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## **Integrative genomics analysis of blood and microbiota data suggests a NAFLD-related disorder in SLAdd minipigs**

Marco Moroldo, Peris Munyaka, Jérôme Lecardonnel, Gaëtan Lemonnier, Eric Venturi, Claire Chevaleyre, Jordi Estellé, Claire Rogel-Gaillard

Minipigs are a group of small-sized swine lines (i.e. 20 to 90 kg) with major physiological differences compared to conventional pigs, and most of them tend to be obese. The inbred SLAdd (DD) minipig line is homozygous at the MHC locus (Hp4.4 haplotype) and is especially susceptible to obesity.

Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease in Western countries that is linked to obesity, type 2 diabetes mellitus and cardiac pathologies. Minipig lines could be useful animal models to study this disease.

To characterize the metabolic disorders that affect DD pigs, we measured intermediate phenotypes from blood and faeces and used Large White (LW) pigs as controls. Three datasets were produced, i.e. complete blood counts (CBCs), microarray-based blood transcriptome, and faecal microbiota characterized by 16S rRNA sequencing.

Compared to LW pigs, several NAFLD-related blood parameters such as hematocrit and platelet distribution were higher in DD pigs, whereas lymphocyte counts was lower.

Transcriptome profiling identified 3,046 differentially expressed genes (DEGs), many of which were found in NAFLD-related pathways, such as 'adipogenesis', 'insulin resistance', 'sirtuin signaling', 'hepatic fibrosis', 'mTOR signaling' and 'endoplasmic reticulum stress'.

16S rRNA sequencing confirmed these findings, but highlighted obesity more clearly. The Firmicutes to Bacteroidetes ratio was higher in the DD (2.7) than in the LW group (1.6). The

Clostridiaceae and Prevotellaceae families and the *Clostridium* and *Streptococcus* genera were more abundant in DD pigs, while *Prevotella* was less abundant.

To refine this analysis, we used integration methods. A first sPLS analysis highlighted associations between CBCs and DEGs such as *RAB40B* and *VNN2*. A second sPLS identified links between genera such as *Prevotella* and DEGs such as *FUT1*, *STX12* and *DIRAS2*. Lastly, an MFA analysis showed that the data structure was mainly determined by the breed.

Our results show that DD pigs present symptoms of a NAFLD-related disease. Thus, exploring intermediate phenotypes of minipig lines could identify new models to study metabolic diseases.