

# Rare genetic disease, global health and genomics: the case of R337h in Brazil

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## **Introduction**

The emerging relationship between genomics and a terrain of global health aligns arenas of social practice, cultural meaning and political value that might until recently have seemed antithetical. Developments in genomic research and medicine since the turn of the twenty-first century have long been associated with the promises of so-called personalized medicine, linked mostly to costly, high-end technological interventions focused on facilitating the choice of individual patients and their families who have resources or means to access and act upon genetic information (Tutton, 2014). These are health care scenarios which until recently were mostly thought to be available only in North America and Europe. Global health, by comparison, most commonly refers to populations and references a wider set of challenges to health, particularly in resource-poor contexts. Advocated solutions typically often include non-medical or non-technological interventions to address and ameliorate structural health inequalities and disparities (Beaglehole and Bonita, 2010).

The increasingly visible meeting points between genomics and global health challenge an assumed opposition between these domains, raising questions about the dynamics of their realignment and their potentially newly constituting features. These shifts reflect an emerging focus on populations and public health in the context of genomics and interlinkages between epidemiology, molecular biology, environment and human biological variation that are now being explored across a wide variety of national and transnational scientific and medical research contexts. In the last ten years newer and faster-sequencing ‘high throughput’ techniques and technologies have informed and propelled novel arenas of genetic and epigenetic research in relation to a dynamic field of enquiry that is focused on a diverse range of disease conditions, directly tying genomics to large-scale global epidemiological studies. This approach is increasingly seen as central to addressing infectious disease and the growing economic and social burden of common chronic diseases such as cancer, diabetes and cardiovascular disease in developed and emerging economies, where the focus is very much on the generation and multi-utility of large-scale databases (see, for instance, Mayer-Schonberger and Cukier, 2013).

Examining the ways that genomic health care and research are being newly configured as a pathway to global health remains a central task for social scientists (Gibbon, Kilshaw and Sleeboom-Faulkner, 2018) in examining how it is both ‘a product of and vector for globalization’ (Beaudevin and Pordié, 2015). Contributing to an emerging arena of enquiry, this chapter first outlines the context in which a focus on rare genetic disease – which has long been a central feature of genetic medicine – is now being reinvigorated in relation to global health. I show how efforts to address what has been described as a ‘genomic health divide’ and ‘missing heritability’ inform and justify moves to examine and extend genetic research among so-called ‘underserved’ populations. At the same time these efforts are underpinned by ‘new regimes of

innovation' (Callon, 2007) and the pursuit of niche markets facilitated by moves towards disease stratification. It is against this backdrop that an interest in rare genetic disease has become a central 'platform' (Keating and Cambrosio, 2003) for the translation of genomics. Drawing on Rabeharisoa et al.'s (2014) discussion of how a contrasting 'politics of numbers and singularisation' has come to define the varieties of activism constituted by rare-disease patient organizations, I examine how this provides a particular point of leverage for examining the intersection between rare genetic disease and global health agendas. I explore the local articulation of these dynamics by examining the 'biomedical collectives' (Cambrosio et al., 2003) that have mobilized around a particular biomarker identified at high population frequency in Brazil and associated with a normally 'rare' cancer syndrome. In examining how rareness and the variety of politics it enfolds is defined and put to work across terrains of local and global social action, this chapter shows how it is a constituting feature of the partial and sometimes uneasy alignments between genomics and global health.

## **Inequities, genomics and global health**

Questions of inequalities and genomics were explicitly articulated in the broad context of the WHO's Human Genetics Programme in the early and mid-2000s. While the importance of genetics to health has been recognized by the WHO since the 1960s, the more recent focus on genomics has centred on widening access to and use of research resources and medical genetic services in efforts to address what has been described as a 'genomic divide between rich and poor' (see, for instance, Thorsteinsdottir et al., 2003). Calls to 'bridge global inequities' are articulated in terms of the need for economic investment, research, clinical provision and the global expansion of genomic services and technologies.

Recent work in anthropology has also examined how the issue of genomics and health inequalities has become part of the landscape in which an expanding scope for genetic research and medicine is currently unfolding. This has brought to light the complex intersections between health disparities, genomics and racial justice, particularly in the US (Bliss, 2012; Lee, 2013). Nonetheless, how a discourse of social justice becomes articulated in relation to genomics is dependent on particular social and often colonial and post-colonial histories of ‘race’, racism, multiculturalism, public health provision and the changing governance of research vis-à-vis health disparities, as well as transnational collaborations (Fullwiley, 2011; Fullwiley and Gibbon, 2018; Santos et al., 2014; Wade et al., 2014; Whitmarsh, 2008).

A concern with inequalities, social justice and genomics has more recently become explicitly aligned around a notion of ‘missing heritability’. While often defined as the currently ‘unknown’ genetic variants and epigenetic pathways that may be associated with a range of increasingly common diseases (Maher, 2008), this is a concept which has also been deployed in calls to widen programmes of genetic research to global health care arenas outside Western Europe and North America. This was a key message of an article published in 2011 in *Nature Genetics* entitled ‘Genomics for the World’, where calls for genotype information from ‘minority populations’ and ‘other ethnic groups’ were emphasized to ensure that ‘those most in need are not the last to receive the benefits of genetic research’ (Bustamante et al., 2011). An emphasis on the ‘humanitarian’ dimensions of expanding genomic research to include ‘underserved groups’ brings to the fore how questions of social justice and inclusion are central to situating genomics as a pathway to global health, while also raising challenges and concerns about the ethical complexities of the ‘research/care hybrids’ that emerge at this interface (Gibbon and Prainsack, 2018; see also Gibbon and Aureliano, 2018).<sup>1</sup> At the same time, as Steve Sturdy points out

(chapter 7, this volume), efforts to diversify and widen the parameters of participation in genomic research beyond North America and Europe are also about ensuring the relevance and accuracy of genomic data for populations in those same regions. From this perspective, ‘missing heritability’ encompasses not only currently unknown genetic variation or the urgency of genotyping diverse populations for ‘humanitarian’ reasons in terms of widening access to participation and resources, but also the ongoing viability of genomic science and medicine for ‘Western’ consumer markets.

## **Stratified medicine and regimes of innovation**

The way that an expanding terrain of genomics and global health brings to the fore questions of social justice and inequalities in considering as yet ‘unknown’ genetic variants relevant to particular populations or geographical regions also reflects the increasing moves towards disease stratification. Described sometimes as ‘precision medicine’, or more ubiquitously as ‘personalised medicine’ (Tutton, 2014), this is an emerging but still mainly promissory dimension of genomic health care. It has nevertheless been made most visible in the field of oncology, at the ‘tangled intersection’ (Keating and Cambrosio, 2013) between translational research and clinical care. It is a meeting point which entails transformations not only in the expanded ‘biomedical collectives’ (Bourret, 2005) that now coalesce around the field of cancer genetics but also in cancer patienthood, described by Kerr and Cunningham-Burley (2015) as ‘embodied innovation’.<sup>2</sup> While the stated aim of stratified medicine is to move beyond a ‘one size fits all’ approach to more accurately characterize patient populations and subgroups for better and improved targeted treatment, this is also tied to what Callon (2007) has described as ‘new regimes of innovation’ and the development of differentiated ‘niche’ pharmaceutical

markets. In a global context this means taking account of how the necessary involvement and needs of different populations are positioned as vital components in fulfilling (and making equitable) the future health promises of genomic knowledge. It entails, as Rayna Rapp points out, examining how ‘different publics are becoming part of exquisitely stratified research populations that now serve as potential global resources and market beneficiaries’ (Rapp, 2013: 574).

In an arena where the global and globalizing vectors and terrains of genomic research and medicine are unfolding, a focus on ‘rare’ genetic disease is being explicitly situated as central to the translation of genomic health care and, as a result, entwined with issues of disease stratification, the development of niche markets, missing heritability and social justice.

## **Rare genetic disease and translating genomics**

An interest in rare disease in genetic medicine is not new. With 80% of so-called rare diseases thought to be genetic in origin and many related to single gene alterations, the feasibility of a focus on rare diseases in genetics has long been recognized. What is notable is the shift in scale and scope of national and transnational initiatives addressing ‘rare’ disease and the way they are explicitly situated as a ‘platform’ for the wider application of genomics to public health, particularly in the context of large-scale, high-profile genetic research initiatives. As one scientific commentator reflecting on the application of next-generation sequencing for rare disease put it, ‘hardly a day goes by where there is not another discovery of a gene for a rare disease’ (Danielsson et al., 2014).

The expanded scope for newborn genetic screening in the US and the UK, which is now targeted at identifying a wider range of rare but potentially disabling conditions before symptoms

develop, is extending the space of the clinic in genomic medicine (Timmermans and Buchbinder, 2012). The UK's high-profile 100,000 Genomes Project set up by Genomics England, a company established by the Department of Health in 2012, aimed at sequencing the genomes of 100,000 people to produce a 'lasting legacy for patients, the NHS and the UK economy', has an explicit focus on so-called 'rare' diseases, as well as cancer and infectious diseases. As one of the briefing documents from Genomics England states:

Rare diseases present an ideal opportunity to establish a platform for the application of high-throughput genomics in routine NHS practice. As a group rare diseases affect 6% of the UK population and more than 85% are caused by a single gene defect. Many are chronic and associated with substantial morbidity and premature mortality. Early diagnosis enables accurate genetic counseling and prevention and may lead to new treatments based on genetic stratification. (Genomics England Science Working Group, 2015)

Nevertheless, definitions of rare disease vary. In the US rareness is defined in terms of prevalence, a condition that affects less than 200,000 people. While the European Commission's definitions on public health rely on a prevalence threshold which is lower (1 in 2,000), but further qualified with reference to conditions that are 'life-threatening or chronically debilitating'. Taking this variability into account, WHO figures suggest that there are 6,000–7,000 rare diseases worldwide and that they affect 8% of the world's population. As a number of social scientists working in this arena have illuminated, the estimated numbers of those affected play a key role not only in framing scientific and medical interest and gaining resources for research but also in the way that publics and patients engage with rare genetic disease.

## **'The politics of numbers and singularisation': rare genetic diseases and activist communities**

Work examining the role of patient organizations has been of particular importance in examining the changing meaning and significance of ‘rare’ disease. Exploring and comparing patient organizations, mainly in Europe and the US, a number of social scientists have tracked how ‘rareness’ is variably produced and engaged with by different patient organizations and activist communities in efforts to raise awareness, access resources and, in some cases, shape research trajectories (Rabeharisoa, 2003; Rabeharisoa and Callon, 2004; Rabeharisoa et al., 2014; Huyard, 2009). Much of this work describes how certain of these groups, particularly during the 1990s, participated in making equivalent the notion of rare disease and patients’ exclusion, so that rareness appeared as the cause of discrimination against patients and, as a result, became a political issue. As the work of Huyard also demonstrates, such activities led in the US to a lowering of the threshold for clinical trials involving so-called orphan drugs and diseases, and thereby succeeded in transforming ‘uncommon disorders’ into ‘rare diseases’ (Huyard, 2009). Rabeharisoa et al. suggest that efforts on the part of patients to make visible the ‘undone science’ of rare disease, based on principles of fairness, equity and social justice, have until recently very much relied on ‘politics of numbers’ (Rabeharisoa et al., 2014). One of the messages consistently articulated by many patient groups is that while individual ‘rare’ diseases may indeed be rare, the total numbers affected in this way are significant and have a detrimental impact on public health. This is a discourse that is strongly reflected not only in the publicity material of patient organizations but also, more recently, in the UK government’s Strategy for Rare Diseases, which states:

The total number of rare diseases is steadily increasing because genetic research is beginning to explain disease patterns that we did not understand before. Research shows that 1 in 17 people will suffer from a rare disease at some point. In the UK this means more than 3 million people will have a rare disease – so rare diseases are not that rare. They represent a significant cause of illness, making considerable demand on the resources and capacity of the NHS and other care services. (UK Department of Health, 2013: 5)

Nevertheless, activism around the quantification and aggregation of rare diseases stands in contrast to a different strategy adopted by other patient organizations, characterized by what Rabeharisoa et al. (2014) describe as a ‘politics of singularisation’. Here a clear-cut stable definition of rareness is substituted for an attention to specificity as part of an ongoing ‘qualification of relevant differences and similarities’, such that patients and the collectives they belong to are ‘simultaneously constituted and continuously reassembled’ (Rabeharisoa et al., 2014: 212). They suggest that this is not necessarily about individualization or reductionist biologization of rare disease but instead can potentially lead to the exact opposite. That is, different specificities in the biological pathways, signs, symptoms and experience of rare disease conditions can result in the formation of new collectives or new pathways to access broader and diverse research terrains beyond the parameters of any specific rare disease.<sup>3</sup> At the same time there is an acknowledgement by these authors that ‘singularisation’ of rare genetic disease can serve to strengthen and is also itself nurtured by the opening up of niche pharmaceutical markets.

This research is very much focused on the role of patient organizations and their relationship to scientific expertise in reconstituting the meaning and significance of ‘rareness’. Nevertheless, I would suggest that a discussion of the politics of ‘numbers’ and ‘singularisation’, provides a point of leverage in examining how an expanding interest in rare genetic disease in the context of globalizing genomic medicine is being calibrated to local and global contexts in specific ways. To further illuminate these dynamics I turn to the case of rare genetic disease in Brazil, drawing on ethnographic research undertaken in the domain of cancer genetics in the south of the country.<sup>4</sup>

## ***Oncogenetica in Brazil***

The development of specialist cancer genetics clinics and services in Brazil has emerged since 2010, in the wealthier and relatively more economically developed southern part of the country. With extremely high rates of breast and prostate cancer in these regions (equivalent to the population prevalence in the US map; INCA, 2014), it is a location which not only reflects regional differences in cancer incidence but also relative differences in wealth and, to some extent, access to health care services. The scope of Brazilian clinical cancer genetics, while increasingly fuelled by the growth of private genetic testing and screening, is also very much centrally linked to university hospitals and specialist research units. Nevertheless, it is limited by the lack of integration of genetic services more generally into the public health system, and consequently constituted by a degree of dependency on research collaborations. As a result there is a close and dynamic relationship between emerging clinical services, which are focused on promoting a neglected preventative approach to health care through risk-based interventions, and research objectives linked to national and transnational collaborations (Aureliano, 2015; Gibbon, 2015b). The undefined boundary between cancer genetic research and clinical services has been noted as a significant feature of cancer genetics elsewhere (Hallowell et al., 2009; Kerr and Cunningham-Burley, 2015), and is more widely indicative of the ‘clinical collectives’ that have become a defining feature of translational research in cancer genetics (Bourret et al., 2005; Cambrosio et al., 2014). Nevertheless, the relative lack of integration of cancer genetics into public health services and a dependence on research funding (both national and transnational) make such boundaries more than usually fluid and, as a result, complex in resource-poor contexts such as Brazil.

One of the articulations around the necessity for cancer genetics in Brazil has been an emphasis on identifying what are described as the currently ‘unknown’ parameters of cancer

genetic risk in Brazil and the need to *padronizar*, or standardize, testing protocols and criteria in order to know the genetic variants that pose a risk for the Brazilian population. This emphasis in part reflects the questions of social justice, ‘underserved populations’ and ‘missing heritability’ that are characteristic of a global genomic health agenda outlined above. This lacuna has also fuelled research efforts to identify common so-called ‘founder mutations’ that might be of relevance to certain populations or that might explain the higher incidence of cancer in specific regions of the country. The economic logic that lies behind these goals, related to reduced costs, was an aspect that the health professionals I met constantly emphasized in their work.

Nevertheless, efforts to identify the currently unknown genetic parameters also reflect the real everyday challenges of making meaningful sense of genetic risk in the clinic, given the potentially limited applicability of risk estimates and protocols derived from elsewhere. This challenge was reflected in the guidelines for managing familial cancer in Brazil produced by the Instituto Nacional de Cancer (INCA), which stated;

The Brazilian population has its own characteristics due to its ethnic and cultural diversity, with regional variations, which makes impossible the application of data obtained in other regions of the world about the risks and frequency of mutations related to hereditary cancer syndromes. This highlights the need to know and characterise these mutations and optimise clinical screening in ways that consider the particular aspects of our population. (INCA, 2009)

On numerous occasions I witnessed the extensive efforts of clinicians who, having obtained a family history from the patient in the clinic, would painstakingly work their way through various online risk-modelling tools. They would flick hesitantly between the models and risk-calculating programmes available through international online portals, seeing if there were significant differences depending on the criteria entered, trying to decide which risk estimate best fitted their patient and to make decisions on recommended interventions and care protocols. One of the stumbling blocks was often what to put in the box related to ancestry, particularly when they

often felt that the narrow categories of ‘Caucasian’ or ‘African American’ or ‘Ashkenazi Jewish’ (often the only ‘ethnic’ identifiers that were available to them in the risk-modelling tools) simply didn’t fit the profile of the patients they encountered in the clinics. In the context of high-profile genetic research fields such as those focused on the two BRCA genes associated with an increased risk of breast cancer, the concern to *padronizar* Brazilian cancer genetics has informed an ambivalent engagement with, and also a critique of, the relevance and meaning of categories of population difference.<sup>5</sup>

In Brazilian cancer genetics, therefore, clinical need is constituted with reference to an ‘underserved population’ in the context of mostly yet ‘to-be-discovered’ genetic components or the uncertainty of variants with unknown significance that may ultimately contribute to understanding and addressing the high and growing incidence of cancer in Brazil as part of a neglected preventative approach to health (Gibbon, 2015b).

## **The case of R337h**

In the expanding field of *oncogenetica* in Brazil there has been a growing interest in a particular genetic variant known as R337h and located on the TP53 gene, which has been described very explicitly in scientific literature and clinical discourse as a ‘Brazilian Founder Mutation’. Germ-line mutations on the TP53 are infrequent – estimated to be around 1 in 5,000 in the US – but have been linked to a rare cancer syndrome known as Li-Fraumeni, whose carriers are estimated to have a 90% lifetime chance of developing a range of cancers (Malkin et al., 1990).

In the early 2000s a series of Brazilian studies began to suggest that a specific germ-line mutation on the TP53 gene, R337h, was particularly common in the south of the country, with research associating this mutation with ostensibly rare cancers specifically in children, as well a

range of more common adult cancers such as breast cancer.

The variant R337h was initially associated with a high incidence of adrenocortical cancers in children in the southern state of Parana (Ribeiro et al., 2001). Since 2007 Brazilian researchers have also linked the mutation to breast and other types of cancer in the neighbouring southern states of Rio Grande do Sul and Sao Paulo (Achatz Waddington et al., 2007). While generating a good deal of controversy and debate in genetic research communities in Brazil, the state of Parana's decision in 2006 to screen all newborn children through the '*teste do pezinho*', or blood spot test, for R337h has also revealed the high population prevalence of the mutation, found in 1 in 300 of all children screened, or 0.3% of the population. This finding has been replicated elsewhere by much smaller studies investigating the high incidence of breast cancer in southern Brazil (Achatz et al., 2009; Giacomazzi et al., 2014).

The purported population prevalence of R337h in the south of Brazil has had a key part in efforts by members of the Brazilian cancer genetic community to constitute it as a significant public health problem, where a 'politics of numbers' has been used to generate national and international interest in and engagement with this area of scientific research. The purported global rareness of adrenocortical cancers in children and of Li-Fraumeni syndrome has been constantly juxtaposed against the estimate that 1 in 300 people in particular regions of Brazil are carriers of the genetic variant, thereby providing foundation to the claim that these normally 'rare' cancers and cancer syndromes are not so rare in Brazil. In one national meeting which brought together leading researchers working in the field of Brazilian cancer genetics in 2011, R337h was discussed in terms of its being likely to account for between 2,000 and 4,000 cases of cancer a year and was described in terms of having 'clear implications for public health'.

Accounts in popular national newspapers have similarly emphasized the numbers of those likely

to be carrying R337h in the south of Brazil, as compared to the limited numbers of persons affected elsewhere – quoted in one article as the ‘280 persons affected by the syndrome in the world’ (Tarantino, 2011). In the clinical contexts that I observed there was a similar emphasis on the numbers likely affected. While the question of ‘rareness’ globally was emphasized less than the frequency of R337h in the southern part of Brazil, there was nonetheless a certain ambiguity in the way that the specific known regional frequency of the mutation was conveyed in clinical contexts. For example, R337h was often described to patients as the ‘Brazilian mutation’ (*mutação brasileira*) that was common ‘among us’ (*comun em nosso meia*).<sup>6</sup>

The dynamic movement between both a relational association and *difference* with the ‘rare’ Li-Fraumeni syndrome by Brazilian researchers has therefore been central to underlining the relevance of R337h. It is also notable how the identification of the variant R337h in Brazil has also been used by Li-Fraumeni researchers and patient organizations in the US as evidence of the growing incidence of the syndrome or to highlight the neglected needs of those with the condition, as well as to help to constitute the syndrome as a platform for broader-terrain scientific research. This was reflected in the comments about R337h research in Brazil by the researcher who first described the syndrome, Joseph Fraumeni. In an article in a popular Brazilian journal reflecting on the relevance of R337h he stated: ‘we are rethinking the study of rare diseases with this syndrome ... it’s a way of advancing our study of the molecular causes of cancer’ (cited in Tarantino, 2011).

Nevertheless, the exact population prevalence of R337h in Brazil, its association with different cancers and the epigenetic or environmental factors associated with its variable expression are all subject to ongoing research and debate. Here the reconfiguration of ‘rareness’ is variably contested within different sectors of cancer research and paediatrics in Brazil. The

shift to describe R337h in Brazil as a ‘conditional cancer pre-disposing mutation’ (Giacomazzi et al., 2014) whose expression is dependent on as yet unknown environmental components reflects a terrain in which the association with cancer risk continues even as new epidemiological findings about the prevalence and penetrance of R337h make estimations of that risk more rather than less complex. Moreover, while some researchers in São Paulo and Porto Alegre have emphasized data which shows an association with breast cancer, arguing that testing for R337h must be included in programmes of hereditary breast and ovarian cancer screening in the southern regions, researchers in Parana continue to contest these findings, suggesting a lack of evidence for an association of the variant with Li-Fraumeni syndrome and maintaining that R337h is associated primarily with adrenocortical cancer in children. This has been met with openly published critiques by those who see the newborn population screening for this mutation in the state of Parana as irresponsible, given the association which they claim to have identified between R337h and the Li-Fraumeni cancer syndrome, in which carriers can develop a range of cancers as both children and adults (see Achatz et al., 2009).

These scenarios are characteristic of what Rabeharisoa and Bourret have described in terms of the ‘clinic of mutations’ that increasingly characterise genomic medicine where bioclinical entities, similar to R337h, are subject to often contested and temporary qualifications. At the same time these debates and controversies haven’t obstructed attempts at innovation in ways that reveal the niche marketing possibilities that are nascent in these developments. This includes the initial efforts of one São Paulo university to develop cheap rapid-testing technology for mass population screening of R337h (see Arruda and Sensato, 2013). While the development of this technology was linked to patent approval stated for use in public hospitals, the development of such techniques would likely also be extremely viable in the commercial sector

in Brazil.

Below I provide a further illustration of these dynamics and the way that a ‘politics of numbers and singularisation’ were put to work and made evident during one key event in my fieldwork where the regional frequency of R337h, as well as its variable expression and metabolic pathways, were used for particular kinds of mobilizations at the dynamic interface between patients and researchers.

## **Mobilizing patients and research**

In June 2011 I participated in a unique event in the southern city of Porto Alegre, where a number of the families of those who had been identified as carrying the particular mutation R337h were invited to what was described as a ‘family meeting’ set up by the researchers in the public hospital. About forty or so patients were waiting in the auditorium when I arrived, sitting mostly in small groups, with one large extended family – a number of whom had travelled overnight by bus from the interior parts of the state, paid for by the hospital. In the presentations that took up most of the morning information was provided about the discovery of the mutation, its frequency in the south of the country and its association with what was previously thought to be a ‘rare’ cancer syndrome, Li-Fraumeni. Some qualification was provided to patients that the syndrome in Brazil appeared to be different from the classic syndrome identified elsewhere, with suggestions that this particular germ-line mutation did not necessarily confer the high 90% lifetime risk of developing cancers associated with TP53 germ-line mutations in Europe and the US. A large map of the region identifying the clusters where those carrying the mutation had been identified was shown. The researcher in fact pointed out how all identified carriers had, as she put it, ‘a common ancestor’ because of the association of the syndrome with a founder

mutation and given its seemingly high regional population presence. While the map was of interest to many of the patients and families their questions were much more focused on what was being done to treat and prevent the disease, to provide care and resources for those in the areas that were most affected. Was there, as one person asked, going to be a vaccine? The response of clinicians was hesitant but centred on how this research was about developing preventative health care strategies for affected communities. Another patient, talking about his gratitude for the research that was taking place in relation to the families, said ‘you are doing so much for us, what can we do for you?’<sup>7</sup>

The final part of the morning was a talk from a younger scientist who was carrying out new research looking at the function of R337h. He explained its importance in helping to know why, as he put it, the ‘risk was different for carriers of the mutation in Brazil’ and ‘why some people had the mutation but never developed cancer’. He explained how he was investigating the possibility that R337h could be specifically associated in Brazil with metabolism and diet and that this might mean that they would be able to develop a therapy, even a dietary supplement, to treat those identified as carriers. The meeting then finished, and those who wanted to participate in this new avenue of research were invited to come and donate blood and sign the consent form, and all were invited to a lunch provided by the hospital.

In these exchanges we see the extent to which not only the activism of researchers is engaged in co-producing patient communities but also the different ways in which the ‘rareness’ is assembled such that R337h is simultaneously *connected to* and *differentiated from* the syndrome known as Li-Fraumeni. We see how an emphasis on the specificity of the condition in Brazil becomes a means of enlisting local research subjects while also engaging a wider international research community. The possibility presented to the patients that the particular

expression of R337h in Brazil might be linked to metabolic function (discussed in terms of diet with the patients and families) was of great interest to the families and also a new and exciting research avenue for the scientific team. My discussions with different members of the team later revealed how a great deal of hope was pinned on explaining the wide variability in the expression of the disease in Brazil, particularly given that many of those identified as carrying the mutation had not been diagnosed with cancers. At the same time this novel research trajectory also places the focus on what is globally an ostensibly rare condition within a broader paradigm of transnational cancer research centred on examining the genetic and epigenetic pathways that link metabolism and cancer more generally. It was significant that this was a research trajectory which had already involved collaborations with research teams in the US.

But other mobilizations were also visible in the exchanges that took place at this event, which came to light in a conversation I had with one of the participants whom I met in the weeks following this meeting.

Jose is part of a large extended family that had had multiple cases of cancer and many deaths. He had been at the meeting with several members of his extended family, a number of whom had been identified as carrying the R337h mutation although he himself had not had cancer and was not a carrier of R337h. When we met he talked specifically about how this had been an opportunity to exchange experiences, and also to concretise a sense of group identity.<sup>8</sup> This was how Jose talked about his experiences:

When I saw everyone entering we saw that they were all persons who had the mutation. We all looked at each other ... But we slowly got used to each other. We saw that we are not alone with this. I said to my family 'let's talk with them, exchange our ideas'. That lunch together was a real opportunity to chat and get to know each other. So it was really good. Someone from the group who has the same fault can find a way through this, or reassure others. Really, this group, we have something in common.

It's a really strong connection. It's genetic whether you like it or not, not family but a genetic connection. So I think we have to try and get together using the internet so we can talk about these things.

The case of R337h in Brazil is illuminating for thinking about how the focus on rare genetic diseases as part of a globalizing terrain of expanding genomic medicine is also subject to a process of localization. Here 'rareness' is being dynamically formulated at the interface with questions of social justice linked to underserved communities at the same time that it is conjoined to research exploring the viability of 'rare genetic disease' to account for and sustain research into 'missing heritability'. The aggregation and disaggregation of similarities and differences with the Li-Fraumeni syndrome that is unfolding around R337h, far from destabilizing, in fact becomes a vector through which specificity can be highlighted and used to mobilise research and potentially, as the account outlined above suggests, also nurture nascent patient activism. In this sense the case of R337h in Brazil illuminates the local and global processes by which 'rare' genetic diseases are becoming a 'platform' through which new 'biomedical collectives' are being constituted. This not only aligns and extends national and transnational research communities but also reconfigures the role of patients and research participants.

## **Conclusion**

This chapter has examined the complex vectors around which a resurgent interest in 'rare' genetic disease is being formulated across a diverse terrain of research, forging new if still partial realignments between genomics and global health where questions of social justice intersect with disease stratification, but also with the potential for market innovation. In this context work to address 'undone' science and bridge the 'genomic health divide' becomes entangled with efforts to assemble 'rare genetic disease' as a platform for genomic and increasingly post-genomic

research in the hope-filled pursuit of translational research, personal medicine and preventative health.

Drawing on one particular case study, the case of R337h in Brazil and the Li-Fraumeni syndrome, I have shown how a ‘politics of numbers and singularisation’ provide a point of leverage in examining how a global focus on rare genetic disease is unfolding in specific locations. Crucially, the activist communities at stake in these developments include clinicians and researchers pursuing both transnational research *and* the rights of ‘underserved’ communities as they attempt to stabilise risk associated with mostly ‘unknown’ genetic variants. At the same time patients or families seeking rights to care, treatment and intervention are not passive actors but are recruited and enrolled into research, although this is often in an effort to secure hard-to-access basic medical services and care. In conclusion I provide further reflection on other developments in Brazil that are also transforming and reconstituting the meaning of ‘rare’ genetic diseases where specific kinds of patient activism and citizenship are implicated.

In November 2013 a popular television network that broadcasts from the Brazilian Senate dedicated a whole programme to rare genetic diseases.<sup>9</sup> It brought explicit attention to the high numbers of those thought to be affected by such conditions in Brazil, between 13 million and 15 million people according to the Ministry of Health. More significantly, presenting in detail the experience of a few families with these conditions, focus was drawn to the lack of appropriate attention on rare diseases in public and private health care. The stories of a family with hereditary ataxia and a young teenage girl with cystic fibrosis were outlined, highlighting not only the dearth of appropriate health care available to them but also how, in each case, the families had pursued or were pursuing judicial cases in the courts to ensure that they had the resources, medication and facilities to care for their loved ones. As Waleska Aureliano suggests

in her analysis, the message conveyed by the programme is that the recent upsurge of judicialization in Brazil is linked to limited and inadequate medical resources for rare and, in many cases, genetic disease (Aureliano, 2015).

The rapid growth of health judicialization in Brazil has been noted by a number of commentators (Aureliano and Gibbon, forthcoming; Biehl, 2013; Diniz, 2009), illuminating a phenomenon in which thousands of Brazilian patients across different social and economic classes are now effectively suing the government for the right to health care resources. This includes not only medication but also other treatments, examinations and tests, predicated on a constitutional commitment in Brazil to provide health care for all. It is significant that the first such successful cases of judicialization have occurred in the context of participation in clinical trial research for medication related to mainly rare genetic conditions, although patients are pursuing, and very often successfully obtaining, the right to health care resources for a wide range of conditions. In 2013 a geneticist in cancer genetics clinics in the south of the country commented that of the thirty or so patients they see each week in the public health hospital at least one is going through a judicialization process to secure rights, mostly, in these cases, for genetic testing – procedures which are not currently available via the public health system.

While the role of the pharmaceutical industry in promoting judicial cases for access to drugs and treatment points to the complex ways in which judicialization has been and is developing in Brazil (Diniz, 2009), we must also, as Aureliano highlights, be careful not to assume that this ‘judicialised citizenship’ is necessarily predicated on the individual’s ‘rights’ to manage one’s health (Aureliano, 2015). She suggests, rather, that judicialization might more often be seen as a struggle for better health care from the state, supported in this case by a responsive judicial system (see also Grudzinski, 2013). In this sense these are developments that

point to the relevance of ‘bio-legitimacy’ (Fassin, 2009) as a central feature of how citizenship and activism are situated in relation to the politics of rare genetic disease in Brazil (see also Guilherme Do Valle and Gibbon, 2015).

It is at the same time hard to see the recent upsurge in cases of judicialization as separate from the 2014 Brazilian federal directive to form a national policy for the Comprehensive Care of People with Rare Disease, especially as this followed intensive lobbying by scientists and patient associations (Aureliano, 2015; Melo et al., 2015). While the consequences of this new directive are still unfolding, it marks a watershed in the attention to rare genetic disease within the Brazilian public health system, ensuring, in theory, comprehensive diagnosis and clinical attention for up to ten rare genetic diseases in reference centres located across the country. Those identified as carriers of R337h associated with Li-Fraumeni syndrome in Brazil are currently not included. However, just as patient litigants in Brazil have been seeking rights to genetic testing for the BRCA genes it will be important to monitor how the new directive for rare genetic diseases unfolds and whether we will see the emergence of judicial demand either for genetic testing in the case of R337h or for carriers, in order to obtain routine screening as part of preventative health care approach.<sup>10</sup> It highlights the need for ongoing and critical examination of who and what gets excluded and included in the shifting scientific and medical focus on rare genetic disease, as the local and global dynamics of genomic research and health care become ever more complexly entwined.

## **Notes**

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<sup>1</sup> See Lakoff (2010) for further discussion of how the expansion of ‘humanitarian biomedicine’ has brought the specific issue of ‘neglected disease’ to public prominence.

<sup>2</sup> See also Bourret et al., 2014.

<sup>3</sup> One illustrative example discussed in the paper by Rabeharisoa et al. includes a patient association in France concerned with extremely rare autoimmune disease linked to bone marrow depression. The organization PNH chose not to align itself with larger rare disease umbrella organizations but instead to emphasize the uniqueness of the condition. This enabled them to develop strong connections with a particular specialist hospital who were subsequently contacted by an American pharma company to test a new class of immunosuppressants which the patient association supported, ensuring that the drug was brought to market in the shortest time possible (Rabeharisoa et al., 2014: 207).

<sup>4</sup> This included ethnographic research working with and alongside patients, practitioners and scientists in mostly public cancer genetics clinics in three major cities in the southern part of the country during research that was mainly undertaken from 2010 to 2012. My principal focus in this research has been on examining the interface between international agendas for cancer genetics research and questions of population difference and genetic ancestry, the historical and contemporary politics of public health in Brazil and the variable understandings of genomics and embodied risk for cancer among patients and their families.

<sup>5</sup> My research in Brazil suggests that these population categories are made relevant through diverse registers of meaning. On the one hand, the regional specificity of the migratory histories of the southern part of the country is made evident. Yet this

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research is also explained in relation to, and itself becomes evidence of, the ubiquity of population mixture in Brazil, popularly but unevenly associated with a discourse of Brazilian nationhood and identity (Mozersky and Gibbon, 2014). Elsewhere I have argued, along with others (see, for instance, Wade et al., 2014), that this movement and mobility in the way that particular categories of population difference are simultaneously incorporated but also reconfigured and sometimes rejected in Brazilian cancer genetics must be understood in terms of the constantly ‘situated meaning and utility’ (Schim et al., 2014: 18) of genetic ancestry (see, for instance, Gibbon, 2015a).

<sup>6</sup> See Gibbon (2015a) for further discussion.

<sup>7</sup> Such comments illustrate not only the willingness of some patients to participate in and contribute to the research but the dynamics of the exchange on which medical research is often predicated in contexts where the terrain of health care is uneven and inequitable. In this way many patients without health insurance and dependent on precarious public health can, through participation in research, gain access to both real and perceived care in terms of additional screening and monitoring (Gibbon, 2015; see also Petryna, 2009).

<sup>8</sup> Something that may have been partly a result of the researchers’ suggestion in the presentations that all who were carriers of R337h had a ‘common ancestor’.

<sup>9</sup> I am extremely grateful to Waleska Aureliano for bringing this programme to my attention.

<sup>10</sup> This is particularly so when one of the key messages of those involved in this field of cancer genetics research in Brazil, focused on R337h, is that regular and routine monitoring and screening of carriers could reduce not only cancer mortality but also treatment costs.