## A big lad

**Think of a boy, not yet five years old, who is able to hold a 3-kg dumbbell in each hand with his arms straight out. Schuelke *et al.* (*N. Engl. J. Med.* 350, 2682–2688; 2004) report a child with unusual muscle development, who is homozygous or hemizygous with respect to a point mutation that interferes with splicing of the gene encoding the inhibitor of muscle growth, myostatin. Mutations in the orthologous gene in Belgian Blue cattle and in mice lead to an increase in the number of myocytes and in muscle bulk. Transgenic overexpression of myostatin in mice leads to cachectic muscle wasting. It is possible that a lesser reduction of myostatin can promote muscle development in humans, as the child's heterozygous mother was a professional athlete and four of her male relatives had unusual strength. Myostatin is a soluble protein of the TGF-β family that binds an activin IIB TGF-β receptor, thereby altering the profile of skeletal muscle gene expression by Smad activation. This pathway is therefore a likely source of natural variation influencing human physical performance, as well as the focus of therapies for diseases that involve muscle wasting.** ***MA***

## Backing into an association

The mapping of complex multifactorial diseases can be greatly assisted by the development of new statistical methods for association studies. Using a previously developed algorithm, Shaw-Hwa Lo and Tian Zheng now apply new statistical methods to the analysis of inflammatory bowel disease (*Proc. Natl. Acad. Sci. USA* **101**, 10386–10391; 2004). The authors examined 235 case-parent trios, representing a subset of a previously characterized data set. The methods use an algorithm (the backward haplotype transmission association algorithm, or BHTA) that examines a subset of markers, ranks these for association and systematically removes the one marker that contributes the least. The algorithm continues until all remaining markers show association. This method accounts for interactions among disease loci and represents an advance over traditional methods of screening individual markers and genome-wide scans. Using these methods, the authors screened 402 markers, selecting 48 that showed association above a defined threshold. They confirm the association of previously identified susceptibility loci and uncover four uncharacterized loci with strong association. This study illustrates the usefulness of applying new statistical methods to the analysis of complex human genetic disorders. *OB*

## Allelic variation in maize

Sequencing of the maize (*Zea mays*) genome has identified a high level of sequence polymorphism—about an order of magnitude higher than that in humans. Very little is known, however, about how (or whether) this degree of polymorphism might translate into allele-specific variation in gene expression. Mei Guo and colleagues carried out a small initial survey of allelic variation at 15 loci in maize hybrids (*Plant Cell* **16**, 1707–1716; 2004). Consistent with the highly polymorphic nature of the maize genome, transcript levels of 11 genes showed significant and reproducible differences between alleles, as assessed by allele-specific RT-PCR. Guo *et al.* also compared allele-specific expression between an 'old' (1960s) hybrid and an improved 'modern' (1980s) hybrid, which results in a 50% greater yield. The modern hybrid consistently expressed both alleles, whereas the old hybrid frequently showed monoallelic expression. Moreover, several genes in the modern hybrid showed differences in the allele-specific transcript ratio when exposed to drought or density stress, whereas those in the old hybrid did not. The authors suggest that allelic diversity allows for a more robust response to environmental challenge and may be partly responsible for the improvements introduced by selective breeding. *AP*

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## Transport by huntingtin

Several proteins that interact with huntingtin have been described, but despite the many models that accompany descriptions of these interactions, relatively few have provided mechanistic insight into the disease. Now, Laurent Gauthier and colleagues show that huntingtin enhances vesicular transport of brain-derived neurotrophic factor (BDNF) through increased association of poly-Q huntingtin with huntingtin-associated protein 1 (HAP1) and the dynactin complex subunit $p150^{Glued}$ (*Cell*, **118** 127–138; 2004). The increased association results in reduced levels of dynactin machinery associated with microtubules and a corresponding reduction in BDNF transport. The drop in transport was rescued with full-length huntingtin, but not with additional poly-Q huntingtin. The authors also observed less kinesin HC associated with microtubules in a knock-in mouse model of Huntington disease, suggesting that there are additional defects in anterograde transport. Full-length huntingtin stimulated both anterograde and retrograde transport of BDNF vesicles. Previously, huntingtin had been shown to affect the transcription of BDNF. The new results imply that, in addition to limiting BDNF expression at the transcriptional level, huntingtin could also be affecting the axonal transport of BDNF. It remains unclear which of these mechanisms is more important forhe antiapoptotic function of huntingtin or for disease pathogenesis. *MS*

## Unraveling NOD2 function

**Mutations in *CARD15* confer increased risk of Crohn disease, but it is unclear how these mutations contribute to disease pathogenesis. Recent studies by Watanabe *et al.* (*Nat. Immunol.* advance online publication, 27 June 2004; doi: 10.1038/ni1092) and Natea *et al.* (*Eur. J. Immunol.* 34, 2052–2059; 2004) now suggest that the product of the *CARD15* gene, NOD2, acts as a negative regulator of the T helper type 1 ($T_H1$) inflammatory response that occurs after stimulation of the Toll-like receptor TLR2 pathway. Watanabe *et al.* showed that $CD11b^+$ cells from $Card15^{-/-}$ mice respond to TLR2 stimulation by producing elevated levels of the proinflammatory cytokine IL-12. This response, which is mediated by NFκB, mimics the enhanced $T_H1$ inflammatory response typically seen in individuals with Crohn disease. Conversely, Natea *et al.* report that blood mononuclear cells from individuals homozygous with respect to a *CARD15* frameshift mutation had a diminished anti-inflammatory cytokine release after exposure to TLR2 ligands. Together, these studies suggest that *CARD15* mutations contribute to Crohn disease pathogenesis by impairing the ability of NOD2 to downregulate the $T_H1$-mediated inflammatory response triggered by exposure of antigen-producing cells in the gut to bacterially-encoded TLR2 ligands.** ***KV***