result of ethnic stratification because the results of analyzing 19 random genomic markers failed to detect spurious associations. Further support for the effect of COMT genotype on prefrontal physiology came from a function MRI assay (neuroimaging), which detected deviations in activity by genotype group.

The convergent findings of this study implicate COMT genotype in prefrontal cortical function and schizophrenia. As is the case with many genetic variants associated with complex traits, the effect of this single polymorphism is relatively small. Only 4.1% of the variation in performance on the WCST is accounted for by this variant, suggesting that it is neither necessary nor sufficient in causing schizophrenia. Furthermore, additional populations must be examined to determine how much these results can be generalised to other schizophrenic patients (non-familial) and other ethnic groups (non-Caucasian). The use of this genetic marker as a risk factor for schizophrenia or response to therapeutics is unclear. Nonetheless, the data suggests a viable mechanism whereby genetic variation can influence schizophrenia.

1 Egan, M.F. *et al.* (2001) Effect of COMT $Val^{108/158}$ Met genotype on frontal lobe function and risk of schizophrenia. *Proc. Natl. Acad. Sci. U. S. A.* 98, 6917–6922

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Heavier weight on tubby

Obesity is a severe global health problem that develops as the result of a complex interaction between genetic, psychological, socio-economic and cultural factors. Because of its multifaceted nature, only a small number of defined experimental models have so far been described in the attempt to identify the biological determinants of this disease.

In 1996, a mutation of the mouse *tub* gene was shown to cause an autosomal recessive obesity syndrome characterized by its late-onset, insulin resistance, hearing loss and degeneration of the retina. Together with *tulp-1–3*, *tub* constitutes a conserved gene family, the products of which are expressed in the brain and feature an N-terminal sequence that bears similarity to the activation domains of transcription factors, and a unique C-terminal domain with DNA-binding activity. Whereas previous studies have suggested that tubby proteins might either function directly as transcriptional regulators or have a role in signaling from the insulin receptor, it was not clear how their loss of function led to obesity. Two recent papers have now shed some light on this crucial aspect, showing how extracellular signals can act through tubby to control the cellular metabolism.

Having observed that GFP-tagged tubby localized first at the plasma membrane of transfected cells and subsequently in their nucleus, Santagata *et al.*[1] demonstrated that the C-terminal domain of the protein allows it to bind specifically to a subset of membrane inositol phospholipids phosphorylated at adjacent ring positions. The structural basis of this selectivity was revealed from a crystallographic analysis of the C-terminal domain of tubby bound to an analog of the head group of one such lipid, $PtdIns(4,5)P_2$, showing that a conserved lysine residue intercalates between the two phosphate groups of the ligand. Subsequently, the authors found that the G-proteins $G\alpha_q$ and $G\alpha_{11}$ specifically bind to tubby at the plasma membrane and induce its nuclear translocation upon activation by ligand stimulation of Gα-coupled receptors, such as the acethylcholine receptors M1 and M2 and the serotonin receptor $5HT_{2c}$. Santagata *et al.* were finally able to show that $G\alpha_q$ exerts its effect by activating PLC-β, which in turn hydrolyses $PtdIns(4,5)P_2$ to dissociate tubby from the plasma membrane and trigger its translocation into the nucleus. As a result of this complex cascade of events, tubby would in principle be able to regulate the transcription of downstream genes, thus acting as a critical intracellular messenger of GPCR signaling. The implications of this major work are supported by similarities in the phenotype of $tub^{-/-}$ and $5HT_{2c}{}^{-/-}$ mice. Furthermore, their relevance is even higher as the authors show evidence suggesting that the same regulation also applies to the other members of the tubby family.

A second hint at tubby's function comes from an independent study from Koritschoner *et al.*[2], who noticed that expression of the *tub* gene was reduced in the cerebellum of hypothyroid rats. Because the thyroid hormone receptor (TR) and tubby are co-expressed in several regions of the brain, this suggested that *tub* could be under the positive control of thyroid hormone (T3). Indeed, the authors present clear biochemical evidence for this regulation both *in vivo* and *in vitro*. In light of the fact that $TR^{-/-}$ and $tub^{-/-}$ mice also display overlapping phenotypes and that alterations of T3 metabolism often result in obesity, these results point towards a new mechanism of body weight control by the thyroid hormone, mediated by different TR isoforms and by tubby itself.

In humans, mutations in the *tulp-1* gene are responsible for the degenerative disease retinis pigmentosa, and phenotypes similar to that of *tubby* mice are found in syndromes such as Usher, Alstrom and Bardet-Biedl. The discovery that the pathways regulating energy metabolism through G-protein signaling and thyroid hormone converge on tubby has the potential to benefit future strategies for the treatment of these specific pathologies, as well as late-onset obesity in general.

1 Santagata, S. *et al.* (2001) G-protein signaling through tubby proteins. *Science* 292, 2041–2050
2 Koritschoner, N.P. *et al.* (2001) Thyroid hormone regulates the obesity gene *tub*. *EMBO Reports* 2, 499–504

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 0167-7799/01/$ – see front matter