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Calibrating cancer risk, uncertainty and environments: Genetics and their contexts in southern Brazil

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Abstract

Drawing on empirical ethnographic research in Brazil this paper examines how in the spaces between identifying genetic markers and conditional cancer risk, environments and diverse epigenetic logics are emerging and being negotiated among research and clinical communities, patients and their families. Focusing on an arena of research and medical intervention related to a gene variant known as R337h, thought to occur with high frequency in the south of Brazil and linked to the cancer syndrome Li-Fraumeni, it emphasises the relevance of examining epigenetics as an emic category but also its utility as an analytic category. It shows how in a context of not yet fully knowing how and in what ways R337h contributes to increased cancer, a range of different ‘environments’ are invoked that unevenly articulate an emerging and still inchoate and unfolding terrain of understanding. In an arena of expanding genomic research and medicine, where the identification of low risk mutations associated with cancer is increasingly common, the Brazilian case provides a particular lens on the way environments and genes are being meaningfully calibrated and how differently implicated communities resourcefully populate the gaps in knowledge and understanding with consequences for research, care and embodied risk.

Introduction

In an era of so called ‘post genomics’ it has become increasingly common to hear that the ‘central dogma’ of DNA is being superseded by an understanding of genes as necessarily and continuously interacting with a range of differently constituted environments inside and outside the body. The spatial scope and temporal scale of these gene and environment interactions, often described in terms of ‘epigenetics’ is broad and diverse, encompassing the effect of cellular processes on gene expression, the embodied consequences of trauma or stress during the life course, and, in some cases, the inter-generational inheritance of epigenetic markers (Landecker and Panofsky 2013). This means that defining epigenetics is often a ‘muddle’ (Fox-Keller 2010:5), with ‘epigenetic processes’ characterised by multiplicity and diversity (Pickersgill et al. 2016). It is a ‘muddle’ that social scientists have nonetheless begun to articulate and engage. Some point to how the increasing presence of an ‘interactionist consensus’ (Landecker and Panofsky 2013 : 349) in epigenetic research examining genes and environments has the potential to engage with a pre-existing social science emphasis on inequalities and social determinants of health. At the same this work illuminates how a ‘molecular imagination’ often continues to dominate (Landecker 2011). As Darling et al point out a view of disease risk which is increasingly seen as simultaneously

‘outside’ the body *and* ‘inside’ genes appears to sustain research which continues to be ‘molecularised’, orientated ‘into the body’, in an effort to qualify and quantify the epigenetic effects of environments (2016, see also Lloyd and Raikhel 2018). Shostak and Moneister similarly point to a ‘political economy of perceptibility’ at work in the way that particular environments are made visible in the context of epigenetic research, while others are obscured (2015:223). Moreover the possibility of new forms of social determinism that individualise risk and blame in particularly gendered ways has been foregrounded by those attentive to how epigenetic research has increasingly focused on ‘critical windows’ of development that implicate and articulate women’s health responsibilities both during pregnancy and early childhood (Mansfield 2012, Richardson 2015). At a time when the definitional boundaries of epigenetics continue to be somewhat ‘elusive’ (Dupre 2012), where flexible and multiple scientific understandings of what constitutes epigenetics reflects an ambivalence which nonetheless contributes to its ‘success’, (Pickersgill et al 2016, Meloni and Testa 2014), it is important to remain attentive to how the gaps, spaces and uncertainties generated by these developments are being articulated and experienced in specific arenas of social practice.

This paper contributes to a growing body of social science work examining the expanding global and transnational terrains of genetic research and medicine as it increasingly interfaces with epigenetics (Lamoreaux 2016). It examines how, within the still evolving terrain of cancer genetics and the emerging country context of Brazil, researchers, health professionals, patients and their families populate the gaps in knowledge about genes, cancer and environments and how this articulates various kinds of epigenetic logics. Taking a particular trajectory of research in Brazil focused on a gene variant, R337h located on the TP53 gene and associated with the cancer syndrome known as Li Fraumeni, I show how concerns and engagements with variously defined and differentiated environments seep into or are in specific moments made evident in the framing and understanding of conditional cancer risk. In examining how the space *between* cancer genetics and the not always, as yet, fully understood or articulated domain of epigenetics are meaningfully shaped and experienced by health or scientific professionals and among patients in southern Brazil I outline how contexts and environments are made to matter, ‘bubble up’ (Martin 1997) and become ‘bio-active’ (Landecker 2011: 179) in specific research and clinical settings. I examine how, when and in what ways, epigenetics operates as an ‘emic’ category but also emphasise the utility of epigenetics as an ‘analytical’ category in understanding how different implicated communities actively and resourcefully make sense of the uncertainty of cancer risk, genes and environments in the specific socio-historical context of southern Brazil. In this way I highlight the need to engage the broader cultural contexts, beyond the clinic and laboratory environments in which still ‘elusive’ epigenetic processes and logics are being shaped and through which they are dynamically informed.

My ethnographic research was primarily undertaken between 2010 and 2012 in three urban cancer genetic centres in the south of Brazil linked to high profile research centres, universities and public hospitals in Rio and Porto Alegre and one mixed public/private hospital in Sao Paulo. In all these settings I conducted participant observation of clinical consultations and interviewed health and scientific research professionals (including cancer geneticists, geneticists, mastologists, psychologists, nurse specialists, trainee geneticists,

molecular biologists and epidemiologists), as well as patients and families attending cancer genetic clinics who either had cancer, had a history of cancer in the family or were considered at genetic risk for cancer. While some of patients I met had health insurance plans or sought out means to pay for testing the majority of those I met were recruited into clinical cancer genetics via involvement in national and transnational research protocols. At the time of my research clinical cancer genetic services were not provided via the public health care system but relied, and to a large extent continue to rely, on research resources.

I first outline the wider project of cancer genetics in Brazil and show how the R337h mutation on the TP53 gene has come to be central to this broader terrain of research and medical practice. Drawing on published scientific discourse I examine how increasing attention to certain kinds of epigenetic questions and specific environments have being framed in the gap between the identification of R337h and conditional cancer risk. In the next section, I draw on ethnographic material, to examine how among those carrying out cancer genetic research in Brazil a concern with environments, including but not limited to specifically epigenetic effects of the environment, are manifested in different ways. While these are sometimes ‘molecularised’ there is both resistance to as well as a multiplicity in the way that ‘epigenetic logics’ are framed in relation to specific constituting environments. In the third substantive section I turn to how in the clinical communication of conditional cancer risk regarding R337h, environmental modifiers are narrowly defined and how this partly reflects the fragility of care infrastructures in Brazilian cancer genetics. In the final section I examine the way that patients and families respond to and render meaningful the contingency of cancer risk in the context of clinical cancer genetics showing how the role of environments may be variously reconfigured and how particular ‘styles’ of what might be understood as epigenetic thinking may already be present.

Cancer Genetics in Brazil; the case of Li-Fraumeni and R337h

The field of cancer research is frequently cited as an exemplar of how epigenetic science and medicine is having concrete consequences in terms of understanding cancer as a diverse disease, which requires differentiated and targeted treatment interventions. While these therapeutic possibilities are now unfolding in well resourced and funded research centres in ‘western’ health care arenas, they are not integrated into clinical practice everywhere. Nevertheless cancer genetics as a ‘hybrid’ of research and care continues to expand across a global arena (Gibbon et al 2014), including, since the mid 2000’s, in Brazil. Specialist cancer genetic clinics have appeared in the last 10 years in the wealthier and relatively more economically developed southern part of the country, with the hub of clinical based research operating within mostly public health hospitals, linked to universities and research institutes in urban centres. In Brazil cancer genetics is sustained, but also precariously dependent on, national and transnational research collaborations between individual scientists and their research teams, with consequences for which patients are included in research as well as how and what kind of ‘care’ can be offered to them (Gibbon 2017).

The expansion of cancer genetics in Brazil has primarily focused on identifying those at increased risk of cancer on the basis of known genetic variants, particularly in relation to the high profile ‘BRCA genes’, associated with an increased risk of breast cancer. However

given the relative paucity of information in international databases from populations outside Europe and North America the frequent identification of what are known as ‘variants of unknown significance’ (VUS), including those related to relatively well characterised genes such as BRCA 1 and 2, is much more common in low income and emerging economies, such as Brazil. At the same time the question of variable ‘penetrance’ (the extent to which an identified gene variant may be expressed or not) poses a significant challenge to clinical practice, even as it also fuels ongoing avenues of research inquiry related to cancer genetics more broadly. Yet while BRCA genes are a prominent focus of interest in the emerging field of cancer genetics in Brazil, another gene variant has also garnered a significant amount of attention since the mid 2000’s.

Germline mutations on the TP53 gene, which has been described as the ‘guardian’ of the human genome as it plays a central role in tumour suppression, are relatively rare. However an association between mutations on the TP53 gene and a cancer syndrome known Li-Fraumeni (LFS) has been evident since the 1990’s (Malkin 1993). Until recently this was a condition thought to affect around 1 in 5000 people, with carriers having an up to 90% lifetime risk of developing a range of different cancers. Yet the indirect relation between genotype and phenotype has long been noted, with a great deal of variation recorded among carriers in terms of the type of cancer and the age of disease onset (Fortes et al 2015). This variability reflects ongoing debate and discussion concerning clinical criteria and diagnosis related to LFS. Both ‘classic’ and ‘alternative’ criteria, to identify conditions known as ‘Li-Fraumeni Like’ (LFL), are widely used, with clinical and diagnostic criteria continuing to evolve as scientific understanding of the TP53 gene expands (Kamikhara et al 2014). There is acknowledgement across a broad spectrum of recent international scientific publications of the important role played by what are described as ‘genetic, epigenetic and lifestyle’ modifiers (Sange et al 2014). However the focus of research is on the epigenetic mechanisms thought of as central in explaining the observed phenotypic variation, linked in some cases to methylation patterns in the expression of TP53, with genetic and epigenetic modifiers, such as ‘copy number variation’ and ‘telomere length’ also used to explain differential patterns of cancer and age of diagnosis (Fortes et al 2015).

In Brazil the identification of a particular genetic variant on TP53 gene known as R337h first came to light in the early 2000’s, identified with high frequency among children with rare adrenocortical cancers in the Brazilian state of Parana (Custodio et al 2013). There was initially speculation among some communities of researchers that the high frequency of such tumours (10-15% higher than the US) may be linked to the effects of agricultural pesticides in the region.¹ However since 2007 a series of studies in newly established cancer genetic centres in the southern part of Brazil associated R337h with a much broader range of adult cancers, highlighting its potential role in cancer development (Achatz et al 2009). At the same time the findings of a neonatal screening programme, undertaken in the state of Parana since the early 2000’s for R337h, confirmed the prevalence of the mutation in the region found in 0.27% of 171,649 newborns (Custodio et al 2013). Haplotype mapping

¹This initial hypothesis does not seem to have gained much research traction across a broad cancer genetic research community in Brazil or elsewhere (see Armstrong 2014). How it maybe re-emerging or being transformed by evolving terrains of epigenetic inquiry related to R337h and requires further research.

subsequently identified R337h as a ‘founder mutation’ (Achatz and Zambetti 2016) with other studies highlighting how the mutation may be linked to ‘stratified cancer risk’, due to the apparent geographic specificity of its distribution, associated in various publications, with histories of migration to different regions of Brazil during the colonial and post-colonial period (Giacomazzi et al. 2014).

In recent published research by the Brazilian cancer genetic research community R337h has been described as the ‘most common germline TP53 mutation associated with cancer described in any population and the single most prevalent cancer associated allele identified to date’ (Giacomazzi et al. 2014: 3). While framed as having great significance for understanding ‘the biological function of tumour suppression and TP3 more widely’, the frequency of the mutation in the southern region has also been highlighted as constituting a significant national public health issue that ‘remains unaddressed’ (Achatz and Zambetti 2016). At the same time other international studies have described R337h as a ‘conditional mutation’ which is ‘less penetrant’ than other common TP53 mutations linked to LFS (Fortes et al 2013). As with the classic LFS there is great variability in terms of age of onset and types of cancer with many carriers developing the disease later in life and some remaining tumour free. This heterogeneity has also led to some speculation in the Brazil research context that R337h may also be contributing to a broader range of cancers in Brazil in ‘an apparently sporadic manner’ with reference to the role of what are described as ‘genetic, lifestyle or environmental factors’ to explain this variability (Achatz and Zambetti 2016:4). Emerging avenues of inquiry include how this mutation affects the stability of TP53 in a PH sensitive way linked to ‘metabolic adaptation’ at a ‘cellular level’ (Giacomazzi et al 2014). While the prospect of whole genome sequencing has raised the hope of identifying other ‘secondary’ genetic mutations and polymorphisms that ‘co-operate with R337h during tumorigenesis’ (Achatz and Zambetti 2016), it is noted how the ‘exact disease causing mechanism remains elusive’ (Giacomazzi et al 2014).

Drawing on ethnographic research with a range of scientists and health professionals, undertaken a few years prior to these publications, I examine below how different environments came in and out of focus in how epigenetics was situated as an ‘emic’ category in the context of R337h and cancer genetic research in Brazil. Echoing the findings of Pickersgill and colleagues working with epigenetic scientists in the UK, I show how this can encompass both broad and narrow definitions of epigenetics effects of environments (2016). Whilst multiplicity in the way that yet to be known disease aetiologies and gene environment pathways of Li-Fraumeni and R337h are articulated can help to contain uncertainty or harness ambivalence, this is not always the case. At the same time, using epigenetics as an analytical category, we see how regional history and identity and the contemporary precarity of cancer genetics in Brazil shape when and what kinds of environments are made relevant in how health and scientific professionals make sense of the contingency of cancer risk and outcomes.

Situating environments and epigenetics in research on R337h

Among a broad spectrum of the research and clinical community involved in cancer genetics in Brazil that I encountered there was widespread acknowledgment of the need to take

account of ‘modifying environments’ on gene expression, particularly in the case of R337h where the variability of risk was becoming increasingly apparent.

It was for example evident among researchers I met that many patients identified as carriers of R337h continued to be cancer free into their 60’s and beyond. For many this raised questions about whether the 90% risk of developing cancer associated with other TP53 germline mutations and ‘classic’ Li-Fraumeni syndrome applied in Brazil and what else might be causing the disease, or also in some cases protecting carriers from developing cancer. For many this was both alternately fascinating and challenging. Enthusiastically outlining his research this was how one young molecular biologist who worked directly on the functional aspects of R337h, mainly in the laboratory context in Porto Alegre put it;

Carlos: ‘What’s the trigger; why do we have so many people? We have carriers of R337h who spend their whole life without cancer. The penetrance as we have shown is not very high with this mutation. Obviously it could be something in the diet, that exists even in diseases caused by one gene... but there are other modifying factors... so there are other mutations, other polymorphisms in other genes that are modifying the phenotype. So it’s a combination of things, it’s never simple, we know it’s not monogenetic, it’s not just one gene, we have other things that are interfering with the manifestation of the phenotype[...] today more and more we are talking about functional genomics, we know we have the genetic alteration but then what do we do with that?’

In acknowledging that there were now significant numbers of adult carriers of R337h identified without cancer other researchers, like Carlos, also discussed this issue in terms ‘functional genetics and ‘variable penetrance’, rather than epigenetics per se. This preference came to the fore in an exchange I had with a cancer geneticist in Sao Paulo who worked both as leading member of the scientific research team but also in the clinics with patients, as we discussed the data that was emerging from her team’s research about carriers of R337h in Brazil.

Sahra: This question of people who are carriers, or who don't develop cancer that's something epigenetic isn't it as well?

Paula: No not really. Not it's the penetrance. So the R337h penetrance, is around 50-60% so you expect to have some people who will never develop it. But why a person develops a breast cancer or why a person develops a colorectal cancer or thyroid cancer or none at all... is there any other protective dimension or stimulation of tumour development. That is something to be answered.

While some of those I met framed the variability of outcomes and impacts of different mitigating or aggravating factors in relation to intracellular modifiers or the particularities of the genetic profile of R337h, there were nonetheless a few projects that were explicitly oriented as being epigenetic. One female molecular biologist working with the cancer genetic research group in Porto Alegre talked about her work in terms of ‘comparing those who are negative with those who are positive (for R337h) that have also developed tumours... to see if they can find some genes that are silenced in epigenetic processes or not’. Another project being undertaken by a young male biologist was examining an

emerging line of what he described as epigenetic research related to how PH level in the cell affected the expression of R337h. This was how he described it,

What we are seeing is that there are definitely many other things linked it's not just this mutation, probably there are bound to be many other dozens of things *in the cell*. so it doesn't necessarily help today that we have lots of genomic results. We know the patient has the mutation, we know the DNA sequence but what is the impact of this on the protein for instance, *what is relevant in the cell*. The biochemistry has to bring meaning to the genomic data. (my emphasis)

These examples suggest that uncertainties associated with the risk that is conferred by being a carrier of R337h whilst sometimes framed by these mainly laboratory based scientists in terms of epigenetics per se, more frequently relied on a variety of different means of expressing the impact of genes and environments. This might include reference to 'gene penetrance' and 'functional genomics' and/or environmental modifications relevant to gene expression within the delimited context of the cell.² In the still fledgling field of Brazilian cancer genetic research focused on R337h flexibility in way epigenetic effects of environments are highlighted, whilst articulating uncertainties, can, as demonstrated elsewhere, works to 'stabilise' (Lappe and Landecker 2015) and 'contain complexity' (Lloyd and Raikhel 2018, see also Pickersgill et al 2016, Meloni and Testa 2014).

Yet there were notably some scientists and researchers who in my meetings and discussions with them more readily acknowledged that there were very likely broader extra-cellular environmental aspects associated with R337h that moved far beyond the parameters of gene function. This was highlighted in the reflective comments of an epidemiologist and biostatistician who collaborated closely with the cancer genetic research team in Porto Alegre;

I think that for these mutations (referring to R337h), other environmental factors, socio-economic factors aren't at the moment taken into view. The focus on the mutation really only brings pure genetic factors into consideration. Now how much risk of disease having this mutation brings is the question. It's *fundamental* that you have these other factors, socio-environmental, personal factors because the mutation on its own doesn't cause the disease, or other environmental factors may increase the disease, increase the chance of the mutation responding (Ana, Porto Alegre)

The sense of a somewhat narrow view in the current research on R337h, that focused mainly on intracellular aspects, was also evident for others I met who were located much more centrally within the clinical community. For these persons questions about the broader environmental influence on gene expression and cancer risk were relevant alongside further uncertainties about how to take them into account. This emerged most often in discussions about the variable geographic frequency of R337h, as well as the clustering of certain kinds of cancer in the south of the country and the potential relevance of ancestry in explaining these differences.

²It is possible that these would now be framed in much more explicit epigenetic frames of reference given this research terrain has likely evolved since my field work in 2010-12.

Understanding cancer risk in the ‘south’; ancestry as an epigenetic environment?

At the time of my research there was significant scientific interest in the regional distribution of R337h in the southern part of Brazil, that had been speculatively linked to histories of European immigration and internal migration in the colonial and post colonial period (Achatz et al 2009). However in my discussions with researchers and scientists ‘founder’ effects were often linked to a wider reflection on the variable rates of specific cancers in different regions of Brazil; this included the high rate of breast cancer in the south and south east of the country. This often led to consideration of not only the role of European genetic ancestry, but wider aspects of ‘culture’ and ‘identity’ as a modifying factors on cancer incidence and potentially also, in some cases, gene expression. This was particularly apparent in discussions that referenced the widely known fact that Porto Alegre, the city in the southern the state of Rio Grande do Sul, was known as having the highest rates of breast cancer in the country. This was the way one clinical cancer specialist and researcher, who was also a high profile advocate for breast cancer awareness and who collaborated with the cancer genetic team in the public health hospital in the city, reflected on this situation;

Today just living in Porto Alegre is a risk factor... so we did this study [referring to research examining the frequency of R337h among a community affected by breast cancer in the region] to try to find out what is happening. Of course, there are other modifiers, environmental factors and you have the issue of the ‘*cultural finger*’³... I think with respect to ancestry, it’s much stronger the lifestyle habits that you pass on to future generations, culture, much more than genes, because when you analyse breast cancers for example you find there are various types, that they have this or that mutation but that the way the disease manifests is different. So I think that ancestry it’s more this, passing on risk factors, beliefs and not everything is in the DNA... because it’s something cultural here, and the population is formed in a particular way.

In their work on disease related gene-environment research in the US, Darling and colleagues note how a focus on genetic ancestry can open up (rather than close down) questions and concerns about the modifying role of lived social environments on genes (2016). In their research this included the embodied consequences of social inequalities related to racism. While structural inequities concerning racism were not made as evident by these Brazilian researchers, the movement between ancestry as concerning both genetic *and* cultural inheritance enabled some aspects of lived social environments to come into view as a modifying factor informing cancer incidence in the region.⁴ At the same time the framing of ancestry in terms of embodied cultural practices that are passed on ‘to future generations’ in ways that are, as this clinical research puts it, not ‘in the DNA’ resonates with an understanding of what might be termed Lamarckian inheritance. As I explore in the later

³This expression is not translated but were her exact words she used in English. She may have been referring to ‘cultural fingerprint’

⁴Later this cancer specialist suggested that the high rate of breast cancer could be related to something in the environment in the region referring to water pollution. She did not however elaborate. While a focus on genetic ancestry facilitated discussion of cultural ‘behaviours’ it did not seem to easily widen a paradigm for research that included questions of pollution.

sections of this paper, this has a particular historical profile in Brazil. The fluid and somewhat flexible movement between a focus on ancestry as genes, culture or tradition among some of the researchers I met illustrates the need to also engage the logic of epigenetic as an analytic category. That is to examine the contexts and terrains where the modifying role of wider environmental dimension on gene expression are being more implicitly invoked in ways that are themselves shaped by culturally specific histories and, in this case also, regional identities. .

While many scientists and researchers acknowledged therefore that environments were necessarily implicated in the development of cancer and R337h there is, both multiplicity and variability in how environments are made to matter and the extent to which this is explicitly or implicitly contextualized in terms of epigenetics. For a small minority of professionals the focus on R337h in Brazil was in addition positioned as part of promissory horizon of personal medicine and targeted treatments, with current uncertainties and questions regarding penetrance, functional effects and environmental modifiers simply a step in moving toward this goal. Talking about an emerging swathe of what he described as ‘multi-factorial studies’ one young trainee geneticist from the research team in Porto Alegre said, ‘so for us it’s going to be amazing to know we can say, if you have this polymorphism or that polymorphism which isn’t very penetrant but if you smoke or drink you will have a greater chance of having this type of cancer, so you’ll have this more focused (*mais pontual*) approach’. Another biological scientist in the same research team, who was carrying out research on how regulatory factors related to how PH level in the cell affected gene expression of R337h, recognised that this was currently ‘basic research’ but was adamant nonetheless that it would, as he put it, ‘have an application, perhaps clinical’, adding ‘so that would be fantastic’. The ‘oscillating’ dynamics in epigenetic science between epistemic ‘modesty’ and ‘ostentatiousness’ noted by Pickergill et al (2016) among UK epigenetic researchers, is therefore also evident in the context of Brazilian cancer genetics. It provides another illustration of how diversity works to contain and harness uncertainty in epigenetic related research.

However there were other health professionals and scientists, mainly those who worked more directly with patients at the clinical interface, who were much more hesitant about the immediate potential for personalised treatment and interventions associated with R337h, and who expressed specific concerns and doubts about the current clinical utility of this particular area of research. Below I explore how these were articulated by clinical professionals and how they informed the way the uncertainties associated with effects of environments were communicated to patients in the clinic.

Framing the contingency of R337h as cancer risk in the clinic

For some of those members of the clinical and research team who met patients on a weekly basis the emerging complexities about gene-environment and the potential epigenetic pathways at stake in the case of R337h raised a number of more immediate and practical problems in the communication of risk and outcomes. Sonja a clinical cancer geneticist in Porto Alegre talked very directly about the very real challenges and sense of conflict this generated for her.

R337h is a serious problem. I don't know to what extent it's pathogenic. I don't know how exactly or how many exams they should do. I don't think its Li-Fraumeni classic, but what should we do? ... I don't think all professionals are honest about the uncertainties that we don't know 100% yet... I do ask myself if we should be offering this test (referring to R337). I don't know.. it's a big responsibility..it would be much easier to say to the patient you just do this examination and it will protect you from cancer'.

This was also echoed in the way Paula, a scientist who also liaised quite frequently with different patient communities in co-ordinating research projects talked about how she had a 'little bit of problem with R337h'. She put it like this,

'we are giving the patients a diagnosis but we don't have sufficient studies to say exactly what this means.. we are opening up issues that we are only starting to discover.. perhaps it would be better to hold back, to not confuse everyone. At times we are not sure and we may end up confusing the patient as well' (Paula, Porto Alegre)⁵

These sentiments must be partly understood in the context of a regulatory context in which a genetic test for the R337h biomarker was only available in Brazil, at the time of my research, within the parameters of research protocol or if it had been privately paid for. Nevertheless given these expressions of doubt and hesitancy among some of those who worked in the clinics it was not surprising perhaps to find that in the consultations I observed the question of modifying environmental factors on gene expression was only delineated in very particular ways. Whilst care was taken to explain that the identification of a deleterious biomarker or mutation would not automatically lead to cancer for any particular family member, certain, qualifying statements were more common than others in communicating risk information. In the clinics of Sao Paulo and Porto Alegre, where there was marginally more time or, in the former, resources for clinical appointments, a phrase frequently heard was "if you have this mutation, it's not certain you are going to get cancer". At the same time fleeting reference might be given to '*outros fatores*' (other factors) linked to '*estilo da vida*' (lifestyle), in discussing risk. Sometimes this was rendered more specific in relation to age, especially as data seemed to suggest that certain cancers associated with R337h and the syndrome Li-Fraumeni were more common in children compared with adults. Patients might in addition raise questions concerning how genetic risk interacted with the effects of diet. This was a particularly common query in Porto Alegre, whereas in Sao Paulo, questions might be raised about the daily stress of city living or pollution, often glossed as '*o transito*' (traffic). While these were readily acknowledged by medical professionals in their dialogue with patients as *potentially* modifying dimensions, these were not aspects that were recorded or further explored in the clinical consultations I observed. In contrast to the possibility of being able to identify the presence or not of R337h through genetic testing these were currently unknowable uncertainties which, while fueling and compelling various avenues of scientific research, were more difficult to define and qualify in the clinical arena. A

⁵There were also some scientists who articulated similar doubts. One molecular biologist from Porto Alegre for instance said 'perhaps we will never know absolutely know what is happening...there isn't a 100% rule. There are so many factors that could be involved'. He also added however 'the more we study the more doubts we have but we have to move forward with this.'

disinclination to discuss epigenetic effects of environmental modifiers is perhaps to be expected in the clinical context given that, at the time of my research and even now, these are mostly aspects with unknown outcomes and impacts on cancer risk and aetiology.

Hesitancy about the clinical utility of identifying R337h in part therefore explains how 'context' as a modifying environment is explained to patients in the communication of risk, in ways that appear to de-limit discussion about environmental or other epigenetic factors. However it is also important to consider the institutional context in which cancer genetics is practiced in Brazil, at the fragile interface *between* research and care. That is where a patient's eligibility for inclusion in clinical care is dependent on precarious and time limited research funds and collaborations, compounded by inadequate and uneven basic health provision; a reality which subsumes day to day clinical practices in cancer genetics as it does in other areas of Brazilian public health. This was particularly evident in the cancer genetics clinics within public health hospitals, such as those that operated in Rio and Porto Alegre, which were more exposed to resource limitations. In this context the uncertainties that quite literally matter for both patients and clinicians, were often about being able to access and offer 'care', where a minimum level of attention was more likely to be guaranteed (Gibbon 2017). In this sense the wider financial and institutional instability of public health care provision and cancer genetic research in Brazil, directly shape and themselves help 'contain' concerns about how currently unknown contingencies associated with R337h are communicated in the clinic. It is important to note too that the challenges which shape how the uncertainties of environments and their epigenetic effects are articulated to patients in the clinic are not likely to be confined to emerging economies, such as Brazil. As cancer genetics and epigenetics becomes more 'mainstreamed' into the clinic and as issues of finite resource allocation in public health services and medical research gain different sorts of traction, these challenges will likely reverberate in other international medical arenas.

If there was a tendency to bracket and delimit unknown modifying environmental variables concerning cancer risk and R337h in the clinical encounters I witnessed, this did not preclude a dynamic, lived and embodied understanding of the uncertainties of cancer risk among patient. In my meetings and interviews with patients outside of the clinical appointment, it became evident that genes were for them nearly always shaped by and interacting with specific environments, including pollution, food, stress, and in particular negative social relations, with both individual and cross-generational consequences. Drawing on epigenetics as an analytic category I examine below how patients, like professionals, are also actively engaged in bringing meaning to understanding conditional cancer risk as this relates to R337h.

Embodying Genes and Environments as Cancer Risk

I start this section with an ethnographic vignette from an interview I undertook in 2011 with a patient from Porto Alegre, Lucas, who was in his mid-forties. He was from a large family, many of whom lived in the interior of the state. He himself was currently unemployed. He had a long and complex history of cancer in the family with a number of deaths and diagnosis of cancer affecting different generations, including younger nieces. A number of his family had been identified as carriers of the R337h mutation, although he himself had

tested negative and had not developed cancer. Some weeks before our scheduled meeting Lucas had been at a somewhat extra-ordinary meeting, organised by the clinic to bring together some of the families who had been identified as carrying R337h. At this meeting over 40 people had spent the entire morning listening to presentations about the research related to R337h, including information about the apparent increased prevalence of the mutation in the southern part of the country. This had also included a presentation by a younger member of the scientific team who was carrying out research looking at the function of the mutation. He explained at the meeting how the mutation could be associated ‘with metabolism’ and how this might explain ‘why some carrying the mutation had developed the disease and why others hadn’t’. He also suggested that there was a possibility that this research would mean being able to develop a therapy or as he put it a ‘dietary supplement’ to treat those identified as having the mutation to reduce their risk of developing cancer. In the interview that I had with Lucas a few weeks later he recounted the meeting, specifically recalling the new avenue of research that had been discussed by the young scientist, he told me;

‘I remember one or two things.. in Brazil it’s much more concentrated especially in the southern regions. But this made me realise in that talk about diet it’s got a lot to do with food. The food of the *Gaúcho* is a lot about meat. ⁶ They don’t have proof of course but the *Gaúcho* food has a lot of connection to the past, the Italians introduced really strong food and the Germans too of course so for example Polenta – normal polenta is delicious but fried polenta! ...so this is the habit of the *Gaúcho* to have many things together mixed up so then they become really dangerous...then the question of fat enters but you know a person thinks that they need to have that because it’s habit as well, the body is really connected to the psychological, it’s psychological too because it’s what we’re used to’

Lucas’s comments provide a starting point for reflecting on how patients caught up in the still emerging field of Brazilian cancer genetic research interpret information about the contingency of cancer risk and, like those medical and scientific professionals, actively fill in the uncertain spaces of knowledge concerning R337h. In the context of the meeting outlined above, between scientists and patient communities, we see how the modifying effects of ‘cellular metabolism’, in light of discussions about the geographic prevalence of R337h, becomes translated by one patient into cultural preferences for certain kinds of food. In this instance regional histories and identities are aligned with the psyche of individualised control and choice. Below I explore further how patients confront the contingent terrain of cancer genetics and conceptualise the environment as modifying cancer risk in relation to R337h in an effort to create meaning amid uncertainty.

For the majority of those patients and families I met who were attending cancer genetic clinics in Brazil, genetic mutations were rarely understood as the sole or sufficient cause of cancer. In most cases genes associated with an increased risk of cancer were almost always necessarily interacting with other factors. Bodies were materially produced as vulnerable to cancer as a result of various outside influences. Patients efforts to make sense of the apparent

⁶The term ‘*Gaúcho*’ refers to the regionally identified people of the southern most state of Rio Grande do Sul.

regional clustering of R337h or awareness of the high incidence of some cancers in the southern part of the country frequently included reference to diet, as illustrated by Lucas's comments above. In the same way that the traditional diet choices of the '*Gaúcho*' might be foregrounded, others, particularly in the city of Porto Alegre, talked about the regional preference for *churrasco* (barbecued meat) or for drinking *chimarrão* (a green mate tea) at very hot temperatures, as possible environmental factors influencing cancer risk. At the same time the influence of negative emotions and problematic interpersonal relations within the family on cancer risk was also particularly marked among those I met. The latter were seen as having a strong agentive action in the body, being both a risk for and a cause of cancer.

I met Marcia who was in her early 40s and worked in a bank, in the mixed public/private cancer hospital in Sao Paulo. As a number of her family had been diagnosed and died from cancer and some had been identified as carriers of the R337h mutation. She found herself in the highly disconcerting situation of having being diagnosed with thyroid cancer but was not a carrier of R337h; a scenario that she said she found herself able to confront because of her '*fé*' or religious faith. Talking to me about the cancers that had been identified in the family she said,

One explanation could be this [referring to genetic factors]. Another could be stress, and another could be certain things that happen in your life. For example I think that I now have cancer after my sister died, it was a real blow when she died. We really suffered a lot with her. Another thing that I think is very influential is how to put it, not exactly low moods (*baixo astral*) but negativity. We all have malignant cells in our body but with your immunity you can combat them. But if you are depressed you can't attack them. I think that it was like that in my case it was because of the loss of my sister.

Our family has a genetic factor, the DNA. But I really believe in those studies too that prove that cancer can develop after a depression or an emotional state. When a person is depressed and has this immunity that is really low, they have this propensity to develop it and it [cancer] takes this opportunity. I really believe this..I think both factors are involved.

Marta from Porto Alegre, also reflected on these dimensions. She had experienced recurrent problems with breast cancer for a number of years, was in her late 50s and had worked as a nursing assistant. She told me she had been adopted but had since discovered her birth mother and other family members had had cancer. She like Marcia was also strongly religious and talked about the importance of her catholic faith in dealing with the challenges of her life. It was these set of beliefs she referred to when talking about what she saw as the cause of the cancer in the family was.

This is a complex question but I've heard it said even though I really don't know very much about it, but I do believe it. There is a psychologist actually on tv on the 'better life' channel, which is a catholic network ..she talks about this question of anger inside you and it left me thinking.. if you don't realise you are angry about something but it's there, it's going to burst out somewhere because it's a feeling that stays there, waiting. So I think it has a connection with cancer.. because your

feelings and your emotions they speak, they speak in your smile, in what you are thinking, they are speaking inside.

She further pointed out how emotions could affect the digestion of food and pass through the body via blood.

Let's say you are anxious for some reason..you'll be eating irritated, with anger or with hate, a grudge or resentment or whatever... Nobody knows what's happening inside you but that feeling is talking to you, so I think at some moment that feeling passes to our blood, and moves inside of us...it might not just be a lack of good feeling but a lack of good food, my mother was very poor and she worked in a factory so you have both these things bad food with the other [emotions] could produce something like this [cancer].

For both Marcia and Marta genetic risk is only made meaningful through ideas about bodily vulnerability that are configured by social relations and emotions, sometimes at the interface with diet and poverty, which accumulate as risk and danger within individual bodies. Long standing anthropological research in Brazil has shown how the sick body is often perceived as being subject to and produced through various exogenous influences, with conditions such as *nervismo* and *nervosa* long thought to be subject to and a consequence of strong emotions and interpersonal relations (Duarte 1986, Rebhun 1994, Scheper-Hughes 1996); an avenue of inquiry that is now being extended in Brazil by those examining the role of emotions in religious healing traditions (Aureliano 2014). Yet while the narratives outlined here resonate with these culturally relevant views of the body as permeable and subject to outside environments, it is an articulation of embodied risk which can also reflect and reproduce an ethic of individualised health responsibility. In this sense patients' understanding of genes and environments, which emerge in the space between knowing, understanding and intervening on cancer risk, are informed not only by long standing popular ideas about bodily vulnerability but in a context in which the necessity of taking care of one's own emotions and the effects of others emotions on oneself are increasingly socially valued. At the same time as Joao Biehl's research has powerfully shown (2001) and as Edmonds and Sanabria also point out in their work on cosmetic surgery and sex hormones (2014) an ethic of 'self care' in Brazil is not achievable for all and never entirely about the self. Tellingly other patients I met in discussing the role of exogenous influences on cancer risk emphasised how this not only impacted individual or individualised bodies but could be passed on between persons and more specifically across generations.

I met Rosiaria, who was in her mid thirties, several months after meeting her husband Gabriel and their then eight year old son Marko at the public hospital Porto Alegre. Marko had been treated there a few years before for a rare adrenocortical cancer, but was now in remission. The family owned and worked local farmland in a rural area in the state of Parana but had made the long journey to the well regarded public health hospital in Porto Alegre. After Marko's treatment they had been referred to the cancer genetics department where they had been told that their son's cancer was associated with the R337h mutation. At the time of our meeting both Rosiaria and Gabriel had been tested for the mutation associated with the syndrome to see which of them were also carriers and were waiting for the result.

While her son Marko had now finished treatment and was in remission from cancer the investigations by the cancer genetic team relating to cancer risk in the family raised lots of questions for Rosiaria about what had caused her son's illness. As she said,

I've been thinking that it's possible I could have passed this on in pregnancy that it could be that, I think it does happen when a mother goes through a difficult time ... maybe he felt something when I was pregnant because he was in my belly during all that time.. the suffering that I went through then and in my childhood.

Rosiaria in fact elaborated at length about her difficult childhood and adolescence, how her mother had abandoned her and her family at an early age and how living with her mother in law when she had been pregnant with Marko had been it seems especially hard and a somewhat desperate time for her. This is how she put it,

I lived with my mother in law for ten years at the beginning when I had my first son and when I was pregnant with Marko and it was really difficult. She did everything to make me angry, I was all the time irritated and it did reach a point where I thought I want to end this and all this suffering. So I've had people saying to me, "I don't want to put things in your head but what your son has been through could have come from that." It does influence when a mother goes through something difficult like that.. because of what I went through in pregnancy.

At one point in our meeting, despite knowing that Marko carried a gene mutation associated with a cancer syndrome and understanding that it was likely either she or her husband were also carriers she said 'so it's not genetic only hereditary Marko's problem, because of everything I went through could have affected why he had this'. Rosiaria in fact struggled to disassociate the possibility that the cause of Marko's cancer was due to the trauma that she had experienced, particularly during her pregnancy, from the information about Marko having the R337h variant. For Rosiaria what had been inherited were not just defective genes but experiences that had marked her own and her son's body cross generationally.

In Rosaria's understanding of cancer risk in her family we see very clearly how a discourse of individualised and gendered responsibility and blame is perpetuated; dimensions that some have suggested are likely to become particularly resonant in the context of a growing epigenetic research focusing on the significance of fetal and maternal environments (Richardson 2015). However Rosiaria's comments about how the emotional traumas she experienced might have led to Marko's cancer also evokes seemingly Lamarckian understandings of heredity. These are concepts of heredity which had a particular presence in the mobilisation of public health in Brazil in the early 20th century (Stepan 1991). For example *Puericulture* was a form of prenatal care focused not only on the health of the pregnant woman but the lived environment in which reproduction occurred, linked at the time to the emergence of the Sanitary Health Movement in Brazil (Kuhn dos Santos et al 2012). As Stepan points out this was a movement which avoided 'hard and fast distinctions between heredity and environment' and instead 'paid considerable attention to the milieu in which reproduction occurred' which was seen 'as a source of reproductive poisons that could have disastrous consequences for future generations' (1991: 81). Early 20th century public health interventions in Brazil such as *puericulture* were informed by beliefs that bad habits and diseases, acquired over an individual lifetime, could leave permanent markers

across generations; ‘poisons’ present at the moment of conception particularly problematic. Rosiaria’s comments imply that it is a history which continues to resonate in explaining and understanding cancer in the family which is used as a wider cultural resource in efforts to render a space of uncertainty about genes, environments and cancer risk more meaningful. This is reflected in the research of other anthropologists such as Emilia Sanabria whose work on the use of hormones in Brazil who suggests that the early 20th century Brazilian Hygienism movement has been central in sustaining contemporary ideas about the effects of ‘outside’ influences in producing healthy bodies (2016).⁷

Patient’s explanations of embodied risk in an era of nascent scientific explanations about the epigenetic effects of environments and conditional cancer markers such as R337h would appear to enact a ‘recursively forward’ movement (see Gibbon 2017). That is there are striking parallels between patient narratives of embodied vulnerability and the kind of intergenerational epigenetic reasoning now emerging in certain fields of scientific research, which increasingly illuminate how past traumas have embodied consequences during the life course and for successive generations (Landecker and Panofksy 2013). Yet while some of these narratives appear to presciently evoke the parameters of a contemporary epigenetic frameworks of understandings of genes and environments, they are also variously shaped in Brazil by cultural understandings of ‘porous’ bodies, seemingly older Lamarckian ideas of heredity, and an emerging ethic of self improvement that is relationally constituted.

Conclusion

This paper engages with the ‘situated biologies’ (Lock and Niewohner this edition) of Brazilian cancer genetics. Drawing on empirical ethnographic research undertaken in cancer genetic clinics in the south of Brazil and focusing on the case of R337h this article has examined the importance of attending to how the spaces between genetics, epigenetics and environments are actively and resourcefully constituted by scientists, health professionals, patients and their families confronting the post-genomic uncertainties of cancer risk. Engaging epigenetic logics as both an emic *and* analytic category I have emphasised the need to examine the multiple and diverse ways in which genes, cancer risk and environments are being meaningfully calibrated by differently implicated communities.

The case of R337h and its unfolding and still to be defined association in Brazil with a range of cancers and the ‘rare’ cancer syndrome Li-Fraumeni provides an opportunity to examine and understand how this space of uncertainty is shaped and experienced by those engaged in research and clinical practice, as well as those seeking care. For those carrying out cancer genetic research contingency is ameliorated in a variety of ways, framed most prominently in relation to an increasing understanding of R337h as ‘variably penetrant’ but with research on gene regulation and function emerging in parallel. In the main it is the intra-cellular environment and the bio-chemistry of gene expression which emerges as the most immediately significant focus of research; a strategy that might in part be understood as productively articulating uncertainty whilst containing complexity. Nonetheless, a wider

⁷In other papers I have also discussed how this history of social medicine also shapes the ‘activism’ of health professionals and their commitment to public health (see for instance Gibbon 2016). See also Behague 2015 for a discussion of how the long duree of Brazilian public health has shaped the medicalisation of mental health in Brazil.

extra-cellular context comes into view in consideration of differential cancer incidence and clustering of some cancers in the south of the country linked also to the apparent regional frequency of R337h. Here efforts to address ‘ancestry’ actively enable a movement between genes and culture that for some members of this research community re-position history and tradition as modifying environments, if not (as yet) the wider politics of health inequalities. Whilst among the community of mainly lab based researchers I encountered a few expressed hopes about research on R337h leading ultimately to some form of ‘personalised’ medicine, those who worked at the clinical interface were more hesitant about this outcome. Their sense of conflict about the distance between ‘knowing and not knowing’ in relation to R337h meant many were, not unexpectedly, pragmatic in their communication to patients about the contingency of cancer risk. The particular framing of environmental modifications in the clinic reflect therefore the very real challenges faced by health professionals in communicating risk information. Whilst in Brazil this situation is traversed on daily basis, against a background of institutional precarity and finite clinical and research resources it is context for clinical communication of epigenetic effects of environments that is now diversely unfolding across a much broader international terrain of cancer care and research.

Patients also actively populate the gap between identifying genetic markers and conditional cancer risk, drawing on a range of meanings that also from an analytic perspective appear to evoke different types of epigenetic thinking. These reflect popular ideas about the ‘porous’ boundaries of the sick body as subject to exogenous influences, including food, poverty and emotions, but also contemporary discourses of self improvement. In a context of genomic uncertainty there is also recourse to ideas about bodily vulnerability which appear to reflect and reproduce Lamarckian understanding of inheritance. The ways these contemporary ideas of cancer risk resonate with older histories of public health in Brazil (Sanabria 2016) suggest the need to consider how in the distance between genetics and epigenetics pre-existing understandings of the relationship between biology, bodies and environments can potentially being re-invigorated (Meloni 2016). As Janelle Lamoreaux’s research in China illuminates, we need to attend to how different ‘lineages’ of epigenetic research may encompass and be informed by diverse political histories of public health and specific cultural understandings of the body or personhood (2016). This makes it vitally important to examine how differently implicated communities, including not only patients but also health professionals and researchers, resourcefully make sense of the contingency of emerging understanding of the epigenetic effects of environments using a wide repertoire of historically and contemporarily situated meanings to actively populate the space between genes, environments and disease. In the case of R337h and cancer in Brazil this includes how specific histories of public health, and contemporary articulations of regional identity, as this relates particularly to food and ancestry, provide resources for understanding the constituting role of ‘environments’ in cancer risk and the variability of health outcomes. In an era in which epigenetic arguments are becoming more prominent it will be important to monitor how diverse social, political and national histories of public health and culturally resonant articulations of embodied vulnerability and responsibility are resourcefully mobilised or themselves transformed by different professional and patient communities in and far beyond the high profile field of cancer care and research.

As a raft of new technologies facilitate the generation of more data for a wider range of at risk populations across a globalising terrain of post genomics, the identification of low penetrance mutations or variants of unknown or uncertain significance is likely to be increasingly more widespread. In this sense examining how the gaps between the identification of a genetic marker and conditional cancer risk are being actively filled within the context of research, at the clinical interface and amongst patients communities in relation to R337h in Brazil represents an exemplary case that potentially illuminates the dynamics and tensions of a wider evolving terrain of post-genomics and epigenetics. It suggests that understanding and engaging with efforts to ameliorate and negotiate the current and, for the foreseeable future, ongoing distance between knowledge and care in genomic medicine remains a vital task for social scientists.

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