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Corrigendum:

Stratigopoulos et al: 294: R1185-R1196, 2008. (april)

George Stratigopoulos, Stephanie Padilla, Charles A. LeDuc, Elizabeth Watson, Andrew T. Hattersley , Mark I. McCarthy, Lori M. Zeltser, Wendy K. Chung, and Rudolph L. Leibel. “Regulation of *Fto/Ftm* gene expression in mice and humans.” (http://ajpregu.physiology.org/cgi/content/full/294/4/R1185).

In the Abstract, the sentence “*The A allele of rs8050136 associated with lower body mass than the C allele preferentially bound CUTL1 in human fibroblast DNA”* should read “*The A allele of rs8050136 preferentially bound CUTL1 in human fibroblast DNA”.* On page R1193 we state: "*Moreover, CUTL1 preferentially bound to DNA fragments carrying the "C" allele of rs8050136*". This should read "*Moreover, CUTL1 preferentially bound to DNA fragments carrying the "A" allele of rs8050136*”.

There have been discrepancies in the literature regarding the associations of obesity-related phenotypes with alleles of rs8050136. Scuteri et al (2007) associate the “C” allele with lower BMI, whereas Tschritter et al (2007) associated the “C” allele of rs8050136 with higher body mass index (BMI) than the “A” allele. However, Tschritter et al (2007) inadvertently reversed the “A” and “C” alleles of rs8050136 in their paper (Erratum to: Diabetologia, Online: http://www.springerlink.com/content/k1150t348206t665/fulltext.pdf). The “A” (obesity-risk) allele of rs9939609 (Frayling et al, 2007) is in linkage disequilibrium (LD) with “A” allele of rs8050136 (Mark McCarthy personal communication). Thus, it appears that the “A” allele of rs8050136 is the obesity-risk allele

Our *in vivo* data indicate that *Fto/Ftm* are reduced in liver and adipose tissue of genetically obese mice, and in hypothalamus and adipose tissue of fasted genetically obese and wild type mice, consistent with one or both of these genes

mediating suppressive effects on energy intake. As indicated in our manuscript, the transcription factor, CUTL1, binds preferentially to the "A" allele of rs8050136 in human fibroblasts, and RNAi-mediated knockdown of CUTL1 in these cells reduces the expression of *FTO/FTM*. To fit the physiological model that we proposed based on our *in vivo* and *in vitro* data, CUTL1 should preferentially bind to the rs8050136 allele associated with resistance to obesity. Since it does not, alternative models must be considered.

CUTL1 has the ability to increase or decrease transcription in specific cellular contexts. It is possible that – contrary to its stimulatory effects in skin fibroblasts– CUTL1 tonically suppresses *FTO/FTM* expression in neuronal or other (e.g. adipocyte) cell types. Enhanced binding/action at the "A" (obesity risk allele) would lead to lower expression levels of *FTO/FTM*. This response is consistent with decreased expression levels of *Fto/Ftm* in genetically obese mice. It is also possible that CUTL1 is exerting its effects via another CUTL1 binding site in linkage disequilibrium (LD) with rs8050136. There are multiple potential CUTL1 binding sites within the ~47 kb region of LD (www.genomatix.de/online_help/help_matinspector/matinspector_help.html). Alternatively, *FTO/FTM* transcriptional control by CUTL1 is not functionally relevant in this context.
Further experiments are clearly needed.

References

Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the FTO gene is associated with body mass

index and predisposes to childhood and adult obesity. *Science* 11; 316:889-94, 2007.

Scuteri A, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S, Nagaraja R, Orru M, Usala G, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Ehret GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR. Genome-Wide Association Scan Shows Genetic Variants in the FTO Gene Are Associated with Obesity-Related Traits. *PLoS Genet*. 3: e115, 2007

Tschritter O, Preissl H, Yokoyama Y, Machicao F, Haring HU, Fritsche A. Variation in the FTO gene locus is associated with cerebrocortical insulin resistance in humans. Diabetologia 50:2602-3, 2007.