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A Mouse Following in the Footsteps of Human Prehistory

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One of the strongest signals of positive selection in humans surrounds the *V370A* variant of Ectodysplasin A receptor (EDAR). However, its phenotypic consequences and impetus for selection are not well understood. Kamberov et al. nail down when it originated and, using transgenic mice, delineate its phenotypic impacts.

Understanding the recent evolution of our species remains a singularly interesting and difficult undertaking. Within the last 100,000 years, a small founding population of humans in Africa has expanded to colonize nearly every ecosystem on the planet. Coincident with this expansion is evidence of a new cultural and cognitive toolkit that may have buffered or distorted the normal forces of positive and purifying selection acting on genetic variation. Perhaps unsurprisingly, there remains disagreement on the extent to which local selection, i.e., selection that affected a subset of humans, has altered the genetics and biology of living human populations. The first broad-scale descriptions of human molecular variation, at the mitochondrial and Y chromosome loci, showed a picture of human genetic homogeneity: most of the haplotype variation present throughout the world is also present within Africa. The first phases of the HapMap project largely recapitulated this result for the nuclear genome (International Hapmap Consortium, 2005). This observation, on its surface, seemed to leave little room to invoke strong, local selection. However, although often conflicting on what the regions were, some analyses of these HapMap data did suggest some instances of local selection. In this issue, Kamberov and colleagues present a detailed phenotypic description of one of the strongest of these early candidates for local selection: a nonsynonymous variant in Ectodysplasin A receptor (EDAR) (Kamberov et al., 2013).

The *V370A* variant of *EDAR* is a naturally occurring allelic variant found at high frequency in East Asia and the Americas. It was picked up in several early genome-wide scans for local positive selection that identify alleles with population frequency differences that lie on unusually long haplotypes (The International Hapmap Consortium, 2005; Voight et al., 2006; Sabeti et al., 2007). The rationale for this class of scan is that it takes time to accumulate frequency differences by stochastic drift. During this time, recombination will act to break down the haplotypes on which the variation occurs. A positively selected allele should stand out because its increase in frequency occurs in fewer generations, resulting in fewer recombinations and, thus, a longer haplotype background. *EDAR V370A* was prioritized for further characterization because of its derived status from comparison with primates, high differentiation between populations, and interpretable biological impact as a nonsynonymous substitution.

EDAR is a transmembrane receptor that plays a central role in Ectodysplasin A (EDA) signaling, a pathway required for the development of hair, teeth, and exocrine glands. Once bound to EDA, EDAR recruits EDARADD, triggering a signaling cascade that impinges on NFκB and activation of target genes within follicular cells (Figure 1; Cui and Schlessinger, 2006). The *V370A* substitution occurs in the EDAR death domain where the interaction between EDAR and EDARADD takes place. The *V370A* variant has been linked with increased scalp hair thickness and shovel incisor morphology in humans (Fujimoto et al., 2008; Kimura et al., 2009).

To further explore the phenotypic consequences of this variant, Kamberov and colleagues performed a hopeful experiment: they introduced the *V370A* mutation into mice. Although mice cannot be expected to recapitulate all the phenotypic consequences of human genetic variation, in this case the results were surprisingly illuminating. These mice were found to have thicker hair, which bears an uncanny resemblance to the human phenotypic difference for this variant. The *V370A* mice also show differences in mammary gland morphology (increased branch density and decreased fat pad area) and an increase in the number of eccrine (sweat) glands. In a remarkable demonstration of the power of mouse models in understanding recent human evolution, the eccrine gland phenotype, although not previously noted in humans, was found to be associated with *V370A* in a survey of Han Chinese. Instead of recapitulating a known human phenotype, the mouse model suggested a human phenotype that was strongly confirmed.

To further characterize the selection event associated with the *V370A* variant, they estimated the allele's age, geographic origin, and the strength of selection acting upon it. Not surprisingly, given its current distribution, the variant is reckoned to have arisen in central China roughly 30,000 years ago. From the frequency spectrum and spatially explicit forward simulations, they estimated the selection coefficient of *V370A* to be between 0.030 and 0.186. The fitness advantage of *V370A*, then, is comparable to that conferred by the lactase persistence allele, C-14010 (Tishkoff et al.,

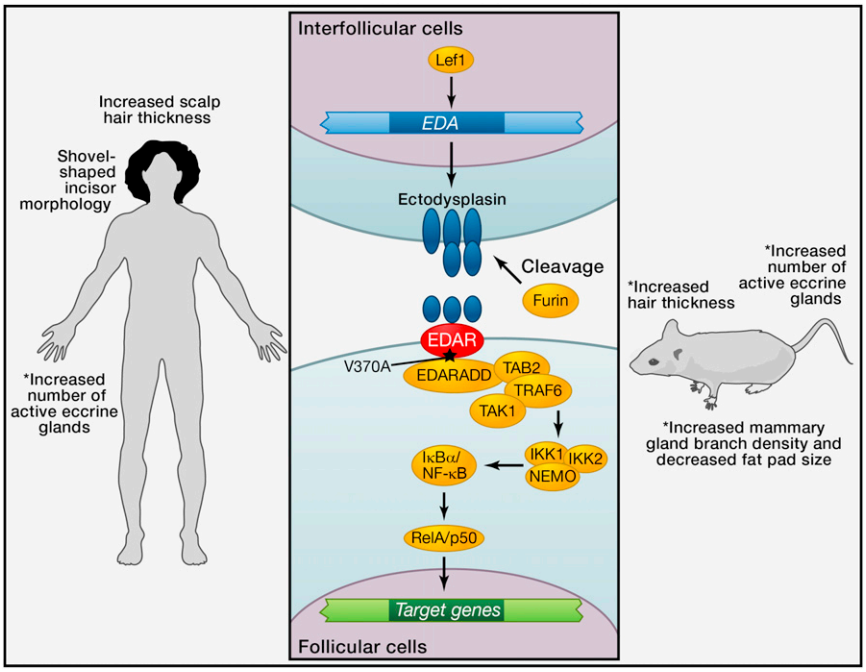

Figure 1. EDA Signaling and Phenotypes Associated with the *EDARV370A* Variant

Ectodysplasin A receptor (EDAR) plays a central role in the development of hair, teeth, and exocrine glands. EDAR is a transmembrane receptor protein whose ligand, Ectodysplasin, is produced by interfollicular cells. On binding Ectodysplasin, EDAR recruits the signaling adaptor EDARADD causing a cascade that results in NFκB gaining entry into the nucleus and activating transcription of target genes. Also shown are the phenotypes associated with *EDARV370A* in both humans and mice. Asterisks indicate previously unknown phenotype associations found by Kamberov et al. (2013) Adapted from Cui and Schlessinger (2006).

2007), one of the most striking cases of local selection visible by analysis of human genetic variation.

Due to the pleiotropy of *V370A*, it is not clear which phenotypic component is driving this strong selection. The individual traits associated with *V370A* in mice and humans offer many plausible, but no conclusive, explanations. Kamberov and coauthors speculate that more eccrine glands may have benefited the active lifestyle of humans in a warm and humid China 30,000 years ago. The changes in mammary glands seen in mice, although not easy to assay in living humans, suggest other possibilities. Because *V370A* results in outwardly visible changes in phenotype, the force of selection may have been amplified by sexual selection or the effects of human culture.

Mouse models have many practical advantages for identifying how subtle variations in genotype affect phenotype, including short generation time, control over environmental factors, and a uniform genetic background on which multiple variants can be placed. It is estimated that 80% of genes in the mouse genome have exactly one homolog found in human and less than 1% have no corresponding homolog (Doyle et al., 2012). Transgenic mouse models have been used extensively to study human disease, but only a handful of experiments have been carried out to model nondisease human variants. This work by Kamberov et al., demonstrates the utility of this approach. Beyond confirming the causative link between *V370A* and previously observed human phenotypes, the mouse suggested new phenotypes and provides an experimentally tractable model for probing the molecular consequences of this variant in the developing animal.

The era of genome scans for selection is now in full swing. These scans have the attractive feature of not requiring any hypothesis about what genes have been affected by positive selection. Ironically, that feature often leads to a road block after the scan is run. Typically, hundreds of genomic regions will show evidence of recent, positive selection, but with no clear driver of that selection. To make matters worse, the strongest signals for selection in haplotype or linkage scans are often the largest genomic regions because the selected haplotype has been carried to high frequency without being eroded over time by recombination. Consequently, the most promising candidate regions also have the most decoy variation. In the companion paper in this issue, Grossman et al. use the composite of multiple signals method to combat this phenomenon, focusing the signal and reducing the size of the candidate regions (Grossman et al., 2013). Soberingly, out of the 412 regions mapped, 177 do not contain any annotated, protein-coding gene. Thus, genome scans for positive selection are perhaps better thought of as the beginning of many research projects rather than the end of one. Through mouse models and other creative means, the full potential of these selection maps can be realized, improving our understanding of how humans were shaped by evolution and perhaps how it continues to affect us to this day.

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