contrary to the gas-accretion case, the velocity dispersion of the final galaxy's stars remains unchanged, or changes little if the mass doubling is achieved through a sequence of several smaller mergers of gas-poor galaxies[7]. Either way, the merging process leaves behind a black hole that is more massive than would be predicted from the mass–velocity dispersion relationship — just like the two black holes observed by McConnell and colleagues[3].

Not everybody agrees that the observed mass–velocity dispersion relationship indicates that black holes regulate galaxy growth by stopping gas accretion with their energy production (Fig. 1a). Studies[8,9] have shown that starting from a set of galaxies containing black holes of random masses, a sequence of mergers can lead to a relationship close to the observed one without the need for energy input from the black hole. However, this simulated relationship deviates systematically from the observed one. These claims[8,9] can be tested by accurately measuring black-hole masses in galaxies with different properties, as McConnell *et al.* did. Progress requires the largest telescopes and the use of state-of-the-art technologies such as integral-field spectroscopy, to map the motion of the stars in two dimensions, and adaptive optics, to correct the blurring effect of Earth's atmosphere and achieve sharp images[10]. The future looks bright for black-hole studies using the next generation of 40-metre telescopes, such as the European Extremely Large Telescope, which will significantly increase the number of galaxies that can be reliably investigated. ■

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GENETICS

Noise rules

The idea that gene variants alone control an organism's traits is overly simple. A study of the effects of gene interactions on the outcomes of random variation in gene expression reveals the complex reality. SEE LETTER P.250

HANA EL-SAMAD & JONATHAN S. WEISSMAN

Ever since Gregor Mendel and Thomas Morgan crystallized the idea of the gene as the heritable unit, biologists have been trying to map the relationship between genotype (the complement of gene variants present in an individual) and phenotype (an individual's physical characteristics). On page 250 of this issue, Lehner and colleagues[1] provide insight into the complexity of this relationship by showing how random variation in the expression of members of pairs of interacting genes can act synergistically to affect the development of a complex organism — the roundworm *Caenorhabditis elegans*.

Notable advances in DNA sequencing during the past few years have made it possible to define the genotype of any individual rapidly and cheaply. As a result, scientists glibly talk about the possibility of pinpointing individual genes that influence every aspect of our being, from our propensity to get cancer to our chances of living to be 100 years old. However, this appealing vision oversimplifies a much more complex reality. There is no one-to-one relationship between genotype and phenotype — even identical twins can have radically different personalities, disease susceptibilities and life trajectories.

Although many factors contribute to the mapping of genotype to phenotype, the influence of two of these is especially challenging to account for. The first is 'noise' — the molecular fluctuations inherent in biological systems that cause random switching of genes on and off. The second is that genes do not act alone, but work together to form functional cellular networks. That results in complex genetic interactions in which the phenotypic impact of a particular variant (or allele) of a gene is dependent on an individual's full genetic make-up. For example, it is not uncommon for individual alleles to be beneficial on their own, but lethal when two copies are present.

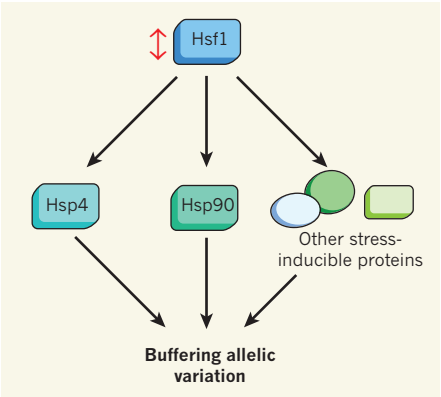

Figure 1 | Noise regulons and gene expression. Noise regulons are synchronized stochastic changes in functionally related genes, and are coordinated by an upstream signal. In this example, fluctuations (red arrow) in the expression of the transcription factor Hsf1 cause the coordinated expression of stress-response proteins, including the molecular chaperones Hsp4 and Hsp90. These proteins then cooperate to buffer the effects of a mutant allele. Such a mechanism helps explain why loss of *tbx-9* in *C. elegans* causes abnormal development in only half of the worms affected by this mutation, a phenomenon studied by Lehner and colleagues[1].

Alone, either of these factors could generate an elaborate relationship between genotype and phenotype, but there is inevitably a complex interplay between the two. Lehner and colleagues' study[1] examines this interplay. Previous work[2] has investigated how noise in gene expression influences the effects of a defective allele of the *C. elegans skn-1* gene. Notably, the *skn-1* mutant allele leads to defects in intestinal development in some, but not all, individuals; such incomplete development of a phenotypic trait is known as partial penetrance.

Using a clever approach (known as fluorescence *in situ* hybridization) that enables the exact number of RNA molecules in a cell to be counted, this study[2] established that random fluctuations in certain factors lead to a variable 'all-or-none' expression of the transcription factor gene *elt-2*, which is dependent on *skn-1*. In wild-type worms, the system is robustly buffered against such fluctuations. But in the *skn-1* mutants, the variability is unleashed, so that *elt-2* is not activated in some cells, hence preventing normal development of the gut. These results illustrate how quantitative fluctuations in upstream components of a signal-transduction system can lead to qualitative differences in a downstream developmental event.

Lehner and colleagues[1] further explore the impact of stochastic fluctuations on the partial penetrance of a mutation, while also examining their interplay with the gene network in which the mutant allele is involved. In particular, the authors address the question of how fluctuations in factors expressed early in development affect subsequent developmental switches. This necessitated the development of a new experimental strategy, because in the previous work[2] the worms were killed to measure messenger RNA levels, thereby precluding the observation of later developmental events.

The authors[1] used transcriptional reporters — in which a second copy of the gene of interest drives the expression of a fluorescent protein — to follow variations in gene expression in live worms. A key requirement of this approach (verified by the authors) is that fluctuations in expression of the reporter accurately reflect fluctuations in expression of the endogenous genes. This means that the reporter is tracking expression noise resulting from differences in cellular environment — extrinsic noise[3] — rather than the random turning on and off of individual promoters.

Lehner and co-workers first investigated why mutations in the T-box transcription factor gene *tbx-9* that completely abolish the gene's function cause an incompletely penetrant defect in *C. elegans* larval development: roughly half of the animals lacking *tbx-9* develop normally; the other half have muscle and epidermal defects. The authors observed that overexpression of *tbx-8* — a gene closely related to *tbx-9* — eliminates the defects caused by loss of *tbx-9*. What's more, loss of *tbx-9* in their mutants caused upregulation of *tbx-8*.

More strikingly, the authors observed that differences in *tbx-8* expression were a strong predictor of the phenotypic effects of *tbx-9* loss — *tbx-9*-mutant worms that expressed *tbx-8* at a low level were considerably more likely to develop abnormally than were genotypically identical individuals that expressed *tbx-8* more strongly. Thus, stochastic differences in the feedback loop that compensates for *tbx-9* loss by upregulating *tbx-8* contribute to the variable penetrance of the *tbx-9* mutation. Lehner and colleagues observed a similar set of effects with the transcription factors *flh-1* and *flh-2*, which, like *tbx-8* and *tbx-9*, are a pair of related genes that resulted from ancient gene duplication. This type of noisy feedback between related genes may therefore be quite common.

Although these findings represent a step forwards, the variability of *tbx-8* expression could not fully account for the variable penetrance of the *tbx-9* mutation. What, then, is the source of the remaining variability? Molecular chaperones — proteins that assist other proteins in folding — can buffer a wide range of cellular defects, especially the Hsp90 chaperone[4] (also known as DAF-21 in *C. elegans*). Lehner and co-workers therefore investigated random fluctuations in chaperone levels in individual worms as a possible explanation of the missing variability. They found that fluctuations in expression of *daf-21* were a strong predictor of the effects of *tbx-9* loss. Importantly, the effects of the differences in *tbx-8* and *daf-21* expression were independent of each other but synergistic: more than 90% of worms with high levels of *daf-21* and *tbx-8* expression developed normally, whereas roughly two-thirds of the animals in which expression of both genes was low did not.

Lehner and colleagues found that the observed variability in penetrance of *tbx-9* loss in their study can, to a remarkable degree, be accounted for by variations in expression of *tbx-8* and *daf-21*. This, in turn, raises the question of what underlying mechanisms in the cell cause the observed variability and how many other genes are affected by these fluctuations. In the case of *daf-21*, the authors show that the fluctuations are probably part of coordinated changes in the expression of a broad range of chaperone genes, including one known as *hsp-4*. Such 'noise regulons' — synchronized stochastic changes in functionally related genes — are particularly suitable for causing coordinated effects on cell physiology, because the related genes act together to carry out common functions[5] (Fig. 1). However, the authors did not find evidence that fluctuations in *tbx-8* expression correlate with variations in the expression of chaperones, and it may be that there are no other genes whose noise co-varies with that of *tbx-8*. A more tantalizing possibility is that variations in the expression of *tbx-8* also reflect a coherent cellular state in which other members of the *tbx-8*/*tbx-9* pathway fluctuate in unison. This raises the further question of how many such noise regulons exist, and what controls their activity.

More broadly, it is clear from recent studies[1,2] that stochastic fluctuations can have a big impact on the penetrance of gene alleles. A better understanding of the structure of noise — which genes tend to fluctuate together, and how these fluctuations are controlled — should provide crucial insight into the nature of the genotype–phenotype relationship. ■

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MATERIALS SCIENCE

A sense for touch

Will a sense of touch similar to that of humans ever be developed in robots? Results on the physics of friction for fingerprint-like ridges sliding across textured surfaces may lead the way to tactile robotic sensors.

C. MATHEW MATE & ROBERT W. CARPICK

When we rub a finger across a surface, our sense of touch is remarkably adept at distinguishing between different textures[1]. For example, astute clothes shoppers can easily feel the difference in texture between cotton and lower quality polyester fabrics, just as experienced cashiers can spot counterfeit banknotes from the feel of the paper. Writing in *Physical Review Letters*, Wandersman *et al.*[2] provide a major advance towards understanding the physics behind these tactile sensations, showing how a modulated frictional signal is generated by fingerprint-like ridges rubbing against the roughness of an opposing surface. This improved understanding of the relationship between friction and surface textures should have an impact in many areas, but particularly in the field of tactile sensors for robotic design. Incorporating sensors capable of mimicking the human sense of touch has long been recognized[3] as important for improving the ability of robots to grasp objects firmly without damaging them.

Wandersman *et al.*[2] present measurements and analysis of the tangential or friction force generated as a rubbery elastomer block with periodic surface ridges slides over a rough glass surface. The ridges on the elastomer surface, which have periods ranging from 125 to 760 micrometres, serve as stand-ins for the epidermal ridges on human fingers (Fig. 1a). They show that, when pressed against the glass surface to form contact regions several millimetres in diameter, the elastomer deforms around the rough surface texture in the same way as the epidermal ridges would if pressed against such a surface.

With numerous ridges in contact, one might expect that any periodic variation in the friction force due to these ridges would average out; indeed, this can be shown analytically if the friction force generated in each microscopically small area in contact (much smaller than the width of a ridge) is strictly proportional to the local normal or loading force pressing the two surfaces into contact over this area. This linear relationship between the friction and load forces is usually referred to as Amontons' law of friction[4], which states that the friction force, F, is proportional to