

The sociable gene

Finding a working metaphor to describe the function of genes in an organism might help to ease public fears and expectations of genomic research

Genes are no longer what they used to be. Once the powerful determinants of our biological and evolutionary fate, their central importance is now gradually being chipped away. At first glance, this may just sound like an interesting puzzle for scientists: How can the gene be placed correctly in the larger context of biology? But it also creates an important challenge when it comes to communicating genetics to the public: How can the role of genes in disease and health be explained to a public who put their faith in biology's ability to improve their lives?

There is no doubt that the effort to map and sequence entire genomes in order to decipher the genetic basis of life has been a brilliant success. Like many scientific successes, however, it has created a host of interesting new problems. And in the case of the Human Genome Project, it has also created a larger irony. While the public expectantly awaits the fruits of post-genomic research in the form of new therapies and better healthcare, their expectations—and some of their attendant fears—may be based on an idea about genes that will not last long in this new genomic world.

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If that is the case, three questions arise. What concept of the gene will biologists end up using? How will it differ from the ideas that now dominate public discussions of genes and their effects? And how can this difference be communicated best to a non-scientific audience? The last question may be especially urgent in view of the prominence of 'gene talk', the common ideas about genes and gene action

that circulate outside the scientific literature, in news stories, movies, cartoons and advertisements.

Often, a conceptual change in science is of minimal interest outside the relevant field. However, according to Karola Stotz from the University of Pittsburgh (PA, USA) and Paul Griffiths at the University of Queensland (Brisbane, QLD, Australia)—both philosophers of science—it is important to scrutinize conceptualizations of the gene because they play roles "both in scientific discourse and in a much larger set of overlapping discourses in bioethics and public policy, in popular science and, ultimately, in contemporary understanding of what it means to be human" (Stotz & Griffiths, 2004).

Historically, it has been difficult to pin down exactly what a gene is or does. Wilhelm Johannsen's first formulation for the term 'gene' deliberately eschewed specificity, offering the word as "completely free from any hypothesis" (Johannsen, 1911). As the anthropologist Margaret Lock from McGill University (Montreal, Quebec, Canada) has said, the gene is a shape-shifter. In fact, the slipperiness of the gene concept, from the days of Mendelian factors onwards, may have been advantageous for science, exactly because it allowed different definitions. But for several decades, the classical molecular gene concept firmly tied structure to function. A gene was a linear stretch of bases in DNA that corresponded to a linear sequence of amino acids in a particular protein. This immensely powerful idea, which held sway from the mid-1950s, was the cornerstone of modern molecular genetics. And as the philosopher Lenny Moss from the University of Notre Dame (IN, USA) argues, it also helped to perpetuate a lasting confusion about what genes do, by encouraging a hybrid notion of the gene that unites a pair of rather different ideas.

Moss suggests that there are two main ways of thinking about genes (Moss, 2003). One, which he calls 'Gene-P', is an association with a phenotype. This was where Mendel began, with his tall or short plants and differently coloured flowers. The other concept, 'Gene-D', is the modern idea of a molecular sequence. It does not strictly determine a phenotype, but rather what Moss calls a developmental resource. Often, though, the two are conflated, most obviously in the frequent headline news of 'genes for' complex traits.

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The classical molecular idea of the gene helped to encourage this simplistic thinking by suggesting that genetic information dictates the structure of the protein product. It is a short, but of course misguided, step from there to supposing that the gene dictates all manner of other things. Although it is unlikely that any thoughtful biologist was ever a genetic determinist in this simplistic sense, popular accounts of genes often come close. This is because they tie up Gene-P with Gene-D in a peculiar blend of the old and new, in a marriage of preformationism and molecular biology.

Today, however, it is harder and harder to maintain that genes determine even a unique protein sequence. The classical molecular concept of 'one gene, one enzyme', embedded in Francis Crick's central dogma, began to unravel with the discovery of reverse transcriptase in the 1970s. Then came introns, exons, jumping genes, alternative reading frames, and the whole machinery of post-transcriptional and post-translational processing. Even before the Human Genome Project was

complete, Evelyn Fox Keller from the Massachusetts Institute of Technology (Cambridge, MA, USA) suggested that the term 'gene' might have become a hindrance to understanding, both for biologists and lay readers, "misleading as often as it informs" (Keller, 2000). Since then, genes have become even more deeply embedded in complex cellular and genomic networks. DNA methylation, microRNAs and a multiplicity of regulatory DNA sequences all alter the context in which the basic genetic information is interpreted.

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However, it is unlikely that anyone will give up the term 'gene' anytime soon. It is too well established in scientific and popular usage. Any issue of *Science* or *Nature* contains scores of references to genes. That leaves scientists and the public with a key term that may mean different things to different people at different times. As Griffiths put it in a recent seminar at the University of Exeter, UK, "There are an awful lot of extremely complicated ways to be a gene." Griffiths, Stotz and their colleagues are now nearing the end of a large project that probes how biologists in different research areas differ in their use of the term. The full results are not yet in, but they already suggest that "what is now known about the variety and complexity of the processes that allow regulated gene expression in living organisms calls for a new understanding of genes" (Stotz *et al*, 2005).

The increasing complexity of the routes from DNA to proteins is not news to scientists. Still, it is useful to look at just one of the cases that Stotz and Griffiths cite, to remember how hard it can be to determine what constitutes a gene. Consider a DNA sequence transcribed into a pre-mRNA. The RNA contains four exons. In this case, there are two splicing sequences, which combine either exon 1 or exon 2 with exons 3 and 4. But this is not just a matter of assembling two proteins in a modular fashion. Exons 3 and 4 are translated in different reading frames, depending on whether they are spliced with exon 1 or exon 2, so the two resulting protein products have few amino acids in common.

So in this example—which describes the human INK4A/ARF (inhibitor of CDK4/ADP ribosylation factor) tumour suppressor region—do we have one gene, or two? And what criteria do biologists use to decide? These and many other problems of annotating DNA sequences already indicate, for example, that developmental and evolutionary biologists tend to conceptualize genes in different ways. The former lean towards Gene-D, whereas evolutionary biologists tend towards Moss's Gene-P concept (Stotz *et al*, 2004). However, the problems also suggest that the classical molecular gene concept still functions as something of a stereotype for most biologists. Departures from it in particular cases are still regarded at some level as exceptions, even though practically every known gene is now an exception.

Thus, the first two questions—how biologists will conceptualize genes and how this will differ in the twenty-first century—are not easy to answer. Nevertheless, it is timely to start thinking about the third question: How to communicate these new properties of genes to different groups. Not surprisingly, after a 'century of the gene', these complexities have been slow to make an impression on the popular media. The old metaphors for genes and genomes, whether they originate in scientific discourse or in popularization or the rhetoric of research promotion, are familiar. Readers learn about the map, the code, the Book of Life, the blueprint, the recipe, the master molecule. And they often get the message that DNA is destiny.

Although it has been correctly pointed out that such renderings of the gene are misleading (Weigmann, 2004), surveys indicate that they continue to dominate journalism about genetic discoveries and their implications (Nerlich & Hellsten, 2004). Some have questioned how much this matters. Studies of readers suggest that they interpret the blueprint metaphor, for example, less deterministically than is often supposed (Condit, 1999). However, there does appear to be an emerging mismatch between the image of the gene in the public realm and recent scientific understanding. If it is desirable to have informed public debate about genetics and its applications, it would be helpful to align these images better.

But it is often still a struggle to find words to summarize what scientists think

they know. The philosophers are doing their best. For example, Hans-Jörg Rheinberger, Director of the Max Planck Institute for the History of Science (Berlin, Germany), suggests that "there is a whole battery of mechanisms and entities constituting what could be called hereditary respiration, or breathing" (Rheinberger, 2000). This, although charmingly poetic, is not really concrete enough to be an aid to understanding. Nor are journalists going to have much time for Gene-P and Gene-D. And offering non-scientists one of the neat formulations stating that genes are "things the organism can do with its genome" may not leave them feeling much better informed.

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Another way to sum up the significance of all the new findings about the complexity of what is going on inside cells is to suggest, in Griffiths' words at the Exeter seminar, that "In the post-genomic era, agency is being relocated to the genome as a whole and perhaps beyond." This is a nice way of reducing the dizzying details of all that tagging, splicing, signalling and switching, but is still too philosophical to achieve wide currency. What will really be needed to do the job are some new metaphors that convey the interactivity, fluidity and dynamics of genomic systems. As ever, if they are well chosen, they may be a stimulus to scientific thinking as well as an aid to science communication.

As the whole of post-genomic biology is something of a moving target, it is too soon to say which metaphors will be the best ones to choose. But there are probably enough on offer to select a short-list. After all, there are only so many different ways to think about a complex situation, and only so many things to which a living system might be similar. The ones that have been offered so far are musical, ecological and social metaphors.

The musical variations may not get very far, as they are still rooted in a static concept of information. The DNA becomes a musical score instead of a linguistic text

and can be interpreted or used to govern an orchestration. But it is not an interactive or dynamic image.

John Avise from the University of California (Davis, CA, USA), reflects on the increasingly complex roles of transposable genetic elements in genomic evolution and regulation and has therefore advocated both the social and ecological pictures. Perhaps one can see the genome as a commune, he suggests—a tightly bound organization with an intricate division of labour (Avise, 2001). Or, harking back to an image first used by Lewis Thomas in the 1970s to depict the cell (Thomas, 1974), it might be helpful to liken the genome to an ecosystem in which different genes fill different niches.

Other possibilities draw on systems biology and focus on the properties of networks. A road network, for instance, is interconnected in ways that offer many different routes from A to B. An individual gene might then be like a single road. Block it, and the traffic may still get through, although by a more circuitous path (McFadden, 2005).

Probably the most striking image so far comes from Moss. He considers two stages of gene expression that are regulated by impressively large assemblies of molecules. First is transcription, in which the precise selection of exons for an RNA transcript depends on the presence or absence of a variety of transcription factors, which interact both with DNA and RNA polymerase. The second is post-transcriptional splicing, which is the task of the spliceosome, an intricate array of five small nuclear RNAs and as many as 150 separate proteins.

The scientific account of these operations has been built up by painstaking work over decades, and their sensitivity and exquisite modulation is still hard to grasp. Whole popular articles about the spliceosome, for instance, are now appearing that, although admirably clear in exposition, largely eschew memorable metaphors (Ast, 2005). Moss has one, though. The “decisions” about the final configuration of the mRNA are taken on the path from DNA to protein by “ad-hoc committees” (Moss, 2003). Think of each committee, he suggests, as a constituent assembly. The more members it has, the more information they can all draw on about the recent history of events in the cell, and its interactions with other cells. The committee is a way of pooling experience before a kind of consensus is reached about what to do next.

This is all very anthropomorphic, to be sure, but seems promising in several respects. These cellular assemblies create an image of a dynamic and flexible operation that is, like some human committees, wiser than any of the individual parts. It is only the beginning of what will be a long-running literary task, but the ad-hoc committee may win a niche as one of the metaphors of choice for conveying a new sense of how genes—and the cells in which they exist—work.

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The prize of discovery

In identifying exciting research and individual excellence, prizes have an important, although often neglected, role in science

These are the words every scientist would be happy to hear: “This is your cheque. And this is your diploma.” Thus spoke Nobel laureate Rolf Zinkernagel, when handing over the 2005 Louis-Jeantet Prize for medicine to Alan Hall and Svante Pääbo at the Jeantet Foundation premises in Geneva, Switzerland, this April. Hall, Director of the Medical Research Council Laboratory for Molecular Cell Biology and the Cell Biology Unit at University College, London (UK), received the prize for his “pioneering work on the regulation of cytoskeleton dynamics in cell adhesion, migration and polarity”. Pääbo, Director of the Max Planck Institute for Evolutionary Anthropology in Leipzig (Germany), was rewarded for “his innovative research on the evolution of the human genome in comparison to that of other primates”.

Among all scientific prizes, the Nobel is king, topping others in nearly every aspect. It is the most prestigious, has the largest scientific committee, receives the most public attention, awards up to a million US dollars and is handed over by the King of Sweden. Nevertheless, scientific prizes come in all shapes and sizes, ranging in value from a token amount of money to a million euros or US dollars. Some are awarded during small ceremonies; others celebrate the winners in front of huge audiences. Many prizes are given for a specific discovery or contribution to a particular research field, whereas others are awarded for a scientist’s life work or for contributions to society. Most prestigious prizes are international, but a large number of prizes award excellence on a national level. The Ig Nobel Prize, sponsored by the journal *Annals of*