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mapping the new genomic era

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Genes in our knot

Mike Fortun

> Cells, organisms, and genes are not 'discovered' in a vulgar realist sense, but they are not made up. Technoscientific bodies, such as the biomedical organism, are the nodes that congeal from interactions where all the actors are not human, not self-identical, not 'us'. The world takes shape in specific ways and cannot take shape just any way; corporealisation is deeply contingent, physical, semiotic, tropic, historic, international. Corporealisation involves institutions, narratives, legal structures, power-differentiated human labor, technical practice, analytic apparatus, and much more. The processes 'inside' bodies – such as the cascades of action that constitute an organism or that constitute the play of genes and other entities that go to make up a cell – are interactions, not frozen things. For humans, a word like gene specifies a multifaceted set of interactions among people and nonhumans in historically contingent, practical, knowledge-making work. A gene is not a thing, much less a 'master molecule' or a self-contained code. Instead, the term gene signifies a node of durable action where many actors, human and non-human, meet.
>
> (Haraway 1997: 142)

G. rex

For as long as any of us can remember, the gene has been represented predominantly in both science and society as 'the secret of life' (Watson 2003), the 'grail of human genetics' (quoted in Cook-Deegan 1994), the 'code of codes' (Kevles and Hood 1993), and with more prosaic metaphors of 'blueprints' and 'programmes'. Such metaphors are all too familiar, and so for the purposes of this essay I will put them under yet another sign, *G. rex*: the gene as king, ruler, sovereign legislator and ultimate authority.

I choose this representation, *G. rex*, as a way to build on a set of images that Evelyn Fox Keller uses to close the book which has contributed greatly to our understanding of how scientific conceptions of 'the gene' have changed over the last hundred years, *The Century of the Gene* (2000). After documenting and analysing the shifting metaphors that not only accompanied but propelled the study of genes and organisms in twentieth-century life sciences, Keller leaves her readers contemplating two representations of the awe-inspiring thunder lizard, *T. rex*. In the first image from the not-so-distant past, we see *T. rex* erect, head raised and tiny forelimbs jutting forward, a towering figure

structured by the invisible fields of paleotonology and evolutionary theory that positioned this dinosaur as an upright reptile. Evidentiary and conceptual changes in these fields that are not on display with the creature but are nevertheless part of the visual representation, begat a new *T. rex*, now more closely related to birds and with an entirely different but perhaps no less fearsome posture: spine parallel to the ground, head down and forward, and oriented overall, not towards an imposing display of height, but bent towards the hunt, prowling, on the move.

The bones themselves are of course unchanged, as are most of the connections between them; it's exactly the same *T. rex*. Yet it is an entirely different *T. rex*: a new representation re-patterned in accord with new concepts and new imaginings that took place in the research wings of the museum. My *G. rex* is an extension of Keller's visual analogy, joining up with her efforts to analyse how 'the gene' has been re-conceptualised and re-imagined over time.

There are, of course, other ways to metaphorise the emergent paradigm shift that comes with the territory of the 'new genetics'. Medical anthropologist Margaret Lock, for example, deploys not a dinosaur analogy but a cosmological one when she gathers some of the same scientific-cultural changes into the phrase 'the eclipse of the gene', which, in her analysis, is accompanied by the 'return of divination' (Lock 2005). Genes, according to Lock, have been eclipsed because genetic tests for complex conditions such as Alzheimer's fail to provide the 'information' about future health status they promised; such tests are put to use nonetheless, in what Lock describes as less-than-rational divinatory exercises to predict one's future.

Many scientists and analysts of science are casting about for such new metaphors and images, a number of which I discuss in what follows. Our charge is to approach such 'representations of changing scientific representations' critically, but this doesn't mean asking 'is the representational metaphor right or wrong?' so much as it means asking, in terms derived from J.L. Austin's (Austin 1962) speech act theory, 'is this figure more or less felicitous?' – is it well-met, happily encountered, productive of thought and conducive to our most admirable behavior? Even though Lock's 'eclipse' metaphor evokes something important about the contemporary moment, for example, I do not find it especially felicitous. Analysing changing scientific representations of 'the gene' in terms of a cyclic occlusion or a cosmic play of enlightening and darkening suggests fixed entities on vast orbits, where the alternatives have long been been laid out and the passing of one (modern reason in the form of genetics) only entails the re-arrival of another (a more primitive divination). With genetic astronomy eclipsed, the narrative appears to run, genetic astrology again rules the darkened day.

In my reading of the new genetics, what 'the gene' is undergoing is less about obscuring or hiding and more about a repositioning and refiguring through extension: the gene is not being eclipsed, it is being abducted into new, more complex, more diffuse, and more powerful albeit delicate patterns, networks, systems – or knots, as I will collectively metaphorise these terms here. The king, *G. rex*, is not dead or eclipsed – it's a knot.

From not in our genes to genes in our knot

Few representations of scientific objects are more consequential right now than these representations of 'the gene', that 'material-semiotic actor' (Haraway 1997) that occupies such a crucial place not only in genetics but in all the life sciences – and not only in the

life sciences, but in all of our collective life, in all its complexity and difficulty. For better and for worse we are conscripted into 'genetic citizenship' (Heath *et al.* 2004), charged with duties of governances that require literacy and active participation. In this essay I want to recapitulate some of the scientific and cultural changes that historians, anthropologists, and others have analysed in genetics, and to consider the implications that changing scientific representations of the gene have for us 'genetic citizens'. The new representations of genes and genomes that are emerging as a result of the genomics revolution are, I will argue here, of enormous value to life scientists who are coming to better understandings of organisms in all their robustness as well as their fragilities. By 'better' understandings, I mean 'more complex', and by 'more complex' I mean 'more attuned to the knotty realities that are living systems'. And now, in parallel, the rest of us 'genetic citizens' need better understandings of what genes and genomicists have become, where 'better' again means: more complex understandings of genes and of the people who study them, and more complex understandings of how genetic knowledge implicates 'society'. Complexity is not, of course, a good in itself, and can be formulated in different ways. I valorise complexity here because thinking in its terms has both resulted from and driven advances in genetics, opened up connections between genetics and other scientific fields, as well as between genetics, the social science and humanities and 'the public'. Today, for example, through the rubric of 'complexity', geneticists themselves seek out both environmental health scientists (who can help them understand the gene–environment interaction that is now a cutting edge focus of genetics research) as well as the health policy analysts, anthropologists and community leaders who can help them understand how new forms of genetic knowledge might circulate. Complexity is not the answer, but the new condition of possibility.[1]

I hope this essay will assist readers in tuning into the complex realities of today's gene and today's genomic researcher – realities which I tie together under the rubric of 'knots'. Why knot? This metaphor first suggested itself to me as a playful reversal of the title of that important book which also became a kind of unspoken slogan among social scientists critiquing genetics and geneticists in the 1980s and 1990s, *Not in Our Genes* (Lewontin *et al.* 1984). At a time when sociobiologists and other scientists were making audacious claims about genes as 'selfish', all-powerful biological royalty, such a straightforward refusal and opposition – Not! – was a powerful and necessary social, political and scientific counterargument to all kinds of biological essentialisms and their associated eugenic gestures. A genetic reductionism that was more often than not 'crude' elicited, in perhaps dialectical fashion, arguments favouring or privileging 'the social' or 'the environmental' as a counter-discourse to the 'discourse of gene action' (Keller 1995) on which genetics and allied sciences like sociobiology so heavily, albeit productively, depended.

To be sure, such a kingly representation of the gene as dictator (in both senses of the term), the precious, all-powerful, eternal germ-plasm safely ensconced within the 'giant lumbering robots' (Dawkins 1976) which they controlled, was never entirely hegemonic within the life sciences. Historians and historian-scientists such as Keller, Jan Sapp (Sapp 2003), and Scott Gilbert (Gilbert *et al.* 1996) have shown how developmental biologists, in particular, tended to think and work within conceptual and experimental paradigms that were far less genocentric than that implicit with the *G. rex* paradigm. Moreover, if the gene was 'the secret of life' for much of the twentieth century, Ross Harisson, Alexis Carrel and other pioneers of tissue culture kept the nineteenth century's contender for that metaphoric title – the cell – alive and well (Landecker 2007) – literally and metaphorically, if you will pardon the partial redundancy.

Scientists themselves, in other words, have often been the most dependable and vital source of alternative metaphors and representations for organisms and their components. Indeed, few have been more dependable and vital than population geneticist Richard Lewontin himself, who gave us *Not in Our Genes* (1984), and whose more recent book title goes some way towards suggesting my knot – *The Triple Helix: Gene, Organism, and Environment* (Lewontin 2000). Nevertheless, even this representation could still use some additional twisting. 'It is not possible to do the work of science without using a language that is filled with metaphors,' Lewontin affirms in his opening sentence (Lewontin 2000). He then proceeds to critique most of the familiar metaphors in play in genetics, commenting that: 'Any computer that did as poor a job of computation as an organism does from its genetic "program" would be immediately thrown into the trash and its manufacturer would be sued by the purchaser' (ibid.: 17). But as Lewontin admits toward the end of his short book, there is a 'distinctly negative flavor' to his text, which almost exclusively details the (inevitable) shortcomings and failings of genetic metaphors, while leaving their more productive aspects unanalysed. Indeed, there is something reductionist about Lewontin's own analysis, especially at the end of the book, where the causes of large-scale scientific change are effectively reduced to a few technologies. Hence, for Lewontin, the introduction of 'the new technique of protein gel electrophoresis' into evolutionary genetics in the 1960s becomes a story of how 'a single easily acquired technique changed and pauperised … an entire field of study'. He sees the later 'invention of automatic DNA-sequencing machines' as creating a situation in which 'the problems on which geneticists work have become those that can be answered from DNA sequences' (ibid.: 128–9).

Lewontin was not wrong – and, again, his reading was critical and 'felicitous' (in Austin's sense). But it did not capture the whole story. Many confounding technologies, processes and events have shaped what genetics has become; it has taken and will continue to take many kinds of readers to make sense of it.

Lewontin's *The Triple Helix* was published, for example, in 2000, which from other perspectives marked a promising watershed. In a 2000 review article in *Nature*, 'Exploring genome space', molecular biologists Ognjenka Goga Vukmirovic and Shirley M. Tilghman (who later became president of Princeton University) wrote of the 'intellectual and experimental sea change' (Vukmirovic and Tilghman 2000: 820) that all of biology was undergoing, primarily as a result of the massive amounts of genetic, protein and other information that was by then pouring out of university, government, and corporate laboratories. 'This avalanche of data', they wrote, was unleashed by the 'fortuitous confluence' of radical improvements in numerous technologies: DNA and protein sequencers, mass spectrometers, nuclear magnetic resonance (NMR) spectrometers, x-ray crystallography and other imaging technologies, to name only a few which they mention. Although they explain that the data deluge had only 'whet our appetite for more', the intent of their article was to step back momentarily and to describe 'some of the challenges that biologists face as they acclimatise themselves to this change in the data landscape' (ibid.).

It is worth recalling that the development of these avalanching-producing, landscape-transforming technologies had been a prime motivation and rationale for the Human Genome Project (HGP), politically astute rhetoric about 'completion' and 'the Holy Grail' notwithstanding (see Fortun 2002). As Charles DeLisi, one of the earliest and strongest advocates of the HGP who was at that time in the US Department of Energy, testified to a US Senate committee in 1987, a main goal of the HGP was

> to develop technologies that would make sequencing … a lot quicker than it currently is … [I]f you want to sequence a hundred thousand bases [in] twenty people and compare their sequences and understand disease susceptibilities, you can't do that, it's not a clinically viable procedure. We can make that a clinically viable procedure. That's the goal, it's not to sequence the human genome, at least initially.
>
> (Senate Committee on Energy and Natural Resources 1987: 12)

Not everyone at that time believed in 'the value of such large-scale data acquisitiveness in biology', noted Vukmirovic and Tilghman (ibid.). But, just 13 years later, the idea 'that data are inherently good' had become 'a central pilosophical tenet for biologists'. Along with this new data landscape of 'genome space', Vukmirovic and Tilghman remarked on changes in financial, disciplinary, and campus landscapes as well:

> It is hardly a coincidence that many universities and research institutes, including our own, are making major investments in multidisciplinary life-science initiatives to explore the complexity of living things. Organisms are networks of genes, which make networks of proteins, which regulate genes, and so on ad infinitum. The amount of complex data that will be generated, and the need for modeling to understand the way networks function, will ensure that disciplines outside of biology will be required to collaborate in this problem, if the ultimate goal to deconstruct such networks is to come to fruition.
>
> (Vukmirovic and Tilghman 2000: 822)

Although 'ad infinitum' is almost certainly an overstatement, it can nevertheless be read as a welcome sign of 'the funny thing that happened on the way to the Holy Grail' (Keller 1995). Although driven and justified by a unidirectional notion of 'gene-action', the HGP instead created a landscape in which genes acted only within complex networks, in extensive, if not infinite, loops of recursive control. The gene has not been eclipsed, and it has not provided easy answers; the gene has been networked or, to employ the messier metaphors I prefer, it has become knotted.

The resulting enthusiasm for 'systems biology' – an enthusiasm which, as I shall explain below, I share – is best regarded as another iteration of a long attempt, decades if not centuries in the process, to articulate a more holistic or organismal conceptualisation of organisms. This was signalled in the chiasmic subtitle '*The Living System – A System for Living*', of embryologist Paul Weiss's 1973 book *The Science of Life*. Weiss's book – which preceded *The Selfish Gene* by three years, and *Not in Our Genes* by more than ten – is another reminder that life scientists themselves can sometimes be the best critical readers of scientific representations. 'What is misleading in the term "genetic determination",' he argued:

> is that it conveys the notion that the development of an organism is simply the mechanical product of a bundle of linear 'cause–effect' chain reactions, reeling off in rigid sequence according to a minutely predesigned plan of clockwork precision. That notion, reinforced by the anthropomorphic language that endows genes with the powers of 'dictation' and 'control', rests on a basic misconception of the nature of biological processes in general and of developmental dynamics in particular. Scientists familiar with the facts, of course, know better …
>
> [T]he current fashion of entrusting the genes with a monopoly on the 'information' necessary for the building of an embryo is bound to find itself caught short.

> For evidently, besides its full complement of 'genetic information', each cell needs still additional 'topical information' derived from the field structure of the collective mass. How otherwise could any unit know just what scrap from its full grab bag of inside information to put to work at its particular station in order to conform to the total harmonious program design? ... To sum it up, in whatever phraseology one may choose to couch it, the basic postulate of a dualism of interaction between coarse-grain field patterns and fine grain gene responses is solidly founded on experimental and logical grounds.
>
> (Weiss 1973: 10, 35)

Weiss' articulation remains compelling today because it so aptly describes what has become cutting-edge genetic understanding, while reminding us that a critique of genetic determinism is not entirely new. Weiss's articulation is also compelling because of the significance it attributes to 'phraseology'. Like Lewontin, Francois Jacob and many other scientists, Weiss understood that the metaphors we think with matter. When it comes to organisms, we have come through metaphor to appreciate more fully (yet again) their interactional constitution, their dynamism, the essential fact of their becoming within entangled systems that are nested, perhaps not ad infinitum, but far, far out from the genetic, to the cellular, physiological, and on to the technological, social and political levels often conceived as worlds apart. Little wonder, then, that scientists feel the need for new representations, new metaphors.

The music and art of genes

With systems biology and post-genomics comes a new, more complex conceptualisation of genes and organisms, and a new set of metaphors that have moved from language referents to the domains of art and music. One place to glimpse the rearticulating of *G. rex* into the 'network of networks' that is also the knotted triple helix of gene/organism/environment is in geneticist Enrico Coen's *The Art of Genes* (Coen 1999). You will not find there the phrases 'Book of Life', 'Encyclopedia of Man', 'Holy Grail of Genetics', 'Code of Codes' or any similar metaphor for DNA, genes or genomes (three things which are neither the same nor different). There is virtually no reliance on those productive articulations of 'information', 'code-scripts' and the almighty determining directions that these things, somehow supposed to be 'in' DNA, providing an origin to the organism. Rather than presenting genes as 'informing' or 'coding'. Coen presents them as 'interpreting'. I trust that you know how to read that shift in sign systems: genes aren't a text that contains commands, so much as they are readers – creative, flexible readers at that – of a more primary text; environment, within the body and beyond it, matters most.

Another shift evident in Coen's book is also noteworthy. Instead of imagining genetics as written texts, Coen imagines them visually, and in terms put in place by visual artists. Van Gogh, Magritte, Islamic fabrics, Durer, da Vinci, Escher and, most importantly, at the end of the book, Heath Robinson, the British counterpart to the American Rube Goldberg, are all in play. Works by these artists and numerous other drawings, illustrations and diagrams are used to depict what it is that genes might be said to 'do' in the post-genomic territory which we inhabit with them. Coen's text suggests that genes respond to 'hidden colors', or, both more and less accurately, respond to 'a distribution

of hidden colors'. Genes interpret and create patterns, themes, and variations on themes. Genes are 'sensitive' to certain 'scents'. They elaborate on forms, shifting and expanding them. Genes find themselves so deeply imbricated in 'chains of events' that one is forced to speak, write, and think of knots, as Coen indicates:

> Let me summarize the main points ... Flies and flowers contain a set of identity genes that are expressed in various regions of the organism to produce master proteins. This distribution of master proteins is equivalent to a map or patchwork of hidden colors ... The map of hidden colors provides a frame of reference that can be interpreted by many genes through their regulatory regions. The combination of binding sites in a regulatory region acts like a specific molecular antenna, responding to the pattern of hidden colors in such a way that each of these genes comes to be expressed at certain times and places in the organism ... The pattern of hidden colors arises through a chain of events, involving one set of hidden colors building on another set of hidden colors, which in turn depend on another set.
>
> (Coen 1999: 103, 131)

Which in turn ... keep on turning, keep on depending on the next additional pattern, until one has a massive knot – or perhaps a symphony.

In his book *The Music of Life*, Denis Noble lays out a number of reasons for 'opposing the otherwise colourful metaphor of describing the genome as "the book of life"' (Noble 2007). He explains that, in trying to reduce life to any of its multiple hierarchical levels – genome, proteome, cell, organs, brain, or even 'self' – the 'deep rooted' ambiguities and interpretabilities of our conceptual apparatus tie us up in 'philosophical knots' (ibid.: 127). Noble brings his book to a sudden and rather stunning end in a chapter entitled 'Curtain call: the artist disappears'. Under an epigram of a Zen koan, Noble writes that he chose 'music' rather than book, programme, code or any other linguistic metaphor as the most appropriate metaphor for life because 'music also is a process, not a thing', which must be 'appreciated as a whole' (ibid.: 143). 'We can choose our own metaphors, they don't need to be imposed on us,' he writes, adding for good measure Wittgenstein's dictum: 'That whereof one cannot speak, one must remain silent' (ibid.)

Perhaps this is the trajectory implied by Vukmirovic and Tilghman's ad infinitum: in the search for new metaphors for the newly networked gene, we move from codes, to interpretations, to knots, and thence to nots – the limit beyond which speech and representation are not possible.

A farewell to razors

What does this 'sea change' (to recall Vukmirovic and Tighlman's metaphor) in genetics look like, not from the meta-level views of Coen and Noble, but rather from the vantage point of the working geneticist who might have once hoped for something more determinable, if not determining, from genes? Here I will discuss the particular case of asthma, a puzzling complex condition for which it was once hoped, not so long ago, that genetics would provide some simple answers. While the 'avalanche of data' that Vukmirovic and Tilghman describe as unleashed from the technological revolutions of genomics and related enterprises put a fairly quick end to that hope, it did not end the promise of genomics. Excitement continued, configured differently.

The new large databases of gene and protein information, coupled with large studies of populations, still promised to help 'unravel' some of the complexity of conditions such as heart disease, diabetes and asthma. Unmitigated optimism soon gave way to more sober assessments, however. In the first few years of the twenty-first century, the number of publications announcing 'genes for' these complex illnesses increased dramatically, but questions were not far behind. Genomic studies 'involving large datasets', wrote the editors of the *Public Library of Science Medicine* in 2005, 'especially ones that have a clinical outcome, are so poorly reported (or possibly so poorly done) that many are not reproducible' (*PLoS Medicine* editors 2005).

Genomicist John P.A. Ioannidis even issued an all-encompassing critique, 'Why most published research findings are false' (Ioannidis 2005). Genomic studies of complex, multifactorial diseases in large population groups were particularly prone to Ioannidis's critique, since

> a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; ... where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance.
>
> (ibid.)

Knots are not easy.

While Ioannidis calls the search for 'genetic or nutritional determinants of complex diseases' – where these determinants confer (as they do in the majority of cases) fairly small risks – 'largely utopian endeavors' (ibid.), he is nevertheless a leader in the US Center for Disease Control's HugeNET – the Human Genome Epidemiology Network. HugeNET – which is more accurately labeled a 'Network of Investigator Networks' (see Ioannidis 2005), is another exhibition of the new knotty, recursive logics characterising genes, genomes, and genomicists too. The current situation is 'plagued with problems', where 'the research evidence is fragmented, and the interface between epidemiology and other biological evidence is poorly developed. It remains unclear how to keep track of the rapidly evolving evidence across fields ... and how to rate the credibility of this evidence' (Ioannidis 2006: 4). HugeNET advocates 'systematic reviews and meta-analyses', and is promoting 'new data synthesis methodologies'. They are also pushing for 'widely accepted rules for assessing the evidence for causal inference in genetic association studies, including the transparency of data processing, magnitude and significance of the proposed genetic effect, extent of replication, protection from bias and concomitant supporting biological evidence' (ibid.: 5). As this suggests, genes in our kNots require more oversight, openness and collaboration than the gene as sovereign code ever did.

The path forward for the genetics of complex conditions is, according to the editors of *Nature Genetics* (*Nature Genetics* 2006), an 'experimental' one, a tentative, even fumbling, probing of an indistinct and potentially vast solution space. The journal, prompted by its referees, has revised its review criteria to emphasise 'accountable statistical design and transparent reporting of hypotheses, results, and data processing'. They nevertheless go on to issue additional caveats, noting that 'success in this risky field is sporadic and that not every study will fulfil all the ideal criteria'. It ultimately falls to 'the community' of researchers, and not journal editors, to develop emergent standards. Here, too, the need for multiple readers is acknowledged.

Genetic and biological complexity are now reflected in greater social complexity in the networks of scientific researchers, as knots beget knots. The case of asthma is indicative of this situation. A 2007 review article discusses how geneticists have now identified 120 genes that have been shown, in at least one study, to be significantly associated with asthma. The genes can be coded according to their many different gene products or effects, which, in turn, can be grouped according to different physiological function – immunoregulation, inflammation, innate immunity, lipid mediators, and so on. They also have multiple sites of activation or operation: some genes are active in the cell nucleus, others in the cytoplasm, still more at the cell membrane, and in extracellular space as well. Like many other geneticists or other researchers investigating asthma, the authors point out that these genes do not cause or explain asthma in any simple way:

> Experience with other candidate genes for asthma (and other complex diseases) has taught us not to be too enthusiastic about early positive findings. In fact, as the number of association studies increases, it becomes clear that the initial report overestimates the importance of the gene ... Finding a genetic association between genetic variants and asthma or asthma-related phenotypes is not straightforward, as it is influenced by the inherent complexity of the disease and methodological issues.
>
> (Bosse and Hudson 2007: 176–7)

No one now, least of all geneticists, needs to be told that asthma is 'not in our genes'. Most geneticists know that genes aren't what they used to be, they have lost their sovereign authority, and if a complex condition such as asthma can be said to be 'in' anything it is 'in' what are now popularly acronymed as GEI – gene–environment interactions. 'Finding a genetic association between genetic variants and asthma or asthma-related phenotypes is not straightforward' because the asthma phenotype is 'not straightforward'. It is a knot: a tangle of interactions so dense and so intricate and so extensive as to prove highly resistant, to say the least, to current conceptualisations and technologies (and their own complex, knotty interactions). There are 120 genes tied into their own regulatory and metabolic and immunologic networks, which are knotted in interaction, and those networks and their interactions are knotted into developmental and evolutionary histories, which unfold in changing, local 'environments' of shifting, differential exposures that are currently a challenge to measure and analyse. Genes are in these knots – they are not dominant determinants (because nothing would seem to qualify as a 'dominant determinant' in asthma) but they are hardly irrelevant either.

Just as asthma is part of a tangled ecology, researchers who work on asthma genetics are also part of an ecology of high-throughput sequencing technologies, in turn implicated in a rapidly growing number of rapidly growing databases of molecular and health information. As is the case for the genetics of all other 'complex conditions', trying to unravel the genetic knots of asthma requires 'huge datasets' consisting of many intertwined parts, all of which are woven out of the blood and from information extracted from and gifted by a very large number of individuals, who thereby become 'populations'. Such large population studies, which are necessary to identify and to characterise the numerous interacting genes which each contribute some small twist to the overall knot of the condition, pose quite different methodological challenges for researchers, in contrast with studies associated with 'simple' Mendelian disorders.

With reference to asthma, genomics does not provide a fundamental explanation or even the ground for further investigations. Instead, it offers a particularly productive entry point for improving understandings of the knotted specificities of the condition. Thus, a researcher such as Fernando Martinez finds that the complexities and specificities of asthma make it necessary to apologise to William of Ockham for abandoning his razor of simplicity. Martinez highlights how the 'weak linkages' among 'flexible', 'indirect, undemanding, low-information' knots of complexly interacting biological response systems produce a heterogeneous condition like asthma, where:

> a specific protein may exert opposite effects when participating in coordinated responses to different external stimuli, and therefore, a genetic variant that increases transcription of that protein my enhance an 'asthmatic response' to one exposure and hinder an 'asthmatic' response to a different exposure. The specific role of any element of the response system is thus determined not only by its intrinsic characteristics but also by the biological context in which it is expressed.
>
> (Martinez 2007: 30)

Moreover, we must add environmental and social context to biological context, as these too become knotted or folded into the biological organism.

Giving up on genetic explanatory parsimony also means giving up on 'the original hope that genetic tests would allow us to identify who is at risk of which complex disease'. But Martinez feels that the more complex view of asthma that genomics has helped to construct at least 'seems more in tune with the degree of heterogeneity and unpredictability of the expression of the disease that is evident in any asthma clinic' (ibid.: 30). Genes in our knot may not be a simple or elegant code to live by or to do science by, but it has the advantage of accommodating more faithfully to the actual complexity of our bodies, to the intricate knots that tie us together and bind us to the changing world we live in.

Conclusion and illusion

Ten years ago Donna Haraway implored the practitioners of science studies to learn how to engage in knowledge-making practices in genetics, as well as in other cultural domains, that produce critical and cross-cutting multidisciplinary, multispecies, and multicultural savvy: 'We need a critical hermeneutics of genetics *as a constitutive part of scientific practice* more urgently than we need better map resolutions for genetic markers in yeast, human, or canine genomes' (Haraway 1997: 160).

Something like this has indeed unfolded. With or without the assistance of historians, philosophers or cultural analysts of science, geneticists themselves are becoming critical hermeneuticists, more attuned to the productive power of metaphor in their own scientific representations, more willing to engage in making new metaphors of their own. Indeed, for some of them the gene itself is now seen as a 'critical hermeneuticist' in its own right, not carrying out a programme or executing a code, but actively interpreting multiple signals at multiple scales within multiple frames of significance. Which is not to say that historians, philosophers and cultural analysts are not needed. Quite the opposite, I hope: multiple, differently focused and talented readers will be imperative.[2] It will not be easy, this building of collaborative engagements for reading the genes in our knots.

But it would be too easy to simply continue with 'not in our genes', as it leaves us off the hook of engagement.

Will there continue to be overreaching claims made for the genes as the most powerful 'secret' or as the 'foundation' of life and health? Undoubtedly. Nevertheless, I think that a larger, more powerful trend is clear: genes are well on their way to becoming something other than what they have been for most of their history. An editorial in *Nature* noted that in 2006 noted that not only did most 'geneticists find it hard to agree on an appropriate definition of a gene', they were also 'unsure whether genes themselves are worthy of the most attention, compared with other parts of the genome, or RNA or proteins, or the way they all interact together in different tissues' (*Nature* editorial 2006). 'Bring on the complexity,' they crowed: 'how dull [geneticists'] lives would be if there were just genes and diseases to be linked, like one of those join-the-dot puzzles' (ibid.) In this call for complexity, or gene–environment interactions, or systems biology, or networks of networks, my guess is that, once again, geneticists will get something more than they bargained for: not just dots, and not just dots joined to other dots in analysable pathways, but knots, entangled with more knots, in a way that exceeds even the most complex genetic representations, be they interpretations, artists' canvases, or symphonies.

Again, that doesn't mean there is no longer a need for critical questioning or 'outsider' involvement. It is only to say that critique has itself become much more complex, as genetic representations themselves become more complex and knotted, and less amenable to the straightforward, oppositional *not*. And the position of the 'outsider' has become untenable or at least unproductive, in a time when everything from the gene to the geneticist has become a network, networked with other networks. So the complex critiques need to be networked, in my view, to an ethic of friendship that recognises that the genes in our knots tie scientists, analysts of science, artists, and every other genetic citizen together. These may be uneasy, fragile and tangled ties, but if genes are capable of working within such knots, surely humans can be too.

We may not have reached the end of scientific representations like 'the genetic code' or even 'the genomic symphony', but I think we have become more adept at thinking and living at their limits. Since limits are funny places where odd things occur, I conclude *not* with a scientist and a scientific representation, but with a poet and her poem – that literary device that does something other than represent. Ruth Stone's poem, *The Illusion* (Stone 2002), does not represent genes, but it does evoke the contradictions, impasses, and wonder of knots:

The Illusion

I am not the genes and the genes are not me.
We are identical twins, separated at birth.
This is my sinew. This is my fertile ovary.
What is worth the universe is also worth me.
I am not me. I am the genes. The double helix.
My future is spelled out. Tool of the universe:
pricks, cunts, genuflections; the orgasm's curse,
brief span, holy thou: I am the neutron fix.
I am the hole, the dark other, the negative between
I was and I am. Wherefore yes, dense and disperse,

blinded visionary that locks the moon in place;
I am the simple sieve that drinks the universe.

Notes

1 This essay, as all my other writing about genomics, is underwritten by years of fieldwork in various genomic settings which do not always correspond to a physical location. My fieldwork on the scandalous genomics company deCODE Genetics (Fortun 2008), for example, occurred only partly in Iceland; the archives of the US Securities and Exchange Commission and on-line financial trading bulletin boards were another important part of that field. In my work on toxicogenomics (Fortun and Fortun 2005), Kim Fortun and I interviewed numerous and diverse scientists at the US National Institute of Environmental Health Sciences and in universities, and attended the first Gordon Conference on toxicogenomics as well as several symposia on the subject convened by the US National Academy of Sciences. Throughout these projects I also had the tremendous benefit of being a member of several 'transdisciplinary' working groups organised by Dr Alexandra Shields to address the intersections of genetics, changing definitions of race/ethnicity, complex conditions such as smoking and asthma, the challenges of gene-environment interaction research, and public health (see e.g. Shields *et al.* 2005). In these latter projects I enjoyed the anthropologist's good fortune of extended, open exchanges with geneticists, physicians, exposure scientists, epidemiologists and other researchers who could be honest and eloquent about the limits of their current knowledge and practice, their doubts and questions about their disciplines, and the new scientific endeavours they were reaching for. Since my deCODE project focused on the 'infelicities' of promising genomics – hype, crude simplifications, the manipulation of truth and stock prices – I am grateful to have had this simultaneous stream of alternative ethnographic insight into the other side of genomics' promise.

2 As one example of what such collaborations might look like, consider Michael Montoya's ethnographic portrait of scientists researching the genetics of Type-2 diabetes (Montoya 2007).

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