GENETICS

Herit-Ability

A genome-wide association study reveals possible variants that influence the complex behavior of educational attainment.

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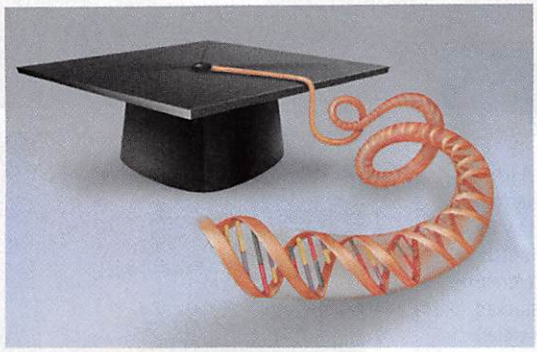
Studies of the genetic basis of human behavior have a history of generating controversy. For example, when studies of identical and nonidentical twins were first used to estimate the proportion of variation in income and years of schooling that can be attributed to genetic variation (in other words, the heritability of going to university and becoming rich) (*1*), one response was that the estimates were "pointless" and that determining the heritability of socioeconomic achievement measures should be abandoned (*2*). Yet, on page 1467 of this issue, Rietveld *et al.* (*3*) claim progress toward identifying genes underlying variation in educational attainment. How should these findings be interpreted, given that similar claims in the past have often not borne out (*4*, *5*)?

Behavior, like other complex traits (such as height and weight), may arise in part from the combined action of hundreds, if not thousands, of individual tiny genetic effects across the genome (*6*). Efforts to locate the contributing variants have proceeded through (unsuccessful) family studies involving the search for the coinheritance of trait and genetic markers, and through candidate gene studies (also generally unsuccessful) focused on genes thought to be involved on the basis of known or presumed neurobiology. Genome-wide association studies (GWAS) test whether a trait is associated with variation at any one or more of hundreds of thousands, or even millions, of markers. There is a consensus that for nonbehavioral traits, GWAS works well, with the caveats that it only finds a small fraction of the loci involved and does not capture all forms of genetic variation (*7*, *8*). However, with notable exceptions (*9*), GWAS of behavior has not had the success achieved for GWAS of weight, height, and diseases.

Perhaps this is because behavior is not genetically regulated like other traits. It could be that a large proportion of the predisposition to autism and schizophrenia is due to extremely rare variants, some arising de novo, which would be undetectable with GWAS methods (because these use only known, relatively common types of genetic variation) (*10*). Alternatively, the genetic effects on behavior might be even smaller and more numerous than suspected and therefore evade detection (*11*).



Achievement genes? Analyses of a genome-wide association study reveal genetic variants that are linked to educational achievement, but each with a very small effect.

The results of Rietveld *et al.* provide some answers. The contribution of each genetic locus to variation in educational attainment (defined in the study as years of schooling and the completion of college) is particularly small. The effect attributable to a locus is much smaller than for physical traits, and only just detectable with the enormous sample employed (about 126,000 individuals). The largest estimated effect (0.02%) is an order of magnitude smaller than those reported for height (0.4%) (*12*) and weight (0.3%) (*13*). However, that finding alone cannot explain the overall contribution of small effect loci. For this purpose, another observation is important.

Suppose that there are only 10 loci contributing to the genetic variation, and that they are the top 10 signals in the GWAS, each contributing 0.02%. If all 10 signals are combined to create a new predictor, one can ask how much of the variation in a new cohort the combined 10 variants explain. This is known as a polygenic score method (*14*). If the correct 10 variants are selected (and some other assumptions are made about similar allele frequencies), the polygenic score in the new population would be expected to account for about 0.2% of the variance (10×0.02). Now suppose that there are hundreds, perhaps thousands, more variants that contribute. Adding these additional variants to the 10 will increase the ability to explain variation in the trait, whereas if only the 10 variants are contributing, then nothing will be gained, however, many additional variants are combined. As shown by Rietveld *et al.*, the more variants are added, the better the prediction. In short, educational attainment looks to be a very polygenic trait.

But why are the effects so small? Is this just because of the poor quality of the measurement in this, and other behavioral studies (*15*)? To some extent, Rietveld *et al.* concede this point. They argue that the GWAS effort might progress by capitalizing on the wide availability of very crude phenotypic measures, such as years of education, to identify genes robustly associated with an outcome of broad social relevance. These genes can then be further analyzed with the knowledge that they are associated with something, even if it isn't known exactly what or how.

The argument that whole-genome methods should inform candidate gene approaches (*16*) has demonstrated utility. Indeed, heaviness of smoking has been robustly associated with variation on the long arm of chromosome 15, using measures of number of cigarettes smoked that are widely available across a large number of cohorts (*9*). This phenotype can be very precisely measured, but is nevertheless a very imprecise measure of actual tobacco exposure, largely because of interindividual variability in how those cigarettes are smoked (*17*). Because nicotine consumption is most likely under the strongest genetic control (*18*), more direct measures of nicotine (and therefore tobacco) exposure provide a much more precise assessment of the strength of genetic association (*15*), while at the same time elucidating the likely mechanistic pathway.

The data from years of education make it possible for Rietveld *et al.* to test the importance of trait measurement, because educational attainment was measured in different ways, sometimes with a brief questionnaire, sometimes in more detail. There was no evidence that genetic effects are weaker in cohorts with coarser measures, which the authors argue is consistent with the view

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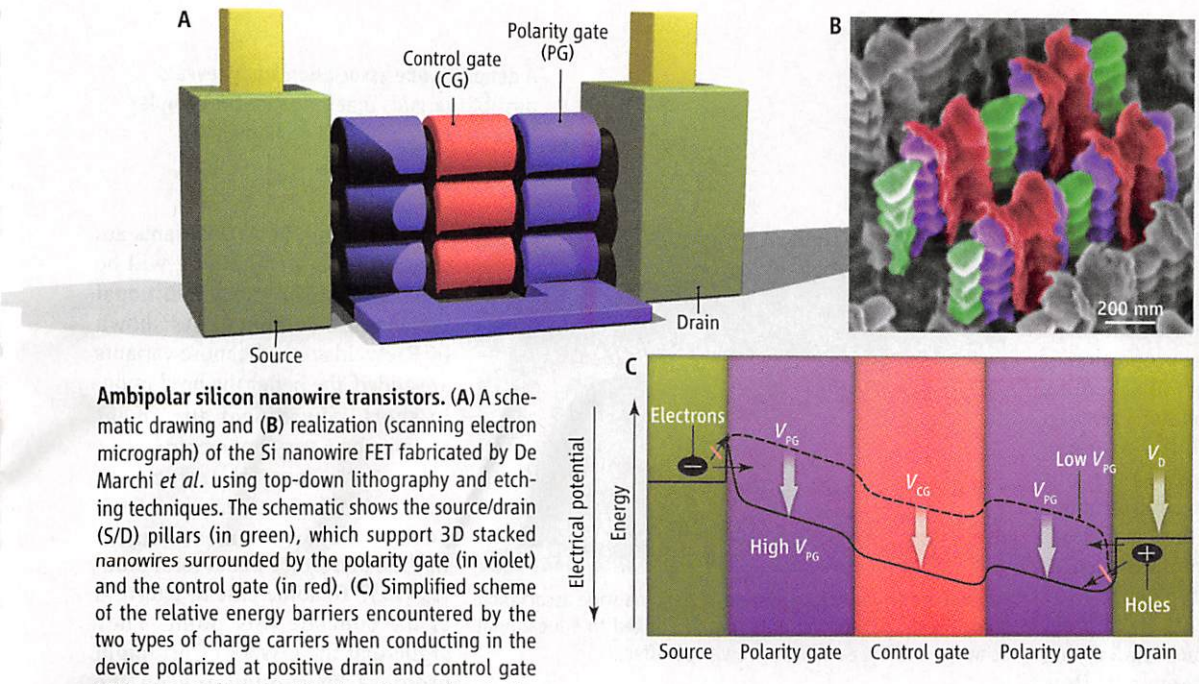

Ambipolar silicon nanowire transistors. (**A**) A schematic drawing and (**B**) realization (scanning electron micrograph) of the Si nanowire FET fabricated by De Marchi *et al.* using top-down lithography and etching techniques. The schematic shows the source/drain (S/D) pillars (in green), which support 3D stacked nanowires surrounded by the polarity gate (in violet) and the control gate (in red). (**C**) Simplified scheme of the relative energy barriers encountered by the two types of charge carriers when conducting in the device polarized at positive drain and control gate (CG) voltages (for simplification, the semiconductor energy band gap between electron and hole energy is not represented). The type of carriers when selected by the polarity gate potential (V_{PG}) can tunnel at the barrier near the metallic source (or drain) and the semiconductor. Adapted from (*1*).

tor is briefly annealed at high temperature (~1000°C). The dopants provide the type of charge carriers needed for the conduction: electrons (n-type) or holes (p-type), virtual positive charges that represents the displacement of a lack of electrons.

Because n- and p-type devices use opposite charge carriers, they conduct (are in the ON state) for opposite voltages applied on the control electrode (gate) V_{CG} (see the figure, panel C). This association of two complementary devices is required for basic logical functions (performed by logic gates). The simplest example is the NOT function (an inverter) that converts a positive voltage to zero, and vice versa. Digital computing combines these simple operations into many more complex logical operations.

Not all devices are limited to a single conduction mode. Ambipolar MOS transistors conduct with both electrons and holes by replacing the n- and p-type doped regions used as source (S) and drain (D) with a metal that can provide both types of conduction. A metal in contact with a semiconductor creates a Schottky junction, whose conduction depends on the energy barrier naturally created between both sides of the metal-semiconductor contact (see the figure, panel C). A low barrier height is needed at the source side to induce large quantum tunneling currents in the ON state through the barrier. Meanwhile a relatively high complementary barrier is needed to suppress leakage current from the "reverse" tunneling by carriers of opposite signs at the drain in the OFF state.

De Marchi *et al.* tuned the barrier height in their devices by introducing a polarity gate near a nickel silicide (NiSi)–Si Schottky junction. The barrier height, which is low for the selected carriers in the ON state, is high for the other type of carrier and prevents any parasitic current leakage in the OFF state. Thus, the fabricated device has a polarity gate, which selects the type of carrier (electrons or holes) in the transistor, in addition to the standard control gate that determines conduction.

Previously, two metals have been used to form different (but static) energy barrier heights to block one type of carrier and let the other type through, for example, with platinum silicide for p-type MOSFETs (PMOS) and erbium silicide for n-type MOSFETs (NMOS) (*5*). Several advantages arise when the Schottky barrier is tuned instead electrostatically (*6*). First, the new device is "intelligent" as a reconfigurable (n or p) switch but also embodies a logic gate (exclusive OR). This opens new ways to design circuits (*7*). Moreover, this approach, with only one type of metal, can be useful for several emerging semiconductor materials when the contact technology remains a problem, as already demonstrated for carbon electronics (*2*–*4*). In other respects, the elimination of dopants drastically reduces the maximum processing temperature needed, which paves the way toward stacking independent transistor layers, or 3D integration (*8*).

Nevertheless, many questions should still be answered to make this structure with three gates perform well. If some basic figures of merit for transistors are considered, the additional polarity gates will introduce parasitic capacitances, serial resistances, and area consumption. Thus, logical functions need to be designed completely differently to maintain the targeted performances, such as low consumption and high speed (*7*). This path has been opened for nanowires by the experimental demonstration by De Marchi *et al.* of new basic logical functions, but evidence at the circuit level remain necessary.

More generally, multiple-electrode nanowire transistors can be a way to make reconfigurable, highly dense logic gates in the future. Previously, 3D "staked" nanowires have been fabricated with two independent control gates (*9*). These devices can be used for power management and innovative logical function design. With polarity control gates, new ways of designing arrays of wires in 3D by low-temperature processes could be imagined. For instance, 3D arrays of nanowire transistors are now considered by industry for 3D memories (*10*). They may be used tomorrow for 3D ICs, and eventually with emerging semiconductor materials.

References and Notes

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