postgenomic" thinking, in which complexity of disease causation is emphasized, is readily apparent in informant narratives.

Keywords

genetic testing; kinship; family; ApoE; Alzheimer's disease; predictive testing; risk; USA; Canada

Introduction

Kinship studies constituted a key research focus within social anthropology for most of the 20th century, but a significant shift in orientation took place in the 1960s when the anthropologist David Schneider drew attention to how much of this research had been biased due to its basis on what he termed the Euro/American "folk model" of kinship. He argued that this model, in which the primary ties of kinship are assumed to be "formulated in concrete, biogenetic terms," is in effect culturally produced, and by no means universal (Schneider, 1968: 23). Schneider's critique of the effects of the "naturalization" of kinship in anthropological research was one aspect of a broader move in the social sciences in which the concept of 'nature' itself was increasingly subjected to interrogation. Ethnographic research that followed deconstructed this "biologism" so evident in kinship studies and

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provided important insights into the epistemology of knowledge production and normative cultural practices associated with reproduction and kinship in EuroAmerica (see, for example, Carsten, 2000, 2004; Franklin, 1997, 2003; Franklin & McKinnon, 2001; Strathern, 1980). Technological advances in assisted reproduction over the past two decades have further challenged the assumption that kin and "blood" relations must inevitably be constituted from sexual reproduction alone, ensuring that kinship continues to be a thriving research subject within the social sciences (Franklin, 1997; Franklin & Ragoné eds., 1998; Franklin & Roberts, 2006; Strathern 1992; Thompson, 2001, 2005).

The subject matter of this special issue of *Social Science and Medicine* – how bonds of kinship may potentially be transformed on the basis of newly acquired genetic information – appears to be invigorating kinship studies yet further (see, for example, Browner & Preloran, 2010; Cox & McKellin, 1999; Finkler, 2005; Hallowell, 1999; Konrad, 2005). However, it should not be assumed *a priori* that all newly emerging knowledge about genes will necessarily radically transform family relationships.

The dominant model in molecular genetics for the second half of the 20th century has been one based on Mendelian segregation of genes in which sound predictions can be made with considerable accuracy about disease risk. However, emergent postgenomic technologies have forced substantial re-thinking about what exactly constitutes a gene, and turned attention to the way in which segments of DNA function variably in different contexts (Jablonka & Lamb, 2005; Lock, 2005; Oyama, Griffiths & Gray, 2001). Although Mendelian genetics can be made use of to create predictions about the numerous comparatively rare single gene disorders seen in the clinic, when dealing with common adult onset disorders the process is very different. The question becomes one of how and under what circumstances a segment of DNA is expressed, and in what ways the segment functions in relation to other molecules and environments internal and external to the body. This situation makes risk predictions exceedingly problematic, and no straightforward conclusions can be drawn about what exactly the "passing on of genes" or "blood relations" implies with respect to disease incidence and family relations. In other words, for common complex disorders, even those family members who share a specific gene in common may well not have a similar risk for future disease.

We set out from the position that nature and culture are co-produced and that biology, history, and culture are inextricably entangled (Barad, 2007; Haraway, 1991; Latour, 1993; Lock & Nguyen, 2010). More specifically, for the purposes of this paper, that calculations about future risk for specific diseases based on genetic testing of individuals are inextricably embedded in technologically produced data about the natural world, much of which is in a state of constant flux (Lock, 2005, 2008). Knowledge about the results of genetic testing for complex disease raises, then, a large number of uncertainties for both scientists and affected individuals and families that profoundly influence the way in which the postulated effects of genes are interpreted. Using late onset Alzheimer's disease as an illustrative example, we highlight the uncertainties associated with information currently being disseminated in the world of the basic sciences in connection with the genetics of this disorder. These uncertainties are mediated and translated by other researchers interested in Alzheimer's disease, among them practicing clinicians, the media, and support groups, for the benefit of

the public at large (Lock, Freeman, Chilibeck, Beveridge, & Padolsky, 2007) who, in turn, if they are interested in such information at all, reflect on what it might mean for themselves and for their kin.

The paper is divided into three parts: first is a brief account of current scientific and epidemiological knowledge about the genetics of Alzheimer's disease. This is followed in part two by a discussion of findings from interviews carried out with individuals who have one or more relatives diagnosed with late onset Alzheimer's disease and who have participated in a randomized control trial in which they have been given information about which variant of the ApoE gene they carry. In part three, we present excerpts from interviews with individuals who also have one or more relatives diagnosed with Alzheimer's disease, but who have not undergone genetic testing. For these samples, data was collected by means of semi-structured interviews following IRB ethics clearance and after obtaining informed consent from participants. Interviews were recorded and transcribed verbatim and then entered into NVIVO software to facilitate analysis of cross-cutting themes. All personal names have been changed to protect confidentiality.

We conclude the paper with a brief presentation of some preliminary findings derived from informal, exploratory discussions with a small sample of people in their 20s and 30s about their understandings of how genes function. We then consider what all of these findings suggest for kin and family sociability as genetic and genomic knowledge is increasingly being brought into the public domain.

Genetics of Alzheimer's disease

In 1993 a publication appeared that for the first time made an explicit association between a variation of the gene known as ApoE and increased risk for the common, late onset form of Alzheimer's disease (Corder et al., 1993). This finding forced some revisions of the received wisdom of the day in the medical world – namely, that Alzheimer's disease in older people is "sporadic" and does not "run in families." The ApoE gene, present in all mammals, is located in humans on chromosome 19 and is essential for lipid metabolism. This gene comes in three universally distributed forms: ApoEε2, ApoEε3, and ApoEε4, and extensive research indicates that the ApoEε4 allele puts individuals at increased risk for AD (Tilley, Morgan, & Kalsheker, 1998). Between 14 and 16% of "Caucasian" (white) populations (the most extensively studied population) carries an ε4 allele, however, it is unanimously agreed by all researchers that the presence of the allele is neither necessary nor sufficient to cause the disease, for reasons that are as yet very poorly understood. In other words, the ε4 allele is an example of a "susceptibility gene," one that contributes to disease causation only under certain circumstances.

Epidemiological findings suggest that approximately 50% of ε4 carriers never get Alzheimer's disease, and that somewhere between 30 and 60% of people without ε4 are diagnosed with the disease (Myers et al., 1996). However, one community-based study in Iowa found that 85% of elderly homozygous ε4 individuals whose average age was 81 showed no sign of dementia when given standard tests for cognitive functioning (Hyman et al., 1996) implying that the relationship between ApoEε4 and AD incidence may be

significantly weaker than is commonly assumed. The situation in connection with the genetics of AD has been summarized by two neurogeneticists as follows: “First, and most importantly, the heritability of AD is high…this had been demonstrated in various studies… over the past decades.” However, “most of the research currently being done has faulty methodology, lacks replication, and is inattentive to haplotype structure” (Bertram & Tanzi, 2004, p. R135). These authors note “while the genetic association per se [of ApoEε4 with AD] has been extremely well established…there is no consensus as to how this association translates pathophysiologically,” nor how it functions in conjunction with the other numerous candidate genes (Bertram & Tanzi, 2004, p. R137).

Adding to the uncertainties, other epidemiological studies have shown that ApoE 4 works in unexpected ways in specific populations (Corbo & Scacchi, 1999). For example, in on-going research conducted for more than 15 years with a sample of over 2000 Yoruba in Nigeria, low rates of AD have been reported, and the presence of an ε4 allele does not place individuals at increased risk. On the other hand, ApoE 4 is significantly associated with dementia among African Americans, although less so than in white American populations (Farrer et al., 1997). These findings strongly suggest that risk-reducing factors (in Africa) and risk enhancing factors (in North America) are implicated, among them other genes, their protein products, diet, environment, and quite possibly yet more variables. An overemphasis on the genetics of AD in the research literature obscures the fact that many other risk factors, including toxic environments, head trauma, education levels, chronic stress, prions, and so on, have also been implicated.

Uncertainty in connection with risk predictions based on the ApoE gene will be further compounded as scientists learn more about other candidate genes currently thought to be associated with AD. These genes are postulated to have very small effects, and similar to the ApoE gene, only under specific, unknown circumstances. Few family members will likely ever hold exactly the same combination of these genes. Furthermore, individual and cumulative effect of these genes in different environments will be virtually impossible to predict (Harold et al., 2009). In summary, an individual’s ApoE status cannot furnish knowledge about a highly probable future in connection with Alzheimer’s disease. By extension, it provides no substantial insight into what is in store for those kin who share the same genotype, greatly reducing the likelihood that family relationships will be profoundly affected. We turn next to a consideration of how people who have been informed about their ApoE genotype respond to this uncertain knowledge.

The REVEAL Study

The findings presented below are based on interviews with participants of The Risk Evaluation and Education for Alzheimer’s Disease Study (REVEAL), that is an on-going NIH-approved, randomized, controlled trial funded by the National Human Genome Research Institute (NHGRI) and National Institute on Aging (NIA). This project has been staged in multiple phases by health researchers at several different research centers in the United States. Designed to “provide healthy adults with genetic susceptibility testing and information about their chances to develop Alzheimer’s disease,” the study also aims to

evaluate the psychological and behavioral impact on subjects of genetic risk assessments and disclosure (for further details see, Roberts, Cupples, Relkin, Whitehouse, & Green, 2005).

Participants come from families where one or more relative has been diagnosed with Alzheimer's disease and are recruited to REVEAL via systematic ascertainment from AD research registries or through self-referral. Before the trial, prospective subjects attend an educational session in which genetic counselors present current scientific ideas about risks for AD, including genetic susceptibility. At this point only a small minority decide to drop out of the study while the rest are randomized into intervention and control groups. In the first phase of the trial, the intervention group received personal risk assessments based on genotyping (ApoE), family history, and gender, while the control group was given a risk assessment based on family history and gender alone. In the second phase, everyone was genotyped. Although these individuals show no sign of AD themselves, it could be argued that they are in effect transformed into pre-symptomatic patients as a result of their participation in the REVEAL project.

Upon the completion of the REVEAL study, seventy-nine participants volunteered to return and take part in open-ended interviews conducted between 2004 and 2006 by a small team of anthropologists. This qualitative sample ranges in age from 37 – 76 years old (56 years on average), has on average 16.8 years of education, and eighty-six percent are women. As will become clear, our findings show that being taught about personalized genetic information does not necessarily trigger profound or radical changes in the way people conceptualize their personal risk for AD, or how they think about family health and familial relationships on the whole.

Familiarizing Risk

In our interviews, only 27% of participants recall their test results accurately a year after completing REVEAL, and a significant number (23%) are unable to recall their genotype or risk estimates at all (Lock et al, 2007). The other half retain the gist of what they have been told, expressing their results in general statements such as "I have a lower risk than I imagined," "I have the bad gene" or "I'm next to worse."

However, recall tells us little about whether or not test results are meaningful. For example, Susan [age 52, ApoEε3/4] complains that the "numbers didn't stick," but remembers something about a "50–50 probability." When asked to write down her genotype on a REVEAL study follow-up questionnaire she thought, "okay, it's 3/4, so that's what I put down, but it's more a parrot thing than a 'yes, I know what this means.'" Rose comments:

> I don't know where those papers [results] are now, but if I'm in a room with 100 people, I would be one of the ones to get Alzheimer's, whatever the percentage is. [The result] puts me at a high risk factor… 80% or so…I'm an 4-4, whatever that means… but do they ever check back with those 20 or 100 people ten or fifteen years from now to see that they actually get it? [age 62, ApoEε4/4]

People instead consistently frame and express their personal risk in more familiar idioms of heredity, family histories and family resemblances. In their accounts, they slip between, on the one hand, an abstract language of genetics grounded in popular science and, on the other

hand, intimate or familiar tropes about the transmission of biogenetic substances that are part of daily language including: “in the blood,” “running in the family,” “part of the family history,” and “in the family line.” In such conversations, reference to the ApoE gene is very often eclipsed entirely by discussions about family history - as though a history of AD, rather than the gene itself, is what puts one at risk for the disease. When asked about how her genetic results relate to her family members, Alexis says:

> They’ll have a high family risk, but other than that, who knows. …I don’t know what their genetics are but I do think about what their chances are - but not having anything to do with the e4. My sister had a small stroke many years ago and she’s at risk. I mean, she has the same family history that I have. [age 53, ApoEε3/4]

An overall fusion of ideas about genetics and heredity is a well-documented feature of “folk” or lay models of heredity and kinship in North America and Europe (Emslie, Hunt, & Watt, 2003; Featherstone, Atkinson, Bharadwaj & Clarke, 2006; Richards, 1996). This conflation is sometimes understood to represent a misunderstanding of the science, but can also be interpreted as a strategy to render it more comprehensible - a means of expressing abstract and complex information in terms that are more concrete and familiar. In blending ideas about genetics and heredity, individuals are better able to perform what Duden and Samerski refer to as a “superimposition of incompatible spheres of meaning” by blending the abstract and concrete, invisible and visible, statistical and individual (2007, p. 167).

Such superimpositions are easier when genetic information corresponds reasonably well with previous beliefs about risk and inheritance. In such cases, people emphasize how the information provided by genetic testing is “not new” to them but only confirms what they already knew or at least suspected. Edward says of his high-risk estimate:

> Looking not just at my father’s side, but also at my mother who has lost three siblings in the last two years who had dementia, it’s been prevalent on her side of the family too. I think any objective person would look at my family tree and say, if I had to place odds, my sisters and I would all be on the wrong side of those odds for the possibility of getting this disease at some point. [age 37, ApoEε4/4]

Yet risk predictions generated by genetic technologies sometimes conflict with those rooted in everyday beliefs about heredity. Some REVEAL participants found their test results to be at odds with their own ideas about the transmission of risk or heritable substance amongst kin:

> I found out my results. My risk was just minimally more than others…To me, that makes no sense, I really believe I don’t have much chance of missing it just by genealogy. I mean…my mother’s family is all – there’s nothing else, just Alzheimer’s. So technically, I should feel better. But I don’t believe it. [Colleen, age 48, ApoEε3/3]

Colleen’s experience with the disease in three family members strongly informs her reason for maintaining that she is at high risk. The visible evidence of risk provided by family history is often more compelling than that based on a genetic test. Anne searches her family history for evidence of her elevated risk:

> This information [that I am at increased risk] affects my entire family, my children especially; because I carry a gene it is quite possible that they have this also. But the only case [of AD] I have really known was my Dad…it's not as though I have others to compare it to…he has a twin sister and I look at this twin sister now and I'm saying, well how did he get Alzheimer's, and she doesn't have Alzheimer's? She's still doing her thing, besides three knee replacements and may be heart medication, she's still fine! [Anne, age 50, ApoEε3/4]

The discord between genetic information and common beliefs about heredity (that twins share the same genes and hence risk) leaves Anne somewhat skeptical of the predictive powers of a genetic test for AD. Her family history suggests to her that the genetic underpinnings of AD are far from straightforward.

REVEAL participants rely on a variety of ideas about heredity to predict who in their families are most at risk for developing AD. Some informants refer to a blended inheritance in which a trait is thought to be the result of a mixing or combination of ones' parents' traits (Richards, 1996). Other people describe a "bundled inheritance" in which a group of traits is understood to be transmitted together as one parcel, or where one parent's genes are thought to be "stronger" than those of the other parent and more likely to transmit a specific disease. Alternatively, observed family patterns of AD inheritance lead some people to believe that the ApoEε4 allele (and hence AD) is inherited only on the female side. In all these instances, visible phenotypic resemblances (physical, mental, and/or emotional) apparently also signify shared genotype or internal similarities including risk for disease. This thinking is exemplified by Anita's comments:

> I know that Alzheimer's runs in the family. I always assumed my sister will get it, not me. I have more of my father's traits. My sister has many more of my mother's traits. So, I Figured if that's the gene, it goes with her trait. [age 50, ApoEε3/4]

Christina says of her high-risk result:

> Well, I really wasn't surprised. I mean, I look like my mother. And my uncle and my mother look alike, and they look like their father. So if I just go by history I would not be surprised that I would carry the risk. [age 52, ApoEε3/4]

Lay theories of heredity tend to remain intact after genetic testing and are in fact actively mobilized to evaluate new genetic information. The above responses foreground an expertise cultivated from experience with AD in the family and demonstrate how people use family linkages to trace visible paths of transmission and locate potential risk independently of knowledge about genotypes.

Familial genes and environments

The majority of people interviewed (80%) consider genes and/or heredity to be probable or possible factors in AD incidence. Yet very few (4%) list genes as the *only* causal explanation and AD is typically understood to be caused by a number of interrelated factors (this is what informants have been taught in the REVEAL education session but it is quite possible that they held these ideas before entering the trial). Genetic explanations are framed in terms of a genetic or inherited susceptibility, predisposition, or vulnerability to AD that, it is assumed,

can be aggravated, mitigated, or prevented by other factors (personal and environmental) over which one has, to a degree, some control. Christina says, for example:

> …there's certain things in terms of diet or exercise, that research has shown, that if you kind of walk tightly around some of these issues, you may not trigger that genetic potential. You have the genetic potential: no question. Whether it shows up or not has a lot to with what you do and your environment. [age 52, ApoEε3/4]

She considers both the biological and social aspects of kinship and contemplates how a familial risk for AD might derive from an inherited genetic predisposition, but also a common family environment or lifestyle:

> Before we had blood markers, all we had were family history risks, so to me that's still genetics, what that information tells you is that something is running in your family either inherent to you, or because of something that your family does. [age 52, ApoEε3/4]

Informants gather information about AD prevention from a number of different sources – the REVEAL study, the media, family physicians, and friends – but there is little consensus about what provokes the gene to "act up." Most rely on firsthand experience with an afflicted family member to provide clues about possible causes or prevention. When Benjamin [age 69, ApoEε3/3] is asked about his AD risk he says: "I thought it would be less because of my lifestyle." He avoids aluminum pots, takes vitamin and lipid supplements, and stays active with sports, grandchildren, and seniors' and church organizations. He is certain that staying mentally active is key, and that this is where his own mother with AD might have "gone wrong." On the other hand, Jolie finds such ideas dubious:

> The one thing that I don't believe will help or hinder Alzheimer's is the fact that they say that you have to keep mentally active and do crossword puzzles or play cards – because my mother was active. She worked at the school lunch program for years, read the newspaper from cover to cover, so she was mentally stimulated. And you look at people like Reagan (sighs) you know what I mean? It's not as if his brain wasn't exercising?! [age 56, ApoEε3/4]

Overall, people are cautious about information to do with prevention, especially when it confounds what they have witnessed in their own family. Rose's comments demonstrate a common way of understanding AD causation in which people exhibit an interest in new findings, but these findings are entertained with mixed sentiments of hope, skepticism, and resignation:

> *Turmeric was one of the things I remember hearing about, and I started using yellow and red peppers and I season my food with turmeric when I can. I had intended to do further research on the internet, but you know when you first get the [genetic] result you think you're going to go out and look up all this stuff to find out a way that you can stop this. But then, after a while, you get lackadaisical about it, just like I have. And I just say, "I'm not going to get it. I'm NOT going to get it." Because whatever tests and stuff you may run, I think the ultimate decision rests with God.* [age 62, ApoEε4/4]

Responses that refer both to efforts to control the future, and the futility of these very efforts, are not surprising given that no known prevention or effective treatment exists for AD. The idea that one can do *something* to mitigate AD suggests that it is not the gene alone that causes the disease; while the belief that there is *nothing* that can be done makes knowing one's genotype somewhat pointless. Both types of responses call into question the value of ApoE testing for AD.

As we have seen, families serve in some ways as "living laboratories" in which newly acquired genetic knowledge is evaluated and tested; people turn to kin for clues about who is most at risk and to inform their ideas about possible causation and prevention of AD. In addition, pre-existing kin relationships determine the way members partially communicate or share their genetic risk results with each other (Featherstone et al., 2006; Green, Richards, Murton, Statham, & Hallowell, 1997). It appears, then, that participation in REVEAL is unlikely to provoke a "geneticization" of either individuals or their families, but instead often results in what we refer to as a "familiarization of genetics."

Alzheimer's disease and the family

How people and families pursue, interpret, and utilize genetic test results depends not only on family history, perceived shared family traits, and family dynamics, but also on the nature of the disease(s) in question. Alzheimer's disease is devastating, but typically strikes late in life and is characterized by slow progression. This means that for many people, the fear of AD is often secondary to more pressing concerns about risk for cancer or heart disease, believed to be more likely to strike first. Many middle-aged REVEAL participants already have experience with other serious diseases, and their responses make it clear that this is often forefront in their minds and takes precedence over concerns about the more distant future.

Worries about potentially being afflicted with demented are also secondary to people's immediate concerns regarding care-giving for family members. Interviews with REVEAL participants are dominated by stories about caring for family members, which often requires a good deal of time, finances and unflagging energy (Lock et al., 2007). It is these intense experiences of "kinning" (Howell, 2001), and not knowledge about the ApoE gene, that apparently affect family relationships above all else.

Nicole calls herself a "veteran caregiver" having nursed her mother for years, and now caring for her father with AD. She resents her brothers and sisters who rarely visit their father, make insensitive remarks, and never offer to relieve her of responsibilities as a primary caregiver:

> In the two years and nine months did they ever say, Nicole, we'd like to take over for you? Never. Not once. I had [paid professional] care-givers who would say, "I'm coming out on Sunday for you, Nicole. You're [taking the day] off, and you're not paying me." They became my family. So there's a lot of good that's come out of this too. Because you realize who's your family, and who is not your family. And your family sometimes is not related to you, nor of the same race, or the same religion. [age 52, Control group]

Even when immediate concerns give way to those about the future, personal risk for AD does not necessarily figure prominently. People who participate in the REVEAL study are primarily motivated to do so because they want to contribute to research or gain access to up-to-date information, and medical specialists. Those interested in the personal genetic assessment are concerned less with what they may "pass along" to kin biologically, than what may be inherited by way of social or financial difficulties. For instance, Nicole talks about purchasing long term care insurance as a strategy for "prevention." Like so many, her hope is that her family will not have to bear the financial burden for her care, should she ever develop AD: *"It's so heartbreaking to see families that lose everything [to pay for care]… cause then you don't have anything to pass on to your children* [age 52, Control group].

Selective uptake of genetic information is not surprising given that scientific knowledge about the genetics of AD is also partial. Furthermore, given that the ApoEε4 allele merely increases susceptibility to AD and under circumstances that are not understood, the gene as a "fragmented fact" is probably insufficient to radically alter the way people relate to each other (Bestard, 2004, p. 262).

Yet people are already familiar with fragmented facts and partial information; they approach genetic susceptibility much as they do other uncertainties in their life. As Laurel [age 51, ApoEε3/4] describes the information she received through REVEAL in this way: *"I thought it was interesting, I think it's fascinating, but you know, I look at all systems of knowledge not as the answer to anything. I just take what I want and leave the rest."* Tara [age 57, ApoEε3/3] likens her test results to a weather forecast, *"there's always the probability of that [AD] happening. It's something like: it's going to snow, but will it snow ten inches or one?"* And Simone [age 72, ApoEε3/3] visualizes her risk in this way: *"There's no guarantee either way, it's [getting AD] just a liklihood; I don't consider it quite the luck of the draw, but neither do I feel that I have control over it. Somewhere in between."*

It is unclear to what degree the public will be interested in, or seek out, ApoE testing when it becomes more widely available. Until such time, the REVEAL trial provides an important glimpse into the ways in which the uncertainty associated with the genetics of AD influences individual and family responses to learning about possible futures. In the following section, we turn to individuals who also have AD "in the family," but who have not undergone genetic testing nor received any formal education about the genetics of AD. Compared with the REVEAL sample, these interviews provide insight into how individuals without access to personalized genetic risk estimates for AD envisage familial and personal risk. They may also provide some indication as to whether or not people will pursue this kind of information as it becomes more readily available.

Speculations about Alzheimer's disease when genotypes are unknown

Between 2002 and 2003, forty interviews were conducted with first-degree relatives (primarily the children) of late-onset AD patients in Montréal, Québec. The participants were contacted at clinics and gerontology units in which their relatives were receiving treatment. They ranged in age from 29 to 70 years and 58% were women. Unlike REVEAL subjects, these informants have not been exposed to any systematic information about the

genetics of AD. The majority are caregivers for their diagnosed parents and are primarily interested in advice in relation to this task. They rely on information about AD obtained from other caregivers, the media, family physicians and advocacy groups. Our research has shown that the latter two of these sources actively discourage genetic testing for AD (Lock et al., 2007).

Not a single participant introduced the ApoE gene into these discussions, yet approximately half the sample believes the disease has - at least in part – something to do with genetics. Interviewees made it clear that physicians downplayed the significance of genetics when discussing Alzheimer's disease with them. Furthermore, pamphlets and information sheets distributed by the AD Societies of Canada, the UK, and the US discourage genetic testing, and emphasize the predictive limitations of the ApoE gene (Lock et al., 2007).

Similar to the REVEAL informants, most people refer to genetics and heredity interchangeably when describing what causes AD. Carla [age 52, three affected relatives] notes:

> I tell myself that the genetics are responsible for the disease. I think it's the family baggage, rather than an aluminum pan or living in a certain area or whatever.

She adds:

> It's true that there were hereditary antecedents. My grandmother suffered through Alzheimer's and my aunt also did. We were aware…we knew eventually something would happen …

And as Catherine [36, two affected relatives] says: *"In my mind it's genetic since my father's oldest brother, he had it too."* Even without specific information about their genes, such language is meaningful and frequently utilized to signify a shared substance or "family baggage," as well as the process by which that substance is passed along.

Again, similar to REVEAL informants, many people use subjective knowledge to predict who in the family may be marked for AD. Physical and social traits are often connected to ideas about genetic constitution and used to predict disease risk. When asked whether she worries about Alzheimer's, Hannah maintains that her brother is more likely to develop the illness than she because he shares so many features with their affected mother:

> My mother worries more about my brother than me. She thinks his personality is similar to hers. My brother looks like her family and is built like them. We are both intense, but my mother doesn't talk, neither does my brother; I talk about my feelings more and he's a more closed person. [age 62, one affected relative]

Just over half of the sample consider AD to have a hereditary or genetic component, but few (15%) believe this is the most important or sole factor. These interviewees tend to hold two to three different (or linked) theories about AD causation and consider the role of the gene alongside other factors such as diet, environment, mental activity, stress, aluminum, alcohol, or surgery. Genetic risk for AD is understood as an inherited predisposition or susceptibility for the disease, but not something that causes the disease. Again, Hannah states:

> I think everything is genetically related, but I think that it would be a propensity towards whatever it may be – asthma, heart disease, AD, cancer – and I think that there's other factors that may make it surface or not. [age 62, one affected relative]

People are ambivalent or uncertain – rather than indifferent – about the role of genetics in AD. Even when the gene is not marginalized in discussion, it is usually embedded within complex theories about AD that stress uncertainty.

Ideas about AD causation and prevention are primarily informed by family history and personal experience with confronting the disease in the family. People emphasize "good living" as a way to mitigate Alzheimer's risk (Lock, Lloyd, & Prest, 2006, pp. 142–3) but some reflect on their parent's "healthy" habits and note that a lifetime of "good choices" may not prevent Alzheimer's:

> I've gone to lectures on Alzheimer's and they say, keep your brain working, keep your brain active, try and do things. But my mum worked her whole life, she played bridge, she played Mah-Jong, you know, she did everything. Her mind was working all the time, so how do you figure that one out? There is no answer. She was very active her whole life. [Bridget, 38, two affected relatives]

> I don't know if there's too much prevention that you can do, other than having a healthy lifestyle, exercising, staying active. Which I do. I definitely feel like I'm a fighter, but I'm sure my mom was too…. So I guess I'm just kind of unclear about it. [Jane, 28, five affected relatives]

Without convincing evidence about what can be done to prevent the disease, some people question the relevance of genetic testing technologies for AD. When asked about genetic testing Sophie was clearly disconcerted by the idea. Her real concerns lay with how becoming diseased would impact her husband and children:

> Dr. C. once said to me, "There's a test," and I said, "do you have a cure?" He said, "no." I said, "Then why should I take the test?" … I don't think I want to know, I mean, my greatest fear is that I don't ever want to put my husband or my children through that. But I don't see the point of knowing. I also believe that people with AD know there is something wrong, especially at the beginning. I mean, this is no deep dark secret. My mother knew and she said to me, "I'm not what I used to be." [age 58, 2 affected relatives]

Frank brings into relief how genetic testing for personal risk compares to more immediate and palpable concerns that preoccupy those caring for someone with AD:

> Without wanting to sound trivial, the medical terminology issues are of absolutely no interest to me. … if some great new research comes along and looks promising, then I'll be interested in that, but why she has it or the genes that she has or how the genes work in the brain…I could really care less. [age 51, one affected relative]

When asked if her mother could have avoided AD, Mary replies:

> My mother is in such a stage of her condition that there is nothing out there that will arrest it, ok? In any way, shape or form…. and we have other medical histories

> to deal with in my family. My father as had colon cancer, my mother had lymphoma, my mother's late brother had lymphoma, so there is clearly some other risk profile in the family that I'm more concerned about than I am about the AD actually. [53, one affected relative]

Not all people in this sample reject the idea of a genetic test, yet most are unclear about how genetic technologies will yield any "new" information. Many already believe that they have some chance of getting the disease, since it is perceived to be something that "runs in the family" (Lock, Freeman, Sharples, & Lloyd, 2006). Yet people often present this risk as indeterminate, on the horizon, and not a pressing concern.

Ideas about AD causation and personal risk are surprisingly similar in our two samples, despite the different exposure to genetic information on AD. This supports the idea that encounters with genetic technologies will not inevitably trigger profound changes in the way people experience kinship or conceptualize familial and personal risk for AD. It also suggests that pre-existing ideas about kinship and heredity grounded in everyday social practice are not only resistant to change, but in fact constitute important tools with which people assess and interpret genetic information.

Intimations of the future?

A good deal of the social science research designed to assess the social impact of genetic testing has been limited to clinical settings and, further, is often confined to families coping with rare single gene disorders. This emphasis has potentially contributed to what some researchers caution is an over-estimation of the power of new biomedical technologies to transform kinship and family relations (Featherstone et al, 2006, p. 18; Franklin & McKinnon, 2001, p. 21). It has been argued that more evidence is needed for the way in which knowledge about new genetic technologies are being taken up by the public at large (Emslie et al., 2003; Kerr, Cunningham-Burley, & Amos, 1998; Richards, 1996).

In order to gain some idea of the degree to which our interview findings were specific to individuals from AD families, with informed consent we conducted informal, exploratory conversations with thirty university-educated adults aged between 25 and 39, half of them women, about their exposure to, understanding of, and interest in genetics. Only one or two of these individuals had experience of common diseases including cancer and heart disease among family members and none reported single-gene disorders in their families.

All 30 of these individuals acknowledge the significance of genes in disease causation, yet virtually every one of them – as did the majority of respondents from AD families – also cited social, environmental, and behavioral variables, including upbringing, education, economic status, environmental pollutants, diet, and personality, as contributors to disease causation. As Keith, age 31, said, *"genes don't give us the whole picture."* He went on:

> A condition might come from genetics, but it's also your mind, and your education, and family, and all these things … that is what makes it hard to understand how genes affect each and every individual. It's so complex, how your body works, how your mind works and how other factors affect you.

In many cases external factors are framed as threats that assail genes. Candice, age 28, argued:

> If your genes aren't "strong enough" to fight a lot of the chemicals and external things…then you could get cancer because your body wasn't able to withstand the chemical intrusion.

And Joyce, 31, noted:

> I could be at high risk of some crazy, rare disease. Maybe I'll just never know because by coincidence I have avoided anything that would turn that gene on or off. It just sits there silently and nothing ever happens to it.

To mitigate external threats, people engage in everyday prevention strategies, such as eating organic food, taking vitamins, exercising, and controlling their weight. They believe such activities to be essential in maintaining healthy gene-environment bodily interactions and many produced vivid accounts about mediating sets of "toggles" and "triggers" that influence gene expression by turning "on" or "off" a range of "switches." Certain configurations of triggers and switches can result in "short-circuits" and "overload" or cause a "sleeping gene" to "awaken," causing illness. Other more optimal configurations are thought to bestow disease resistance:

> I imagine in a disease process it's just like tripping the switch. So if you smoke, you're just flipping a lot of switches which otherwise would never have been switched. … doing things like eating lots of vegetables and consuming anti-oxidants and things keep the switches on or off, whatever they need to be, that's protective. [Joyce, 31 years] Something in the environment, whether it's too much food, or working too much, could cause a short-circuit, an overload in the capacity. Something will set the gene off, whether cigarette smoke, or pollutants, a toxin in food, whether it's food coloring, whether it's a certain chemical. Something will set it off. [Larry, 34 years]

Furthermore, notions about individual power and choice are tied to conceptions of heredity and kinship. Some individuals suggest that they have "greater access to resources and knowledge" than did their parents. As 26-year-old Sheela puts it, "awareness" allowed her "distance from family genes." Larry comments:

> …you can have a predisposition to having diabetes, but if the offspring's diet, and activity level are high, and they're conscious of what they're eating, of their habits, and their stress level, this is something that possibly can be avoided.

Joyce reflects on the history of breast cancer in her family:

> My great-grandmother, grandmother, and mother had it – but also let's look at their lifestyle. None of them breast-fed. My grandmother was a smoker. They all have really high fat diets, low exercise, a lot of alcohol. Maybe I inherited the predisposition, but my lifestyle's so different …

Some people actively try to distance themselves from family medical histories by emphasizing a control over their genes and their potential action. The majority shun the idea of a determined genetic history, focusing instead on individual responsibility and decision-

making as the key to positive health outcomes. Some individuals insist that although they share genetic substance with their parents, they themselves have "unfamiliar" or "transformed" genes due to generational differences inlifestyle. One individual surmised that he may avoid serious illness, unlike his grandfather who was raised on a farm, performed heavy physical labor and *"lived a life that's so different from me and in a different environment from me."* Another individual stated it was impossible to worry about the genetic aspect of her father's diabetes since *"so many variables are different; our diets, the way we live, and how we see the world."*

These exploratory conversations with young adults suggest that they think of genes as, in effect, unstable entities, subject to modification by environment and human behavior and this "postgenomic" perspective is not entirely different from emerging knowledge in the world of molecular genomics and epigenetics (Jablonka & Lamb, 2005; Lock, 2005). Yet their insights are not obtained through direct experiences with genetic testing or counseling, or even in relation to firsthand experience with specific diseases. The tentative findings from these conversations are necessarily limited, but they raise interesting questions about how people perceive gene function as being affected by behavior and lifestyles. If, or when, testing for susceptibility genes (such as the ApoE) becomes more prevalent, this type of received wisdom will perhaps enable individuals to better grasp the uncertainties associated with complex interactions between genes and both macro and micro environments.

Conclusions

Our findings highlight the way in which reactions of individuals to information about genotyping is dependent upon the genes in question, knowledge about how such genes contribute to the expression of a specific disease, and what form the particular pathology takes. Furthermore, the age of onset of the condition, and whether or not anything can be done about prevention and treatment, affects people's responses to genotyping. Claims about the social repercussions of genotyping require, then, contextualization with respect to both biological and social variables.

Rapidly changing knowledge in molecular biology, together with the limited predictive power of the ApoE gene in connection with AD, as well as difficulties in connection with the diagnosis of late onset AD itself (Lock, in press), make it highly unlikely that ApoE will ever have the power to dramatically reconfigure kin relations. Most susceptibility genes have even less predictive power than does ApoE, suggesting that for the majority of complex diseases, while genetic testing may well help research to move ahead, genes – that is, decontextualized segments of DNA – are unlikely to become powerful instruments for predicting future disease.

The empirical findings from all three groups suggest that elaborate accounts about the relationship between genes and environment are "naturalized" in public discourse, and genes as disease *determinants* do not figure prominently in discussion. Furthermore, the genetic risk information given to subjects in the REVEAL trial is interpreted through a process of "familiarization" in which risk estimates are absorbed into and embedded within pre-existing beliefs about who in the family will succumb to AD. These narratives resemble

those of individuals from AD families who have not been genetically tested, strongly suggesting that ideas about embodied risk for AD in families are not dramatically changed as a result of genetic testing. We conclude, provided individuals are given appropriate information about susceptibility genes, including a frank discussion about the limitations of knowledge about ApoE for predicting AD risk, that genetic testing is likely to have few transformative effects on kin relationships and family sociality.

Social scientists have already demonstrated how questions concerning the impact of genetic technologies on kinship often ricochet to reveal how important kinship and family relations are in shaping interpretations of genetic information. However, postgenomic science is increasingly showing how family environments (including diet, lifestyles, and environments) affect gene function and regulation. Not only does the biological inform and transform the social but, of equal importance, the social informs and transforms both the meaning of the biological, and its very substance. These findings contribute to a further demonstration of the instability of the biogenetic substance that David Schneider argued was naturalized in discourse about EuroAmerican kinship. Destabilization of knowledge and substance – in addition to increasing awareness about the way in which biology is inextricably entangled with historical, social, environmental and cultural variables – ensures that research into kinship will remain central to the work of anthropologists and others in the years to come.

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