

A Genetic Basis for Obsessive Grooming

Excessive grooming behaviors, cleansing rituals, and self-mutilation are important features of a range of neuropsychiatric diseases including obsessive compulsive (OC)-spectrum disorders. In this issue of *Neuron*, Greer and Capecchi (2002) report that *Hoxb8* mutant mice exhibit this behavioral phenotype. These *Hoxb8* mutants will be valuable in exploring the genetics and pathophysiology of OC-spectrum disorders as well as strategies for their treatment.

As many a post-doc knows, making a mutant mouse can be so tough that it makes you want to pull your hair out. Not so for Greer and Capecchi (2002), who have engineered a mouse that tears *its* hair out. Greer and Capecchi describe a dramatic behavioral phenotype in mice with targeted mutations of the homeodomain gene, *Hoxb8*. The mice engage in excessive grooming behavior to such an extent that they remove their own hair or that of wild-type littermates housed with them.

Greer and Capecchi engineered mice with two different mutations, one having a *Hoxb8* exon 1 nonsense mutation and a *neo'* cassette in exon 2, and another with the same exon 1 nonsense mutation but a lox P site in exon 2. Both homozygous mutants (*Hoxb8^{neo'}* and *Hoxb8^{lox}* mice) exhibited the excessive grooming, but the *Hoxb8^{neo'}* mutants also showed a skeletal abnormality in the first rib. In an admirable example of genetic detective work, Greer and Capecchi picked up on the fact that first rib abnormalities also occur in *Hoxb9* and *Hoxb6* mutants, and they looked at the expression of these genes in *Hoxb8* embryos. They found that the *Hoxb8^{neo'}* embryos—but not the *Hoxb8^{lox}* embryos—had abnormal expression of *Hoxb9* at embryonic day E9.5, and that a third of the E9.5 *Hoxb8^{neo'}* embryos—but again, not the *Hoxb8^{lox}* embryos—had abnormal *Hoxb6* expression. Their conclusion is that the inserted *neo'* cassette in the *Hoxb8* homeodomain disrupted function of the neighboring Hox genes and led to the rib abnormalities. For their behavioral analysis, they were then able to concentrate on the normally ribbed *Hoxb8^{lox}* mutants.

The mutants groomed themselves to the point of self-mutilation. Behavioral tests suggested that the excessive groomers had normal reactions to touch, pressure, and pain-inducing stimuli applied to the body, and histology showed no evidence of peripheral nerve or skin abnormalities that could readily account for the behavior. But the most convincing evidence that the grooming was not solely in response to local irritation is that when the mutants were placed together with wild-type littermates, the mutants groomed the littermates too, again to the point of inducing baldness. In addition, the mutants groomed more than their littermates when grooming was triggered by external stimulation (water misting).

A key to the behavioral analysis is that Greer and Capecchi made 24 hr 'round-the-clock videotapes of the *Hoxb8^{lox}* mutants and their wild-type littermate controls. These tapes yielded crucial information: first, the excess behavior displayed by the mutants seemed specific to the grooming, body licking, and biting. The mutants did not exhibit excessive stereotypies of other sorts, nor excesses in other natural behaviors (e.g., eating, drinking, nest building). Second, even though the bouts of grooming occurred for twice as much time as in the controls, they occurred at normal times (e.g., before rest) and had the normal action-chaining or "syntax" (Berridge et al., 1987) except that the mutants spent more time in body grooming. Third, excessive grooming of the same type was found in *Hoxb8* mutants derived by backcrossing F1 *Hoxb8^{lox}* mice (on C57BL6/Sv129 backgrounds) for five generations to Swiss Webster (SWR/J) mice to produce another background. Thus the grooming abnormality was behaviorally and genetically specific. In fact, hair loss and skin lesions were already reported for another mutant of *Hoxb8*, generated by van den Akker et al. (1999). Their mice (*Hoxb8^{lacZ}* mutants) exhibited more complex behavioral symptoms and dorsal root ganglion as well as skeletal abnormalities, but one-third of them exhibited self-inflicted lesions of the skin.

In humans, exaggerated cleaning rituals occur in obsessive-compulsive disorder (OCD) and related OC-spectrum disorders. These include a specific behavioral disorder called trichotillomania, involving uncontrollable hair pulling that can be so severe that it leads to baldness and loss of eyelashes and eyebrow hair. Greer and Capecchi, understandably, are interested in the possibility that their *Hoxb8* mutants provide a mouse model of trichotillomania. The human OC-spectrum disorders are familial, and an intense genetic analysis of several of these disorders is underway (Pato et al., 2001). The Greer-Capecchi study suggests that *Hoxb8* mutations might be found in humans with OC-spectrum disorders. There also is an apparent association of some, at least, of these OC-spectrum disorders and autoimmune disorders consequent upon streptococcal infection (Swedo et al., 1998).

The neural defects underlying these OC-spectrum disorders, including trichotillomania, are not known, but there are clues: scanning studies show abnormal activity of the striatum (caudoputamen), the orbitofrontal cortex, and the anterior cingulate cortex in obsessive-compulsive disorder (the so-called OCD circuit), and drugs that increase serotonergic transmission are helpful in treatment (Graybiel and Rauch, 2000). Greer and Capecchi have not yet reported studies of these cortico-basal ganglia circuits and serotonin neurotransmission in the *Hoxb8* mice, but they did carry out an in situ hybridization study to localize *Hoxb8* mRNAs in normal mouse brain. They found widespread expression of the transcripts, including in regions implicated in the execution of normal grooming, and they point out particularly high expression in the OCD circuit. It will be important to follow up this lead by analyzing the neurobiology of

these brain regions and serotonin and other neurotransmitter function in these mice. In addition, it clearly would be valuable to generate region-specific knockout of *Hoxb8*, or to rescue the phenotype with a region-specific transgene.

The *Hox8b* mutants exhibit both excessive grooming and self-mutilation. The self-mutilation may be exclusively the consequence of the excessive grooming, but in neuropsychiatric disorders, these can appear as separate symptoms. The excessive grooming behavior of these mice could be analogous to the excessive hand washing of OCD patients, which can lead to development of skin lesions; both occur as a consequence of seemingly directed cleansing behavior. If this analogy proves to be correct, these animals could serve as a valuable OCD model. But it may not be easy to distinguish between a condition in which such skin lesions occur as secondary consequences of cleansing behaviors (for example, with excessive hand washing in OCD patients) and a condition in which such skin lesions occur as primary consequences of self-mutilation behavior. Self-mutilation (for example, excessive lip biting) occurs as a cardinal feature of devastating human disorders such as Lesch-Nyhan syndrome and neuroacanthocytosis and can occur in other disorders including borderline personality disorder, schizophrenia, and some autistic conditions. Self-mutilation can co-occur in OCD patients, but is not an elementary feature of the disorder. Animal models of self-mutilation behavior have been proposed, in which rats with 6-hydroxydopamine lesions of the dopamine system are given levodopa and exhibit severe and deleterious paw biting (Criswell et al., 1992).

The intermingling of excessive grooming and self-mutilation seen in the *Hoxb8* mutant mice raises the question of whether serotonergic and/or dopaminergic transmission is disordered in these mice. Clinically, drugs that increase serotonergic transmission such as serotonin reuptake inhibitors (SRIs) are useful in treating OCD and OC-spectrum disorders, whereas drugs that antagonize dopamine D2-class receptors can be helpful in treating self-mutilation syndromes. It would be valuable to treat the *Hoxb8* mutants with such drugs to explore the relation between *Hoxb8* expression and the established neurochemical abnormalities of OC-spectrum and self-mutilation disorders.

The fact that the *Hoxb8* mice express such restricted behavioral abnormalities strengthens the possibility that the mouse disorder mimics tricotillomania. If so, the *Hoxb8* mutant syndrome may well open a new window on the genetics of OC-spectrum disorders and help to account for the paradox that on the one hand, so many of these disorders involve aspects of grooming and cleansing rituals, and yet each subtype (and each patient) can express exquisitely specific symptoms.

Finally, it is truly remarkable that such a specific behavioral disorder occurs in mice mutant for one of the Hox genes, prototypic of genes coding for transcription factors important in guiding development (McGinnis and Krumlauf, 1992). It will be of very great interest indeed to see whether other of these highly conserved genes subserve behavioral phenotypes and whether the phenotypes cluster around the kinds of innate, genetically programmed behaviors exemplified by grooming.

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Selected Reading

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Conserved Cues for Axon and Dendrite Growth in the Developing Cortex

The cellular and molecular mechanisms that guide axonal and dendritic differentiation in the cerebral cortex are just beginning to be defined. Many of the molecular signals that guide axons also, and sometimes simultaneously, influence dendritic growth. Whitford et al. (2002 [this issue of *Neuron*]) demonstrate that in addition to their roles in axon guidance and cell migration cue, Slit proteins can also regulate dendritic growth.

The mammalian cerebral cortex requires the proper formation of exquisitely precise neuronal circuits to function correctly. In order for these circuits to develop properly, neurons must elaborate axons and dendrites with specific patterns of arborization. Pyramidal neurons, the primary excitatory projection neurons in the cerebral cortex, undergo extensive differentiation soon after completing migration to their correct position within the six cortical layers. When these neurons first arrive in the cortical plate, they are simple in shape; their apical dendrite extends up toward the pia and their axon grows away from the pia down toward the white matter. With time, the apical dendrite branches extensively, basal dendrites arborize radially from the cell soma, and the axon reaches its extrinsic targets and sprouts collaterals that arborize in specific intracortical layers. Although the development of pyramidal neurons has been well described anatomically, the cellular and molecular mechanisms that guide axonal and dendritic differentiation in the cerebral cortex are just beginning to be understood.

Research into the cellular and molecular mechanisms of axon and dendrite growth has blossomed in the past