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On the History of *Fto*

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Catherine Woodroofe, a technician of the group (at that time at the EMBL in Heidelberg), was responsible for genotyping transgenic mice. One day (end of 1989) she showed up and reported that one mouse from a new litter born in the context of the generation of transgenic mice by microinjection of DNA displayed a malformation of both fore limbs. Since malformations can spontaneously happen, we were interested to see whether first this mouse was transgenic, second this phenotype was inheritable and third linked to the transgene. After a few months of breeding it was clear: the phenotype must be caused by insertional mutagenesis. Due to the limb phenotype, fusion of digits 1–4, we called the mutant Fused toes (*Ft*). Further inspection of the *Ft* mice revealed as the only additional alteration a hyperplasia of the thymus. In consequence these mice died several months after birth because breathing was impaired. Since the phenotype was already detectable in heterozygous animals, we checked homozygous *Ft/Ft* mice and realized an embryonic lethality: embryos displayed craniofacial malformations, pericard enlargements and a loss of left-right asymmetry. These embryos died due to a reduced heart function on about day 10 of development.

Frank van der Hoeven, another technician in the lab, started to clone the transgene integration site. Since only a rearranged version of the transgene was integrated, it took him a rather long time to be successful. However, with this integration site specific probe we were then able to map the mutation to the D region of chromosome 8 in the mouse [1]. About that time the lab moved from Heidelberg to the Medical School in Hannover and the project was continued by new people in the lab. It turned out that the transgene was not simply integrated into the mouse genome but had induced a deletion. Several PhD students (Ralf Lesche, Astrid Peetz, Katrin Ausmeier, Thomas Peters) worked on the characterization of this deletion which was growing and growing with every analysis of chromosomal walking, the method to analyze unknown genomes at that time. Finally, after several years of hard work and another move from Hannover to Düsseldorf, the deletion turned out to be 1.6 Mbp in length, surprisingly affecting in total only six genes [2]. On the one hand three genes which were in part described: the *IrxB* cluster consisting of *Irx3*, *Irx5* and *Irx6* [3], on the other hand three novel genes the first of which was named *Ft1* (today renamed *Fts*) [4]. The two other genes became more fanciful names: Fantom (*Ftm*) because we had a hard time to characterize its 5'end and its expression profile. Today we know that *Ftm* (renamed to *Rpgripl1*) codes for a protein localized at the basal body of cilia being there responsible for quantitative transmission of hedgehog signaling [5]. Furthermore, when mutated it causes the Joubert or the Meckel syndrome [6]. The other gene was the largest (about 350 kbp) which we found affected by the deletion. Therefore, we named it Fatso (*Fto*) [7].

Recently, several groups performed genome-wide association studies for human genes linked to obesity [8–10]. The gene which was reproducibly detected with a high score was *FTO*! (For those who are not familiar with genetic symbols: in the mouse genes are written *Xyz*, in humans *XYZ*). Before the first report about this association was published, Andrew Hattersley, one of the authors of these papers, realized the problem in keeping the argument for the gene name. Therefore, he renamed it in a clever way based on the novel phenotype by keeping the old symbol: fat mass and obesity related (*FTO*).

The basis for association of *FTO* and obesity is not at all understood. The studies have only suggested that it exists without giving a hint for the mechanism. Since sequencing of coding parts of the gene did not reveal mutations [8], regulation of *FTO* seems to be affected. Whether the consequences are changes in expression levels or a temporal or spatial deregulation of gene activity is completely unknown. Since we were interested in *Fto* function we have generated different mouse lines mutated for *Fto* function. Certainly, using these mice as model will help to unravel the relation of *FTO* and obesity and might be useful systems to try to interfere with *Fto* function.

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