The second year is characterised by the continuation of the large scale data collection in Pillar 1 and brings the project to the beginning of the data integration phase.

- a total of 26 strains were sequenced with a minimum depth of 20x (with more in progress) and genome-wide inventories of genetic variations will be included in the upcoming new rat genome reference sequence (WP 1.1 – genome sequencing);
- more than 4000 differentially expressed genes in each heart and liver were identified in the parental strains of the BXH/HXB RI panel (WP 1.2 - transcriptome);
- DNA methylation, chromatin and Pol II state maps were produced for various rat tissues in the RI parental strain as well as nucleosome modifications in the RI panel, leading to eQTLs with potential phenotypic effects (WP 1.3 - epigenetics);
- improved methodology for the platform has shortened the proteome analysis significantly and measurements in 25 tissues and the BXH/HXB RI panel is under way (WP 1.4 - proteomics);
- metabonomic profiling of tissue extracts and biofluids has led to first metabonomic QTL mapping (WP 1.5 – metabonomics).

A data sharing infrastructure was established at the EBI and includes data from all other work packages in order to be integrated for network analysis (WP 1.6 – data infrastructure and WP 2.1 – regulatory networks). phQTLs, mQTLs, pQTLs, eQTLs and epiQTLs derived from the analysis of the large scale data collection in work packages 1.1 to 1.5 were used to generate QTL maps for the identification of hundreds of regulatory networks across different tissues and associated with phenotypes for the exploration of network specific integrated QTLs (iQTLs). This led to causal modelling approaches to link histone trimethylation and expression levels to genome-wide genetic variation across the rat genome.

Methods for the targeted rat genome modification are the target of WP 2.2. Within this work package, a fourth shRNS transgenic rat line has been developed and more than one hundred chimaeric rats were generated through homologous recombination. Efficient and reproducible transgenesis based on the Sleeping Beauty transposon vector has been established. Thus, we seem to be able to address the major problems of transgenesis, namely, inefficient germline transmission and unpredictable gene expression including silencing. Also, knock-out rats have been produced using the Zinc-Finger as well as the TALEN technology, the ENU mutant repository has been completed and minimal congenic strain approaches led to positional cloning of genes involved in experimental autoimmune encephalomyelitis (EAE).

In the heterogeneous stock (HS) rats, the genetic mapping of all phenotypes was completed and integrated with sequence analysis. Implementation of the ancestral haplotype reconstruction method using a mixed models analysis and the subsequent categorization of all sequence variants are likely functional and causal for the relevant phenotypes (WP 3.1 – comparative analysis).

Work packages 3.2 (integration with hGWAS) and 3.3 (validation in human tissues) will be mainly active in the second half of the project runtime. Nevertheless, data is constantly integrated with ENSEMBL and RGD databases and their relevant functionality and human cells and tissues are continued to be collected and processed.

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