

GENETICS

Our Fallen Genomes

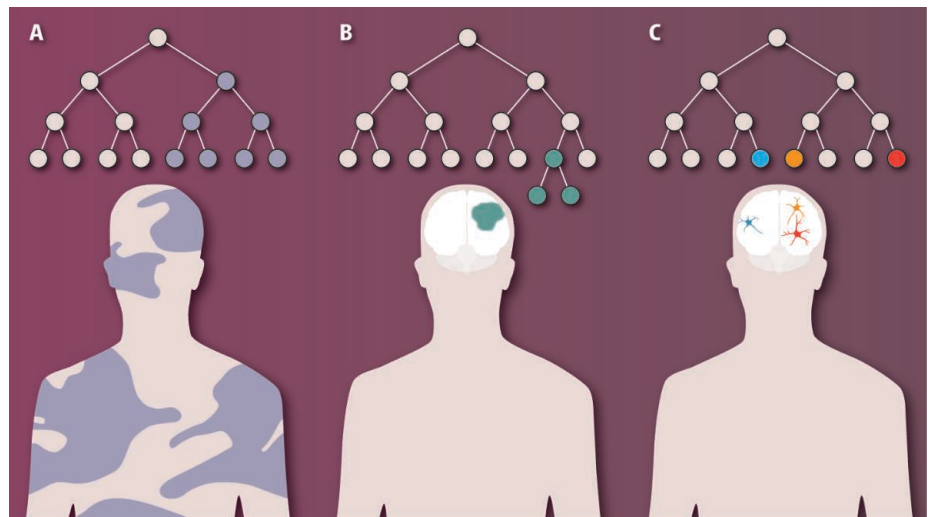
Evan Z. Macosko^{1,2} and Steven A. McCarroll^{1,2}

Few human conceits are as relentlessly undermined by science as humans' naïve assumptions about our own perfection. Charles Darwin abolished one such set of assumptions by showing that "inferior creations" are man's evolutionary cousins. However, Darwin's theory of evolution ultimately abetted a modern conceit—that the genomes in our cells are highly optimized end products of evolution. Genome sequencing is now challenging this view on many levels. On page 632 of this issue, McConnell *et al.* show that somatic mutations are abundant in neurons in the human brain (1).

It is often assumed that genome sequencing will explain disease cases by revealing the causative genetic blemish—the mutation that stands out on a background of otherwise flawless molecular function. But whole-genome analysis shows that dysfunction abounds. Rare and common structural variants, including deletions of long genomic segments, pervade every genome (2). Each human genome also harbors an average of 120 gene-inactivating variants, with about 20 of these genes being inactivated in both copies (3). Far from pinpointing single mutations on a background of perfect function, genome sequencing has instead generated its own needle-in-a-haystack problem: distinguishing the variants that truly matter to an illness from the far-larger number of functional variants that are present in every genome. It is now clear that, beyond simple, monogenic disorders, understanding complex disease will require sequencing thousands of genomes and ascertaining the patterns shared among the genomes of many affected individuals (4).

Many studies are now also finding that genomes are themselves transmitted to individual cells with large apparent mistakes—somatically acquired deletions, duplications, and other mutations. These results have been most clear for disorders involving cellular proliferation, which allows clonal expansion of a mutated genome. The blood of many individuals becomes increasingly clonal with age, and these expanded clones often contain large deletions and duplications; this clonality is a risk factor for developing cancer later

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Transmitting genomes. Deletions, duplications, and other mutations may arise at different places in a developmental lineage. (A) Mutations that arise early in development may cause large-scale somatic mosaicism in the body. (B) Mutations that cause cells to proliferate may lead to detectable somatic mosaicism, even if they arise later in development. (C) Mutations that arise late in development may be unique events in individual cells.

in life (5, 6). Disorders involving hypertrophy and proliferation can also arise from somatic mutations that activate cell-growth pathways (7–9) (see the figure), such as a brain overgrowth syndrome arising from somatic gain-of-function mutations in the *AKT3* gene.

What about apparently normal cells in healthy adults? Such cells may be more likely to harbor large, somatically acquired copy-number variations (CNVs) than is generally thought. For example, 30% of skin fibroblast cells may have somatic CNVs in their genomes (10). In brain, in situ experiments have suggested that large-scale copy-number changes exist in individual cells (11, 12).

McConnell *et al.* have used single-cell genomic analyses to deal another blow to humans' tendency to draw idealized models about how our biology works. The authors first explored genomic variations in individual neurons derived from human induced pluripotent stem cells (hiPSCs). The amplified genomes of individual cells were hybridized to single-nucleotide polymorphism arrays, revealing several CNVs. All 17 of the genomic changes observed were "singletons"—none were present in multiple neurons from the same hiPSC line.

McConnell *et al.* then looked at postmortem brain tissue from the frontal cortex, a

A human brain can cope with many genomic variations scattered among its neurons.

region that has been examined for aneuploidy and other forms of somatic genetic variation (11, 12). They sequenced the genomes of 110 individual neurons from three different brains, revealing somatic CNVs in almost half of the neurons. These deletions and duplications ranged from about 3 Mb to an entire chromosome in size. A small subset of the neurons—approximately 15%—accounted for 73% of the identified CNVs.

As with the CNVs observed in reprogrammed neurons, the CNVs observed in brain-resident neurons were singletons—none appeared to represent an early developmental event. It is possible that in other individuals, such mutations arise earlier in the developmental lineage and become present in a substantial fraction of cells. Such mutations could be part of the genetic architecture underlying intellectual disability, developmental delay, and the more severe, syndromic forms of autism—although somatic mutations seem less likely to explain substantial fractions of highly heritable disorders such as schizophrenia and bipolar disorder.

The observations of McConnell *et al.* may relate to other recent discoveries about how mitotic cells replicate their genomes. Cells replicate the transcriptionally active parts of their genomes in careful, structured,

deliberate ways, then hurry through the replication of transcriptionally silent chromatin (13). Replication errors, including both point mutations and larger CNVs, tend to be concentrated in this late-replicating DNA (14). One implication is that cells are most careless about replicating the parts of their genomes that they are not using. An important direction will therefore be to ascertain the extent to which somatic CNVs affect genes that neurons use, and how these mutations influence the cells' physiological properties.

The brain may be an organ particularly able to cope with scattered genomic eccentricities at the single-cell level. Developmental processes in the brain generate an overabundance of connections, then prune syn-

apses that do not contribute to functional circuitry. Dysfunctional neurons may be given minimized roles in mature circuitry; it is even conceivable that eccentric neurons are creatively incorporated. Although the somatic mutations observed in individual neurons may undermine our sense that neurons should be the most flawless of human cells, we should remember that the great accomplishments of human cognition are in the emergent properties of billions of cells working and rewiring in dynamic ways.

We are often advised “not to let the perfect be the enemy of the good”—to accept a flawed product, in the name of finishing and getting on to the next task. It seems that this is a practice that nature adopted long ago.

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ECOLOGY

Dust Unto Dust

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In the past, great civilizations have fallen because they failed to prevent the degradation of the soils on which they were founded (1). The modern world could suffer the same fate at a global scale. The inherent productivity of many lands has been dramatically reduced as a result of soil erosion, accumulation of salinity, and nutrient depletion. In Africa, where much of the future growth in agriculture must take place, erosion has reduced yields by 8% at continental scale (2), and nutrient depletion is widespread (3). Although improved technology—including the unsustainably high use of fertilizers, irrigation, and plowing—provides a false sense of security, about 1% of global land area is degraded every year (4). As Fierer *et al.* show on page 621 of this issue, the diversity of soil biota in the prairie soils of the American Midwest has changed substantially since cultivation (5). We have forgotten the lesson of the Dust Bowl: Even in advanced economies, human well-being depends on looking after the soil (6). An intact, self-restoring soil ecosystem is essential, especially in times of climate stress.

Soil fertility—the capacity to sustain abundant plant production—was a mystery to the ancients. Traditional farmers speak of soils becoming tired, sick, or cold; the solution

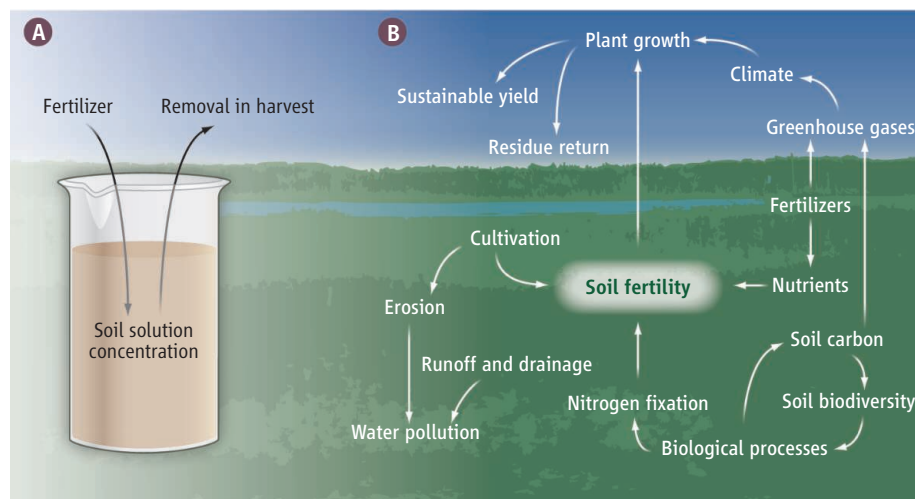
was typically to move on until they recovered. Enlightenment science brought the insight that plant growth combined carbon dioxide from the air with water and nutrients from the soil. By the mid-20th century, soils and plants could be routinely tested to diagnose deficiencies, and a global agrochemical industry set out to fix them (7). Soil came to be viewed as little more than an inert supportive matrix, to be flooded with a soup of nutrients.

This narrow approach led to an unprecedented increase in food production, but also contributed to global warming and pollution of aquifers, rivers, lakes, and coastal ecosystems. Activities associated with agriculture

Modern agriculture diminishes the diversity of soil biota, thereby reducing long-term soil fertility.

are currently responsible for just under one-third of greenhouse gas emissions; more than half of these originate from the soil (8). The eroded sediments and excess nutrients drain into rivers. Diminishing freshwater quality is a constraint on human development in many places, and freshwater biodiversity is the most threatened on the planet (9). Replacing the fertility-sustaining processes in the soil with a dependence on external inputs has made the soil ecosystem, and humans, vulnerable to interruptions in the supply of those inputs, for instance due to price shocks.

The key to understanding the behavior of life-supporting elements such as car-



Soil complexity. Soil fertility management still largely follows a simplistic chemical model (A). Sustainable agriculture requires a more complex view that includes soil biodiversity (B), as shown by Fierer *et al.*



Editor's Summary

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