Dll1 haploinsufficiency in adult mice leads to a complex phenotype affecting metabolic and immunological processes.

BACKGROUND: The Notch signaling pathway is an evolutionary conserved signal transduction pathway involved in embryonic patterning and regulation of cell fates during development and self-renewal. Recent studies have demonstrated that this pathway is integral to a complex system of interactions, involving as well other signal transduction pathways, and implicated in distinct human diseases. Delta-like 1 (Dll1) is one of the known ligands of the Notch receptors. The role of the Notch ligands is less well understood. Loss-of-function of Dll1 leads to embryonic lethality, but reduction of Delta-like 1 protein levels has not been studied in adult stage.

METHODOLOGY/PRINCIPAL FINDINGS: Here we present the haploinsufficient phenotype of Dll1 and a missense mutant Dll1 allele (Dll1(C413Y)). Haploinsufficiency leads to a complex phenotype with several biological processes altered. These alterations reveal the importance of Dll1 mainly in metabolism, energy balance and in immunology. The animals are smaller, lighter, with altered fat to lean ratio and have increased blood pressure and a slight bradycardia. The animals have reduced cholesterol and triglyceride levels in blood. At the
immunological level a subtle phenotype is observed due to the effect and fine-tuning of the signaling network at the different levels of differentiation, proliferation and function of lymphocytes. Moreover, the importance of the proteolytic regulation of the Notch signaling network emphasized.

CONCLUSIONS/SIGNIFICANCE: In conclusion, slight alterations in one player of Notch signaling alter the entire organism, emphasizing the fine-tuning character of this pathway in a high number of processes.