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ESSAY

# The Evo-Devo Puzzle of Human Hair Patterning

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Humans differ from all other living primates in the sparseness of our hair. Even more puzzling than the overall reduction in our fur covering is the layout of the few tufts that remain. Why does hair grow mainly on our scalp, armpits, and groin? How does our genome designate these areas? Clues to the underlying mechanism can be found in mouse mutants and human syndromes, but the mystery remains essentially unsolved. This essay reviews the evidence, pieces together the clues, and formulates a tentative hypothesis in the style of a Sherlock Holmes story. The deductive reasoning of the narrative is aided by what we already know about an analogous locus in the fruit fly that performs a comparable function.

*Homo sapiens* are the only "naked apes," though this phrase, popularized by Desmond Morris, is somewhat misleading. We still have a profusion of hair on our scalp and, as children, the rest of our body makes a fine, transparent "peach fuzz" called vellus. Indeed, the only truly hairless areas of our body are our palms, soles, lips, and parts of our genitalia (Martini et al. 2004). Why did our hominin ancestors lose so much fur? Our best guess is that fur became a liability when they started running long distances and began to suffer from overheating (Jablonski 2010). Under those conditions any mutations that lessened our insulation would have spread through the population. Which genes were impacted? No hair-affecting genes have yet been found among the loci that show evidence of selective sweeps (Enard et al. 2010).

We have little hope of solving this evolutionary riddle until we figure out how hair patterns are delineated during development. Why, for example, do cells in our scalp make stout, pigmented "terminal" hair, whereas nearby cells on our forehead make invisible vellus? How are such boundaries drawn? Put simply, the core issue here is: How is the two-dimensional jigsaw puzzle of hairy versus smooth territories within our skin controlled by our (one-dimensional) genome? Some enticing clues are available in the literature of human syndromes and mouse genetics, but they have not yet been fitted together into a testable model of genetic circuitry. Before examining the evidence, it might help if we had at least a vague idea of what kind of circuitry we're looking for.

The best known "area code" directories in animal genomes are the *Hox* (homeobox) gene complexes (Lemons and McGinnis 2006). They designate body regions along the head–rump axis of our skeleton, nervous system, and branchial arches (Held 2009), but none of those zones coincides with our hairy territories (Duboule 1998a). Moreover, *Hox* complexes are atypical insofar as they exhibit the odd property of colinearity (Wray 2003), where the order of genes along the chromosome matches the order of structures along the body (Duboule 1998b). Generally speaking, animal genes are regulated by "*cis*-enhancers" (i.e., adjacent DNA elements), whose order is scrambled relative to the body parts they control (Swanson et al. 2010). A more typical circuit is the *even-skipped* locus in the fruit fly (Zeitlinger and Stark 2010), where the order of stripe-specific enhancers along the DNA does not reflect the order of expression stripes along the embryo (Borok et al. 2010).

## Might Our Hairy Areas be Demarcated Like Fly Bristles?

An even more apt case study for our purposes is the fly's Achaete–Scute Complex (AS–C), which is diagrammed in

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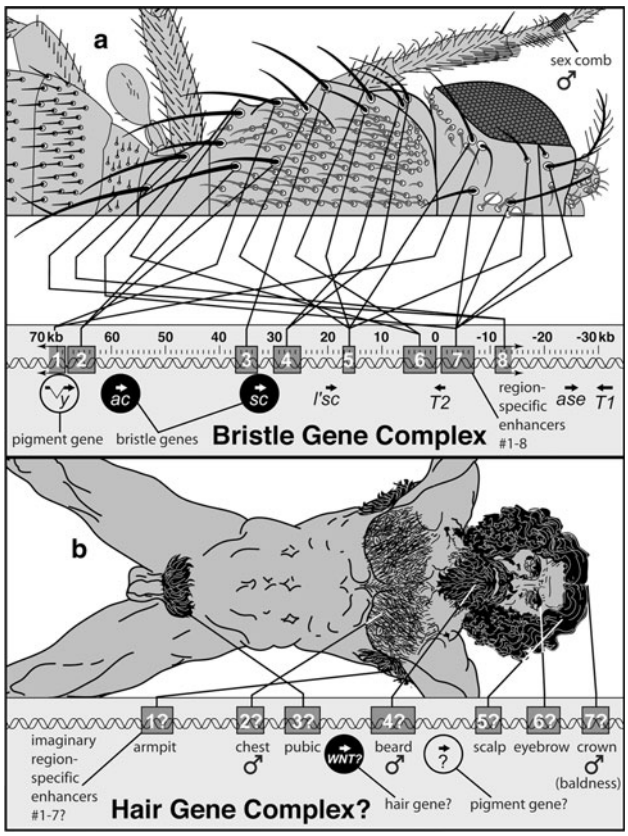


**Fig. 1** Comparison between **a** the Achaete–Scute Complex of the fruit fly *Drosophila melanogaster*, a thoroughly studied locus that controls bristle patterning, and **b** a hypothetical "Hair Gene Complex" that might control hair patterning in *Homo sapiens*. The intent of this analogy is to discern key features of the former so that we can search for the latter more intelligently. Indeed, that is the fundamental intent of the entire essay. **a** Left half of a fly in *top view*. Bristles are of two types, each of which has a shaft and a socket: 20 large "macrochaetes" and many smaller "microchaetes". Sockets are omitted for leg bristles, and interommatidial (eye) bristles are not drawn at all. The row of bristles labeled "sex comb" is so-named because it resembles a hair comb and is present only in one sex (males). Below (*gray panel*) is 100 kilobases (kb) of DNA (*wavy lines*) where the Achaete–Scute Complex (AS–C) resides. None of the depicted genes (*thick arrows*) has introns except *yellow* (*y*)—a pigment gene that is not thought to be part of the AS–C proper. An insulator element evidently isolates *yellow* from enhancers of the AS–C (Golovnin et al. 2003), but a regulatory overlap cannot be ruled out because not all regional enhancers have yet been mapped for the *yellow* or AS–C loci (Simpson 2007). The *achaete* and *scute* genes (*ac* and *sc*; *solid black circles*) are paralogs, as is *lethal-at-scute* (*l'sc*), though *l'sc* acts in the central nervous system. Lines connect macrochaetes with the *cis*-regulatory enhancers (*numbered gray rectangles*) that cause *ac* and *sc* to be expressed there. (Microchaete enhancers are not indicated.) Deleting an enhancer (e.g., #4) removes its cognate bristles (the pair of humeral bristles). The enhancers act independently like separate notices tacked onto a broad billboard (Arnosti and Kulkarni 2005). Adapted from Held (2002). **b** Vitruvian Man of Leonardo da Vinci augmented with beard, armpit, and chest hair. The sketch is misleading because we actually have hair over most of our body. The majority of it is short, fine, unpigmented "vellus," rather than the long, coarse, and colored "terminal" hair that is so obvious to the naked eye (Martini et al., 2004). The only bare areas are our palms, soles, lips, and parts of our genitalia. Below (*gray panel*) is an imaginary human locus sketched to resemble the fly's AS-C. We do not yet know (1) whether such a headquarters for hair patterning really exists, (2) how many master genes (*solid black circle*) reside there, (3) how many enhancers it uses, (4) how they map onto body regions, (5) how they are arranged, or (6) whether the complex has a pigment gene within it or nearby

Fig. 1 (Gómez-Skarmeta et al. 1995). The genes *achaete* and *scute* act redundantly to elicit tactile bristles in the adult skin: in the absence of both genes the skin is devoid of bristles. Within the AS-C, eight *cis*-enhancers cause *achaete* and *scute* to be expressed in certain spots on the surface so as to create an array of 40 big bristles. The sequence of enhancers is scrambled relative to the bristle pattern, but such messiness is irrelevant to how *cis*-enhancers act (Arnosti 2003; Bulger and Groudine 2010). When an enhancer binds its cognate transcription factors (i.e., DNA-binding proteins), it will activate *achaete* and *scute* in the appropriate location, regardless of whether the other enhancers are bound by their factors. In other words, the enhancer array of the AS–C constitutes a simple parallel circuit (devoid of any combinatorial grammar that might lead to morphological integration (Rolian and Willmore 2009)).

Over the eons this "either/or" logic has facilitated evolution (Hallgrímsson et al. 2005) because it has allowed new enhancers to be inserted without disturbing the old circuitry (Marcellini and Simpson 2006). Conceivably, a similar "plug in" modularity may have helped hominins suppress subregions of our fur covering—one patch at a time—until we arrived at our current state (Noonan 2009). In that case, our *cis*-enhancers would not be activators (for the scalp, armpits, and groin) analogous to how the AS–C works, but rather would function as inhibitors for remaining areas of the body (torso, legs, etc.). This "figure vs. ground" riddle should be resolved once we know more about the master gene(s) and their mode of operation.

At this point it is important to stress that fly bristles and human hairs are not homologous (Wu et al. 2004), nor does the human homolog of *achaete* and *scute* (*MASH1*) induce hairs in our skin (Tomita et al. 2000), though the related gene *MATH1* does induce ciliary hairs in our inner ears (Gao 2003). Rather, the purpose of this thought experiment is purely heuristic. To wit, if animal phyla tend to solve spatial control problems using similar genetic strategies—and they indeed appear to do just that (Mackay and Anholt 2006; Sholtis and Noonan 2010)—then the logic of the AS–C could help guide our search for the genes that control human hair patterning.

If so, then what relevant features can we distill from the AS–C that could enable us to focus our scope? If humans do have a "Hair Headquarters" that operates like the

AS–C, then it might contain the following attributes (Held 2002), some of which have already been discussed:

1. A single locus with only a few redundant master genes.
2. A collection of eight-or-so region-specific *cis*-enhancers.
3. A scrambling of the enhancers relative to the areas they control.
4. A loss-of-function (LOF) null phenotype involving hairlessness.
5. A gain-of-function (GOF) phenotype involving excess hairiness.
6. A nearby pigment gene that may share a subset of enhancers.

The sixth characteristic of the AS–C is especially intriguing. It so happens that the fly's master gene for pigmentation, *yellow*, is embedded within the limits of the AS-C. Such a close association makes sense in flies because bristles are pigmented to different extents. For example, the bristles of the sex comb are black, while the bristles of the eye facets are yellow. Conceivably, the very same enhancers that cause bristles to arise at certain sites may also be forcing them to adopt certain colors (Simpson et al. 2006).

What makes the association of pattern with pigment so tantalizing is that men's beards often differ in color from their scalp hair, and other body regions can vary independently as well (Miller 1931). Is it possible that evolution merged our command center for hair color with our headquarters for hair patterning? Our master gene for skin pigmentation is *MC1R* (Hoekstra 2006; Lin and Fisher 2007). It encodes the receptor for melanocortin hormone and is located on chromosome 16 (q24.3). There are no genes in its vicinity whose alleles affect hair pattern, so this first guess appears to have fallen wide of the mark. Nevertheless, it shows how even an incidental clue from the fruit fly could lead to a potentially fertile line of deductive reasoning.

## Is Our Master Regulator for Hair Patterning a *Wnt* Gene?

The only genes that clearly satisfy criteria 4 and 5 are members of the Wnt intercellular signaling pathway (Zhang et al. 2009). Wnts are diffusible proteins that establish patterns of structures in phyla as anatomically diverse as arthropods and chordates (van Amerongen and Nusse 2009). The key evidence from mice is given below, where "hypertrichosis" denotes excess hair and "hypotrichosis" indicates missing hair.

1. *GOF phenotype* hypertrichosis. Overexpression of the stabilized protein $\beta$-catenin, which relays the Wnt signal to the nucleus, induces extra hair follicles in embryos (Närhi et al. 2008; Zhang et al. 2008) and in adults (Lo Celso et al. 2004).
2. *LOF phenotype* hypotrichosis. Ablation of $\beta$-catenin during skin development blocks inception of hair placodes (Huelsken et al. 2001), as does inhibition of Wnt signaling via Dickkopf 1 (Andl et al. 2002).

Aside from its ability to increase or decrease the amount of hair, the Wnt pathway also regulates hair spacing (Sick et al. 2006), hair differentiation (Millar et al. 1999; Shimomura et al. 2010), and hair regeneration during wound healing (Ito et al. 2007). In fact, its nuclear effector (Lef-1) binds directly to regulatory DNA sequences at 13 keratin genes that are involved in hair outgrowth (Zhou et al. 1995; DasGupta and Fuchs 1999). No other signaling pathway comes anywhere close to being so intimately instrumental in hair development (Rogers 2004).

A central role for Wnts in hair patterning was confirmed by a recent genome-wide association study of 80 dog breeds. The key gene responsible for bushy moustaches and eyebrows (*R-spondin-2*) turned out to be a Wnt regulator (Cadieu et al. 2009). Even our suspicion of a link between hair pattern and hair color (criterion 6) may have some validity: excess expression of the Wnt transducer $\beta$-catenin causes early pigmentation of hair follicles (Zhang et al. 2008).

In summary, Wnts are the chief hair-promoting agents in mammals (Schmidt-Ullrich and Paus 2005; Fuchs 2007). The lingering question is which of the many *Wnt* loci might harbor the master gene(s)? There are 19 *Wnt* genes in mice (Van Amerongen and Nusse 2009), two of which are critical for hair development: *Wnt10a* and *Wnt10b* (Zhang et al. 2009). Humans also have 19 *WNT* genes (Fig. 2) (van Amerongen and Nusse 2009), and LOF mutations in our *WNT10A* gene cause sparse hair in the scalp, body, eyebrows, and eyelashes (Bohring et al. 2009). A mild one-gene phenotype is what we would expect if *WNT10A* and *WNT10B* act redundantly, thus compensating for one another's loss, as *achaete* and *scute* can do (criterion 1).

## What Are the Genetic "Area Codes" for Our Hair Territories?

If we do have a Hair Headquarters (HHQ) akin to the AS–C at one or more of our *WNT* loci, then at least some hair syndromes should map to *cis*-enhancers therein (criterion 2). The most pertinent cases would be those that cause extra or missing hair at certain places (criteria 4 & 5) (Garcia-Cruz et al. 2002). A few of the most salient syndromes that are catalogued in MIM—the *M*endelian

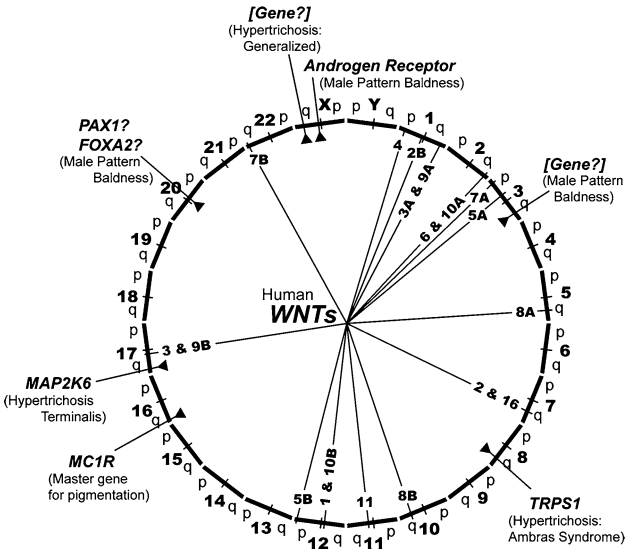


**Fig. 2** Schematic of the human genome annotated to indicate loci important for hair patterning. Chromosomes are depicted as numbered line segments (of uniform size) arranged in a circle, with "p" arms above "q" arms (of equal length) separated by a tick mark (centromere). Our 19 *WNT* genes are indicated by spokes, five of which denote paralogs that are too close to separate at this scale (Kirikoshi et al. 2001). Arrowheads denote a few genes whose mutant alleles strongly affect hair pattern (making more or less hair) or pigmentation (*MC1R*). None of these hair-affecting genes coincides with a *WNT* gene. Nevertheless, as explained in the text, one or more of the *WNT* loci may harbor a "circuit board" of *cis*-enhancers (Borok et al. 2010) that delimit the areas where terminal hair is allowed to grow in our skin (cf. Fig. 1)

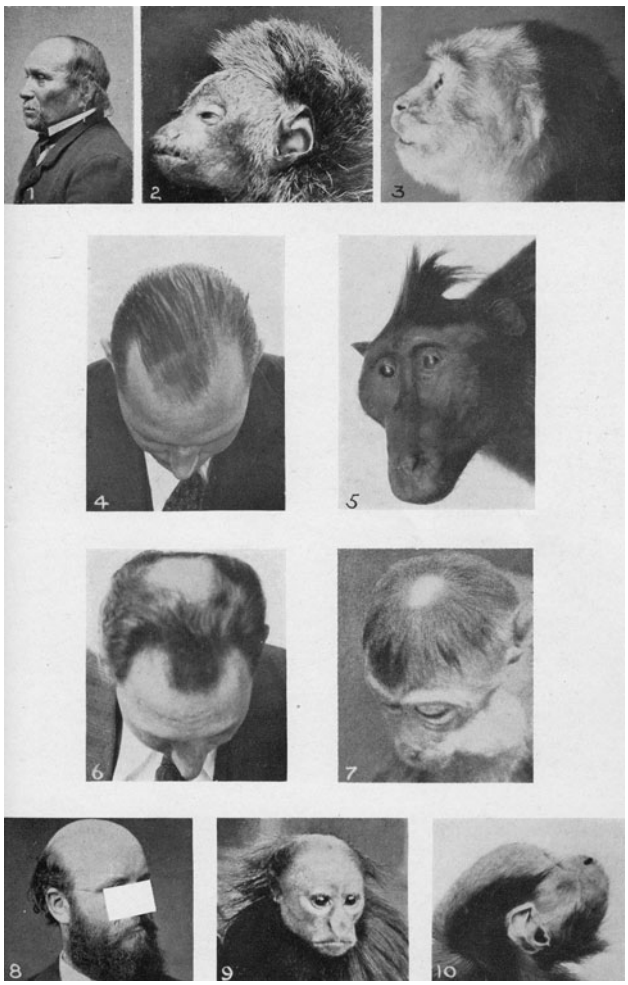

**Fig. 3** Types of balding in humans (*left picture in each panel*) compared with similar patterns of hair loss (or coloration) in other primates: (1) raised hairline; (2) South American monkey, *Pithecia monachus*; (3) South American monkey with lighter hair color in the affected area; (4) receding hairline at the temples; (5) Celebean crested macaque, *Cynopithecus niger*; (6) bald spot at the vertex; (7) toque macaque, *Macaca pileata*; (8) completely bald crown; (*9 and 10*) nearly bald crown in a South American monkey, *Cacajao rubicundus*. This montage comes from a little-known treatise by Miller (1931). It is reproduced here with permission from the Smithsonian Institution

*I*nheritance in *M*an database (www.ncbi.nlm.nih.gov)—will now be considered.

The most common hair loss in any consistent skin area is male pattern baldness (MIM 109200). Nearly 50% of men display this trait by age 50 (Sinclair 1998; Rusting 2001). Affected areas include the temples, vertex, and crown (Nyholt et al. 2003). Surprisingly, these three types of balding are found in other primates as well (Fig. 3) (Miller 1931; Brigham et al. 1988)—implying that hominins had area codes (*cis*-enhancers?) for these regions long before we lost fur from the rest of our body! Balding entails a conversion of terminal hair back to a vellus state (Jahoda 1998)—the very same process that curtailed our fur during evolution (Wendelin et al. 2003). Three major loci contribute to the condition (Hillmer et al. 2008; McLean 2008), none of which is near a *WNT* gene. One is the androgen receptor on our X, which explains the sex bias (Randall 2007). Another is a section of chromosome 3 (q26) with a gene (*TERC*) that encodes the RNA moiety of telomerase, which might explain the late age of onset since telomeres (tips of chromosomes) shorten as we age. Finally, there is a region of chromosome 20 containing *PAX1* and *FOXA2*, which encode transcription factors. Conceivably, they might bind *cis*-enhancers at a *WNT* site. Indeed, a null *FOX* allele removes hair from the body (but not the head) in the Mexican hairless dog breed (Drögemüller et al. 2008), and *PAX1* is strongly expressed in the scalp. If these factors do regulate hair growth, then their DNA-binding sites could lead us to the HHQ (Pan et al. 2010).

Ambras Syndrome (MIM 145701) elicits an abundance of hair on the head and shoulders, including the forehead, nose, and ears (Fig. 4) (Baumeister et al. 1993). It is caused by a gene(s) in the q23 region of chromosome 8. Working with DNA from three Ambras patients, Angela Christiano and her team (Pearson 2007) zeroed in on a gene (*TRPS1*)

**Fig. 4** Ambras Syndrome, as manifest by a 16-year-old Polish boy, Stephan Bibrowsky (1891–1931). Born in Poland to normal parents, Stephan toured with the Barnum and Bailey Circus as "Lionel, the Lion-faced Man" (Drimmer 1973; Kunhardt et al. 1995). Such people were once thought to be atavistic throwbacks to our distant (chimp-like) past (Bergman 2002), but this interpretation is improbable considering that no great apes have furry noses (Held 2009). From von Luschan (1907)

that causes a similar "Koala" syndrome in mice (bushy muzzle) (Fantauzzo et al. 2008). In both the human and mouse mutants, the expression of *TRPS1* is lower despite the fact that its coding portion remains intact, implying a position effect of lesions (breakpoints and deletions) nearby. *TRPS1* encodes a DNA-binding protein that would be capable of binding a *cis*-enhancer at the hypothetical HHQ.

Hypertrichosis Terminalis (MIM 135400) causes extra hair over the entire body (except palms and soles), though again the head is most affected. Three mutant individuals from different Han Chinese families were found to have slightly incongruent, but overlapping, microdeletions on chromosome 17 (q24) (Sun et al. 2009). DNA from an even hairier man with thick, black, long (>5 cm) hair over 96% of his body showed a micro*duplication* at exactly the same site. Four genes exist in the area of overlap. Only *MAP2K6* is a reasonable culprit because deleting the other three genes has no effect. However, enzymes are not typically dosage sensitive, so the notion that MAP2K6 (an enzyme) could have such effects when present in 0.5 (LOF) or 1.5 (GOF) doses seems odd. The authors conjectured that the lesions exert a position effect on a distant *SOX9* gene, whose LOF mutations cause hair loss (Vidal et al. 2005). If *SOX9* is responsible, then we again have a possible lead to pursue since SOX9 is a transcription factor that could bind at one or more *WNT* loci.

Congenital Generalized Hypertrichosis (MIM 307150) evokes hair growth over most of the body, though the face is hairiest by far, the torso less so, and the rest of the body surface milder still. Males are more strongly affected than females, and the ectopic hair in females sprouts in patches—telltale signs that suggest X-inactivation. Indeed, two Mexican families with this syndrome (likely related to each other) were studied, and the trait was traced to a section on the X chromosome (Xq24-q27.1) (Figuera et al. 1995; Tadin-Strapps et al. 2003). Despite the screening of 82 genes within this interval, no underlying mutation has so far been identified (Pearson 2007).

A few other syndromes are known to cause striking, region-specific hypertrichoses. They display hair on the elbows (MIM 139600), neck (MIM 600457), ears (MIM 139500), nose (MIM 139630), or palms, and soles (MIM 139650). In none of these cases has the trait yet been mapped. If the culpable area codes are eventually traced to *cis*-enhancers (at a *WNT* locus?), then we should be able to confirm their roles by coupling the enhancers to reporter genes and seeing whether the transgenes that are constructed in this way can drive expression in similar parts of the mouse body (Sholtis and Noonan 2010).

## How Did We Become the Only "Naked Apes"?

The odd age of onset of male pattern baldness offers a potential clue to how hominins lost their fur. Scalp hair begins to thin after men's peak reproductive age (implying that it no longer helps in attracting females… if it ever did), but it blooms before old age (so it is not a side-effect of senescence per se). How did such a distinctive trait get banished to the purgatory of masculine middle age? Adaptive arguments can certainly be mustered, but it is equally possible that the feature was simply swept up accidentally in a more pervasive shift of developmental timing.

"Heterochrony" is the general term for timing changes in the development of a descendant relative to an ancestral species (McKinney and McNamara 1991). "Neoteny" is a type of heterochrony where the descendant exhibits the same traits as the ancestor but with a much delayed schedule (Gould 1977). Humans are demonstrably neotenous with regard to our fellow apes (de Beer 1958). The most obvious example is the flatness of our face, which resembles that of a baby chimp, minus the noticeably protruding muzzle that characterizes the adult (Fig. 5). Another

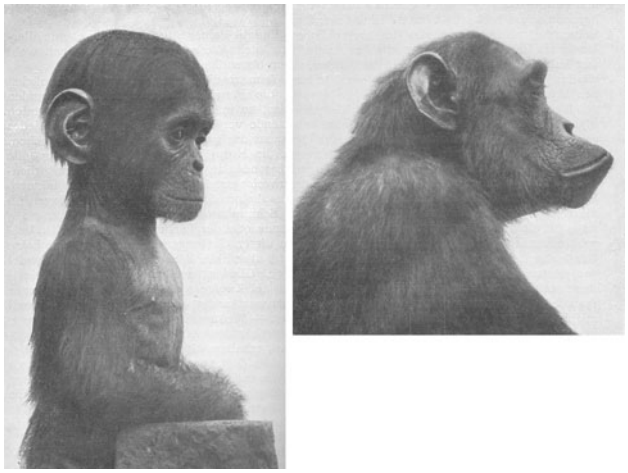

**Fig. 5** Physiognomy of a baby (*left*) vs. adult chimp (*right*). The resemblance of the baby's flat face to that of an adult human was one of the many clues that led Louis Bolk to propose "fetalization" as the primary driving force of hominin anatomical evolution (Bolk 1926). Another corroborating clue is the baby's relatively hairless chest (cf. Fig. 6). This before-and-after dichotomy figured prominently in Stephen Jay Gould's 1977 monograph *Ontogeny and Phylogeny* (Gould 1977), wherein he buttressed Bolk's hypothesis. From Naef (1926)

example is our wisdom teeth, which erupt late. Our hair pattern fits nicely into this trend (Held 2009). To wit, it turns out that newborn chimps, gorillas, and orangutans have hair on their scalps but little elsewhere (Fig. 6),

**Fig. 6** Newborn great apes, all of which display profuse hair on the scalp but sparse covering elsewhere—a pattern typical of adult humans. *Upper left* infant chimp Vindi with her mother Jodi (photographed in 2007), courtesy of Maureen O'Leary, Tulsa Zoo; *bottom left* infant gorilla Goma (photographed in 1959), courtesy of Photo Archive, Basel Zoo; *right* infant orangutan Teliti with her mother Puteri at the Perth Zoo (photographed in 2009), courtesy of Samantha Finlay-Norman

remarkably like adult humans. It is therefore plausible that hominins postponed fur formation in most parts of the body so much that modern humans never acquire a full covering during our entire lives. This intriguing hypothesis was first proposed by Louis Bolk (1926), embellished by Gavin de Beer (1958) and Ashley Montagu (1962), and popularized by Stephen Jay Gould (1977). Most important for our purposes, the hypothesis has genetic implications that are also worth considering:

1. Area codes may be activated in a specific sequence that is conserved among primates. If different area codes educe hair in a definite temporal order, then humans may not actually possess any unique area codes (*cis*-enhancers at a *WNT* site?) of our own.
2. The gradual progression of hair acquisition during men's lifetimes could just be a slow-motion version of the proto-hominin "movie": scalp hair at birth, then beard, armpit, and pubic hair at puberty, then chest hair, back hair, and nose hair toward middle age (along with some loss of scalp hair), and finally bushy eyebrows—a trait so common that Aristotle himself was impelled to remark that "in old age [the eyebrows] often become so bushy as to require cutting" (*Parts of Animals*, Book 2, Pt. 15, p. 658, col. b, lines 19–20) (Barnes 1984).
3. The terminal area codes of the primate sequence may have been delayed so much that we no longer activate them at all, and this dormancy may have persisted for millions of years. If so, then the respective enhancers (for, say, hair on our neck) may have decayed so much by the accrual of mutations that they can no longer be atavistically reawakened (Marshall et al. 1994).
4. Hair graying fits nicely into this scheme (Sarin and Artandi 2007). Gorillas use silverback coloration during their peak reproductive years as a sign of male virility, and proto-hominins may have used gray scalp (and back?) hair in a similar way. Our graying occurs much later in our life cycle (Schneider et al. 2009), though our eyebrows (and certain other areas) remain dark much longer (Miller 1931).
5. Male pattern balding may have once helped attract mates (like the silverback trait) in our hominin ancestors, but then suffered a delay (past our prime) due to the systemic slowdown of other hair-related features, so that it is now mostly a useless vestige.

Thus, we may have become the only naked apes via heterochronic mutations that slowed down the utilization of our area codes without ever changing either their regional identities or their temporal sequence. Unfortunately, we understand even less about how genes are regulated in time than we do about how they are regulated in space (Smith 2003; Hallgrímsson et al. 2009), so it may be some time

before we figure out how evolution tinkered with the gears and ratchets of our genomic clockwork (Weirauch and Hughes 2010).

## Do We Still Have Vibrissae Genes?

As for heterochrony, the fly's AS–C locus has one more lesson to teach us. Looking at the size disparity between large and small bristles, it would be natural to think that the former have more cells than the latter, but that is not so. Every shaft is made by a single cell, regardless of its length (Held 2002). Bristle size is constrained by the time available for the shaft cell to enlarge via cyclic endoreplication (Edgar and Orr-Weaver 2001), and that period is delimited by the birthdate of the bristle mother cell (Simpson and Marcellini 2006). Mother cells of large bristles arise earlier than those of small bristles (Simpson et al. 2006)—a dichotomy lacking in primitive dipterans like mosquitoes (Simpson and Marcellini 2006). Advanced dipterans like fruit flies evolved bigger bristles by shifting bristle birthdates to a much earlier stage (Skaer et al. 2002) via a novel *cis*-enhancer (Gibert and Simpson 2003).

Another distinctive feature of big bristles is their precise positioning. Thoracic bristles arise at uniform intervals along regular lines running along the back (Simpson and Marcellini 2006). Amusingly, the previous sentence would sound familiar to any cat owner, provided that we make a few word substitutions: *mystacial vibrissae* arise at uniform intervals along regular lines running *along the snout* (Dun 1958; Wrenn and Wessells 1984). Vibrissae (long, stiff whiskers) are an ancient and widespread feature among mammals, and they are still remarkably prominent in various monkey genera (Hershkovitz 1977). Why did vibrissae vanish in other primates, including the ancestors of hominins? The most likely explanation is that their utility as nocturnal mechanosensors declined as our forebears became diurnal and came to rely much more on the visual system instead.

We do not yet know whether vibrissae (mystacial or otherwise) are encoded by dedicated genes or just by unique area code *cis*-enhancers within a common HHQ (Schneider et al. 2009). Nor do we know whether humans retain any remnant of the relevant genetic circuitry that could be reawakened under the proper conditions. No syndrome has yet been described where people grow parallel rows of catlike whiskers (McKusick 1998)! Also unknown is whether our brains can still be coaxed to form the amazingly isomorphic arrays of neurobarrels that process tactile inputs from the whisker rows (Oury et al. 2006; Sato et al. 2007).

## Conclusions and Prospects

Various experiments in mice, reviewed above, have implicated the Wnt pathway as the chief culprit in our search for a control center of hair patterning (Fuchs 2007; Schneider et al. 2009). Although none of the hypo- or hypertrichosis syndromes mapped so far localize to any of our 19 *WNT* sites, this lack of concordance does not absolve the *WNT*s of culpability. Some of those syndromes may disable transcription factors that bind at *WNT* loci—e.g., PAX1 and FOXA2 (pattern baldness), TRPS1 (Ambras Syndrome), and Sox9 (Hypertrichosis Terminalis). Inspecting *WNT* promoters for binding motifs could help us winnow the sites to a few that warrant further scrutiny. If the AS–C in fruit flies is a reliable guide, then our hair headquarters probably contains region-specific *cis*-enhancers. Once we find them, we can couple them to reporter genes to see if they drive expression in comparable parts of the mouse body (Sholtis and Noonan 2010). Only then can we begin to deconstruct the sequence of genetic events that stripped our ancestors of their luxuriant fur coats (Heintzman and Ren 2009).

The main issue addressed here has been how our skin is balkanized in our genes. After we have deciphered and tested the genetic area codes, we should be able to figure out why hair is sketched only in certain skin areas and how the follicles in those areas get painted certain colors. Eventually, we may be able to tackle the related puzzles of hair length, density, texture, and polarity, and how these features are likewise regulated on a region-by-region basis (Kidd 1920; Schneider et al. 2009). There too, the hairy little fruit fly may have a few hints to offer us (Seifert and Mlodzik 2007).

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