The genomic cosmos

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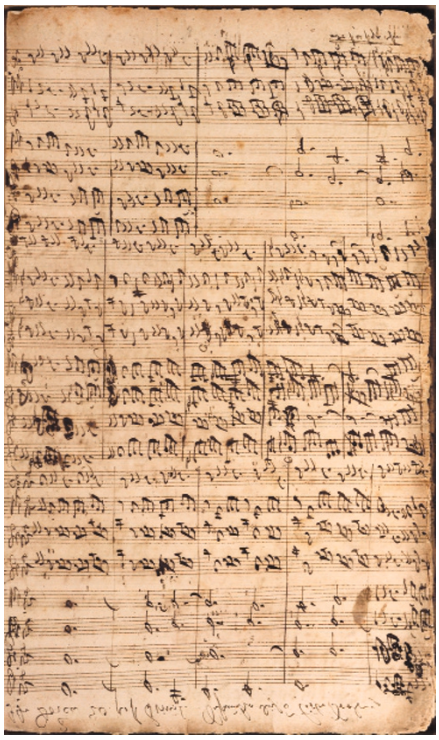
The genetic screen provides an ideal tool for establishing a pan-genomic phenotypic compendium. Experimentally, it begins by showering germ cells with a mutagen such as a chemical, radiation or virus. Over ensuing generations, appropriate breeding schemes bring the mutant phenotype into view, and those of interest are selected and isolated. All regions of the genome are believed to be equally accessible to many mutagens. Smaller genes may be hit less often, but ultimately none is invincible if the screen is large enough. Genetic screens, if of sufficient size, therefore examine the roles of all genes in a genome.

It's amazing that the genetic screen works at all. First, at least in higher metazoans, most genes are used in multiple locales and several stages of development. A phenotype of interest may be buried and confounded by widespread disarray, or not even have a chance to appear because of premature death. Second, many important processes have molecular back-ups, so redundant systems compensate for individual mutations.

But screens have succeeded. First, when done in a large-scale way, to 'saturation', by their all-inclusiveness they have provided a logic, a sense of what can go wrong. Perhaps this is not surprising for single-cell organisms, but many were surprised by just how informative were large-scale screens done on the fruitfly *Drosophila*. These screens proved that the parts of the body plan are not so inextricably linked to each other as to prevent analysis of embryonic development. Individual mutations can perturb single embryonic segments, or patterns of segments, without causing total chaos. The large-scale genetic screens in zebrafish reveal modular elements even to the assembly of vertebrate organ form and function, such that a mutation can delete one chamber of the heart but leave the rest of development relatively untouched.



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In tune? Interpretations of genetic screens can be woven together as in a Bach canon.

This biological logic is revealed by screens even before the cloning of the mutant genes. That embryonic body plan can be dissected as a hierarchy of axial and segmental pathways was intuited from mutant phenotypes isolated in a large-scale *Drosophila* genetic screen well before discovery of the molecular identity of the mutations.

The second level of success occurs after mutation cloning. Each mutation discovered can provide an entrance point to a biochemical pathway. The other components of the pathway may have eluded the screen because their mutations caused no informative effects. But having the one molecular handle provides the needed molecular entrance point. Other elements are accessible by other methodologies. The biochemical intricacies of cell death, for example, have been revealed over the years by biochemical or genetic means in many species, but originated in the genetic screen-based revelation of the *ced* genes in the nematode worm *Caenorhabditis elegans*.

The interpretation, and indeed power, of a screen is observer-dependent. There are many possible thematic interpretations of a screen, all woven together as in an Escher print or Bach canon, and none is most 'correct', although some can provide more experimentally useful predictions than others. Even the defined phenotype for any given mutation reflects but one part of the function of the gene, the one that happens to be most prominent or fall in the field of focus of that particular scientist. Rashomon-like, what is deemed distinctive and important by one observer may go unnoticed by another.

The name given to the mutation reflects this bias of the discoverer. Provision of the gene's moniker may seem poor recompense for hours spent sorting and breeding embryos. But, as Umberto Eco noted of Adam's role in Genesis, there is tremendous power to the Nomothete, the name-giver, the person who creates the language to describe the biological universe. Unlike Adam, the screener's chosen name rarely reflects divine inspiration. Some, such as *notch*, may coldly reflect the phenotype; others, such as *groucho* or *heart of glass*, taste in comedians or rock and roll. Hence, embedded in the name is a bit of scientific folklore, seeming flippant to the formal-minded but endearing to the *cognoscenti*.

What is the future of screens? Methodologically, some will be less random. With all genes defined and, at least in some species, tools to incapacitate them one-by-one (RNAi, morpholino antisense), it will be possible to march along chromosomes percussing each gene for phenotypic resonances. Chemicals can phenocopy mutations and even reveal pathway components that are not accessible in genetic screens, and large-scale screens using small molecules are under way. In terms of the biological targets of screens, so far most have been related to embryonic development. But there are many opportunities for expansion into other arenas. There are already hints from *Drosophila* and zebrafish that the ontogeny of physiological functions, heart-rate control for example, may be tractable to screen methodology. Obviously, molecular understanding of essential function and homeostasis also generates candidate genes for complex diseases. In so far as physiological adaptability provides an umbrella for mutation accumulation, these screens also may illuminate essential components of evolution.

Thus, like Borges seeking to classify and order his universe, which he likened to a library of Babel, our goal no longer is to catalogue the letters on the spines of the books, which we know from the genome projects, but rather to decipher the volumes' phenotypic content. Recent successes indicate that future screens will indeed reveal the overarching logic, order and component units to this universe of phenotypic possibilities. ■

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Genetic screens

"An organism's genome is but a pale non-homuncular image of its universe of biological functions. How can we scan the true biological universe, that of the cosmos of phenotypes?"

FURTHER READING

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