In the German Mouse Clinic (GMC, www.mouseclinic.de) we offer a standardized comprehensive phenotypic analysis of mouse mutant lines (MMLs) to the scientific community. The mice are non-invasively and systematically analyzed in a primary screen (Figure 1) for the key parameters of different organ systems or pathways. In secondary and tertiary tests, experiments for a more detailed phenotypic characterization can be performed. In this multi-institutional approach, scientists from the areas allergy, behaviour, cardio-vascular, clinical chemistry, dysmorphology, energy metabolism, eye development and vision, host-pathogen interactions, immunology, lung function, molecular phenotyping, neurology, nociception, steroid metabolism and pathology contribute with their specialized know-how to the success of the project. In the 14 screens more than 240 parameters can be analysed from each single mouse, yielding in a complete picture of the mutant’s phenotype, and answering the question of the gene’s function and its potential pleiotropic effects. In the first 63 mutant lines that have completed the primary screen, we have found in 95% of the mutant lines new phenotypes in the screens of the GMC (Figure 2).

The German Mouse Clinic is a partner of EUMORPHIA (www.eumorphia.org) and the EUMODIC consortium (www.eumodic.org). In the GMC the standardized protocols are applied that have been worked out in collaboration with our European partners.

As a further step, genotype-environmental interactions will be analyzed by the GMC. Therefore, five environmental platforms have been established where challenge-tests are run. The platforms include challenges for nutrition and diet, air, stress, infection and physical activity.

In the Dysmorphology, Bone and Cartilage Screen of the GMC we established a battery of standardized tests for primary, secondary and tertiary analysis of mice. Alterations in bone and cartilage development, growth and mineralization, modelling and remodelling, as well as aging and immune system effects, can be monitored.

In the primary screen for dysmorphology, bone and cartilage the mice are investigated by anatomical observation at the age of nine weeks. X-ray analysis, as well as DEXA scans, are performed in sixteen-week-old mice. If there are significant differences detectable in the parameters of the primary screen, secondary and tertiary tests can be selected. Depending on the phenotype from the primary bone screen and the results of the other screens within the German Mouse Clinic further experiments will be planned. Morphological changes will be followed up by micro-computed tomography. More detailed information about mineralization defects will be obtained by pQCT analysis. Using a three-point bending test the elasticity and stability of the bone can be analyzed in prepared femurs. In addition, we built up a cell culture lab for the analysis of osteoblast and osteoclast cultures. These cultures will then be analyzed for bone metabolism parameters like RNA-expression profiling, immune-cytochemical analysis or analysis of enzyme activities.

Sixty-three mutant mouse lines and 12 inbred or hybrid strains have already finished the phenotypic analysis in the Bone and Cartilage module. In 26 lines we could not detect any alterations in any of our parameters. In 10 lines we found altered parameters, but without recommendations for further analysis in secondary tests. In 16 mutant lines we could confirm already known skeletal abnormalities and bone phenotypes. In 13 out of the 16 cases, we found additional bone-related phenotypes. In 11 mutant lines, no bone and skeletal abnormalities were known before the GMC pri-
primary screen, and we could detect new phenotypes. Fifteen mutant lines that showed interesting changes in a series of parameters were considered as potential model organisms, and additional mice are in progress of secondary screening or are in preparation for secondary screening.

In the secondary screen, detailed analysis of mutant lines with known defects in bone metabolism is performed. Mutant lines with digit abnormalities and abnormal bone development are under investigation. Final experiments in a mutant line with brittle bone disease have been performed. Two mutant lines that are potential models for rheumatoid arthritis are in progress of characterization. These mutant lines are also of special interest because they might help to detect a major gene responsible for the disease as well as additional modifying genes.

The environmental platform for physical exercise and activity has been established by the Dysmorphology, Bone and Cartilage Screen of the German Mouse Clinic. Two challenge experiments using a treadmill for endurance activity and a jump box for maximum force applications are currently under development.

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References
