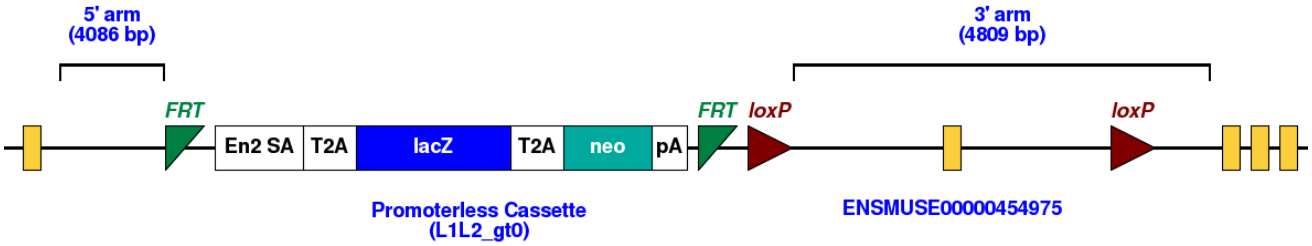
Knockout mouse lines presenting with welfare issues affecting their survival (abnormal survival [MP:0010769]) are processed through a bespoke sub-pipeline known as the "sick mouse procedure" (SMP) to maximise information collected on that mouse line. Matched wild-type controls are also processed to identify phenotypic abnormalities arising from the targeted allele.

Zfp106$^{tm1a(KOMP)Wtsi}$

Zinc finger protein 106

Genetic Background: C57BL/6Dnk;C57BL/6Brd-Tyr^{c-Brd};C57BL/6N

ES Cell Clone: EPD0033_4_C03



Affected genotypes

Homozygous (*Zfp106*$^{tm1a(KOMP)Wtsi/\ tm1a(KOMP)Wtsi}$).

Alternative breeding strategy

Following initial welfare observations, wild-type x heterozygous mating strategy was employed to complete phenotyping work in standard pipeline using heterozygous mice only.

Heterozygous mice showed no significant phenotypic findings on the primary screen.

Welfare observations

Homozygous mice exhibit:

- Progressive neuromuscular degeneration leading to loss of muscle tone.
- Tremors and paralysis of the hind limbs in particular.
- Gradual inability to independently access diet and water. Provision of floor pellets and long water spouts are required from six weeks of age. By twelve weeks of age all homozygotes are Schedule 1 euthanised.

Homozygous Viability:

All genotyped mice from het x het intercross considered. When at least 28 mice are available, viability is calculated. *[>13% = Homozygous viable; >0% and <13% = Sub-viable; 0% = Lethal]*

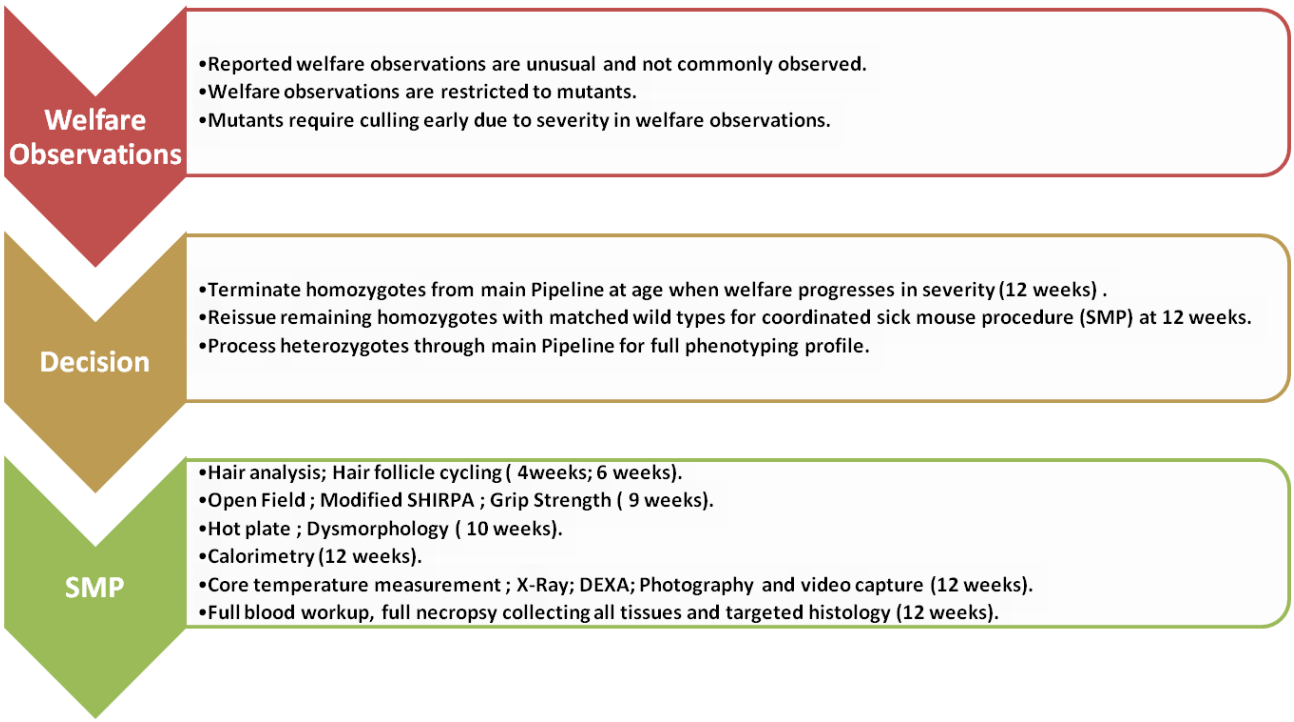
- **Viable** : 78Homs / 370 Total = 21.08 %

Sick Mouse Procedure (SMP)

Initial welfare observations were reported when the first homozygotes were born during the breeding and expansion stage. Homozygotes were still viable when issued to the phenotyping pipelines (4 weeks) but severity progressed rapidly by 6 weeks of age.

Welfare observations in homozygotes described above progressed to moderate severity at 12 weeks of age upon which SMP (see schematic below) was initiated. 10 male and 6 female homozygotes were processed alongside 10 male and 7 female matched wild-types. No further homozygotes were phenotyped due to the aforementioned alternative breeding strategy employed to reduce further welfare implications.

Schematic Outline of Bespoke SMP Pipeline



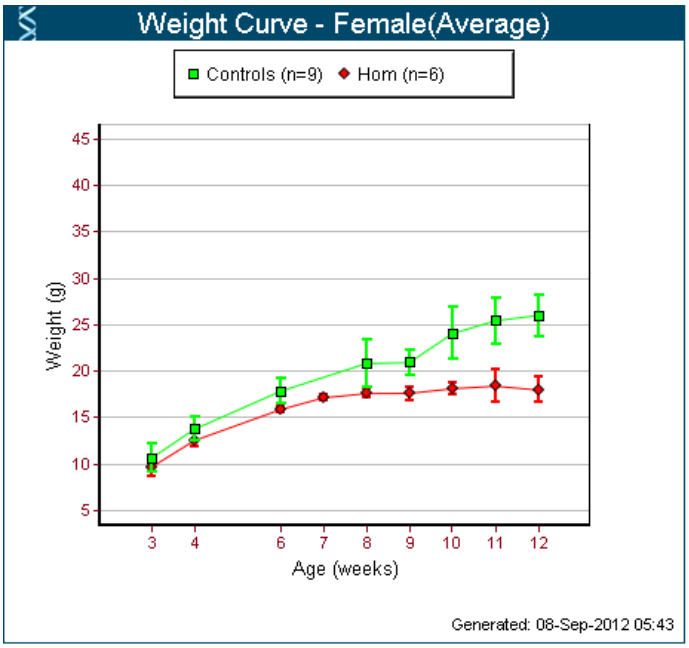
Phenotyping Heat Map

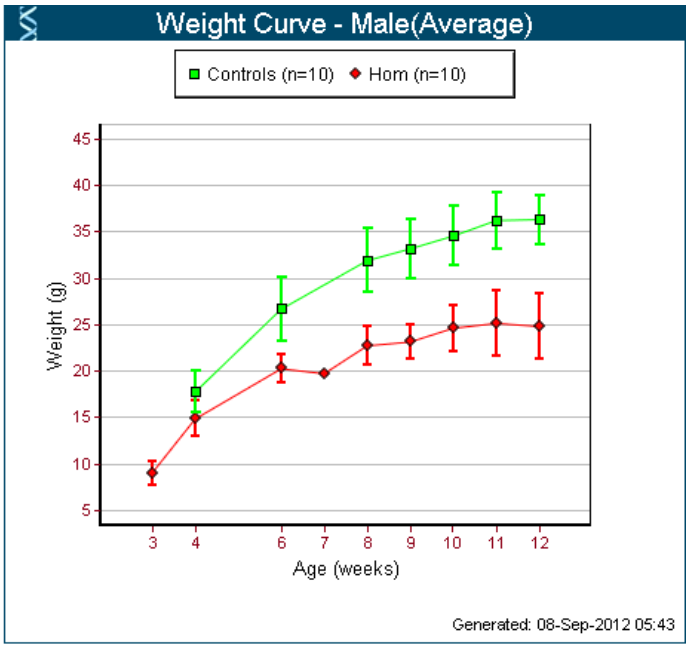
Colony Prefix	Allele Name	Genotype	Weight Curves	Hair Analysis	Hair Follicle Cycling	Open Field	Modified SHIRPA	Grip Strength	Hot Plate	Dysmorphology	Indirect Calorimetry	Core Temperature	Body Composition (DEXA)	X-ray Imaging	Plasma Chemistry	Haematology (CBC)	Peripheral Blood Lymphocytes	Heart Weight	Tail Epidermis Wholemount	Brain Histopathology	Tissue Biobank
MAKB	Zfp106<tm1a(KOMP)Wtsi>	Homozygous																			

Significant / Interesting
Not significant
Resources available

Phenotyping data of interest (significant changes)

In life phenotyping

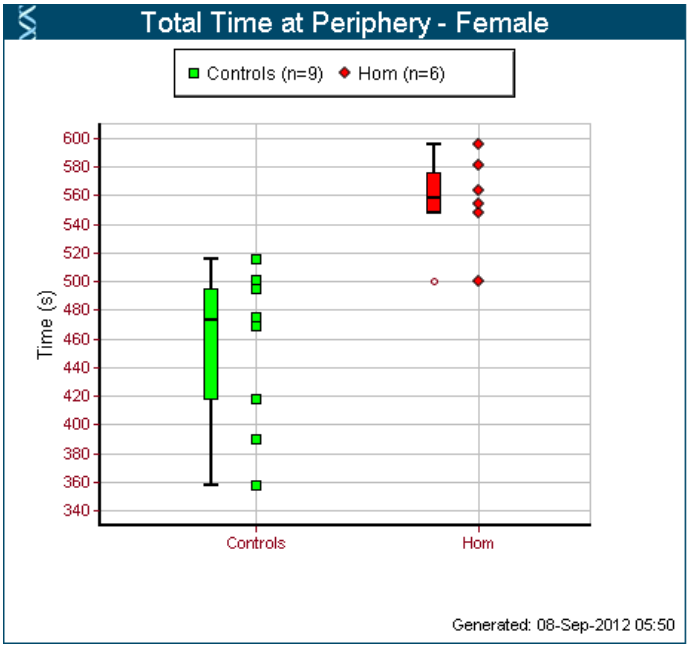


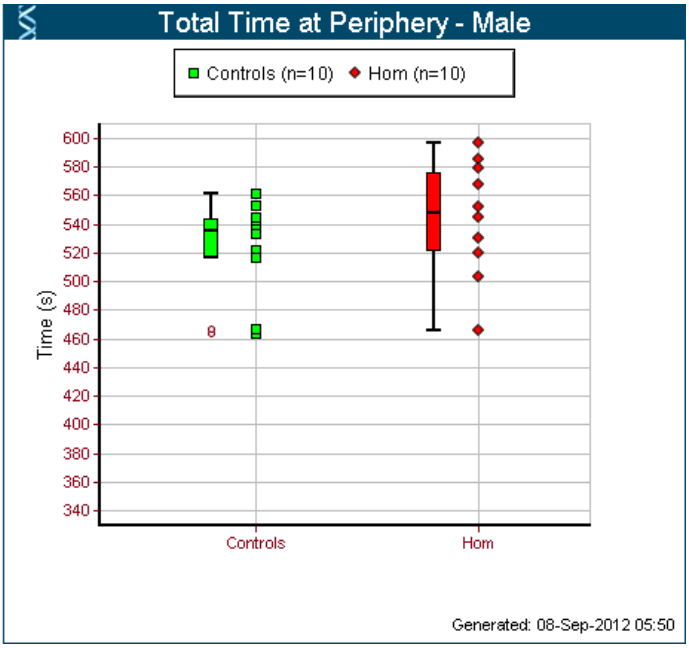


Males and Females - Reduced body weight [MP:0001262]

Mice were fed on High-Fat Diet (21.4% crude fat content, Western RD, 829100, Special Diets Services) from 4 weeks of age.

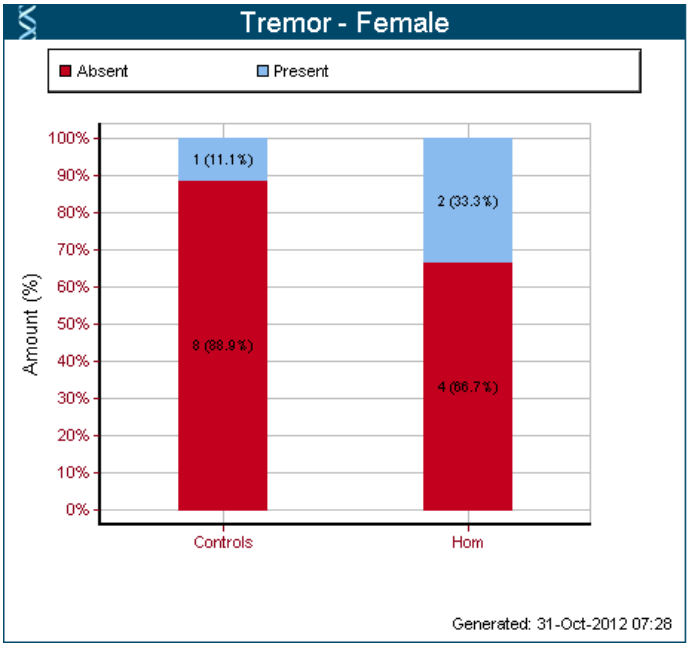
Open Field

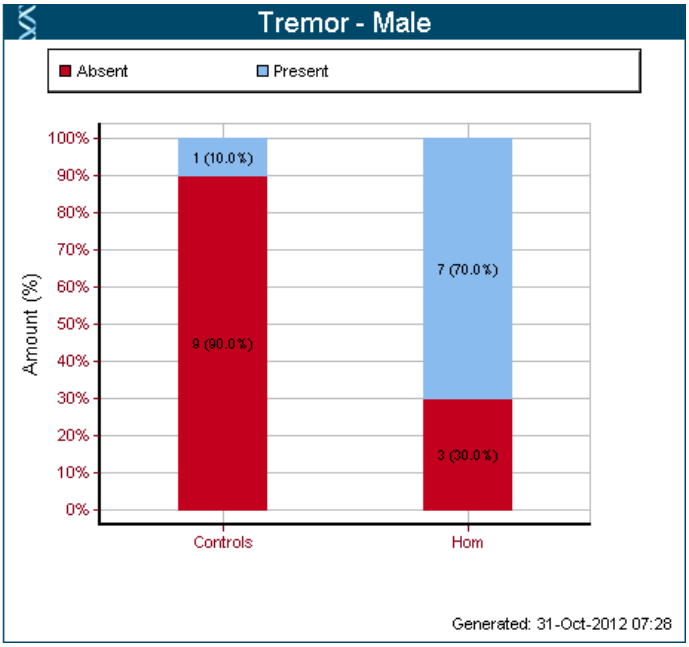




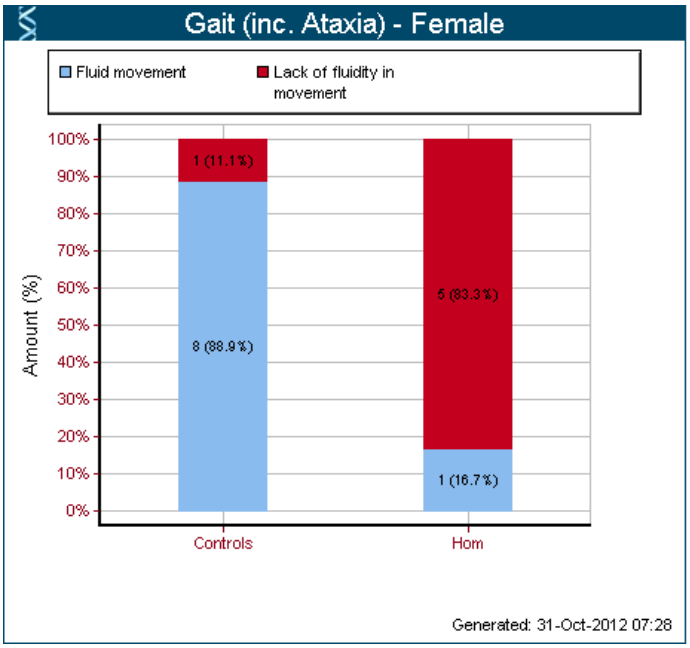
Females - Abnormal behavior [MP:0004924]

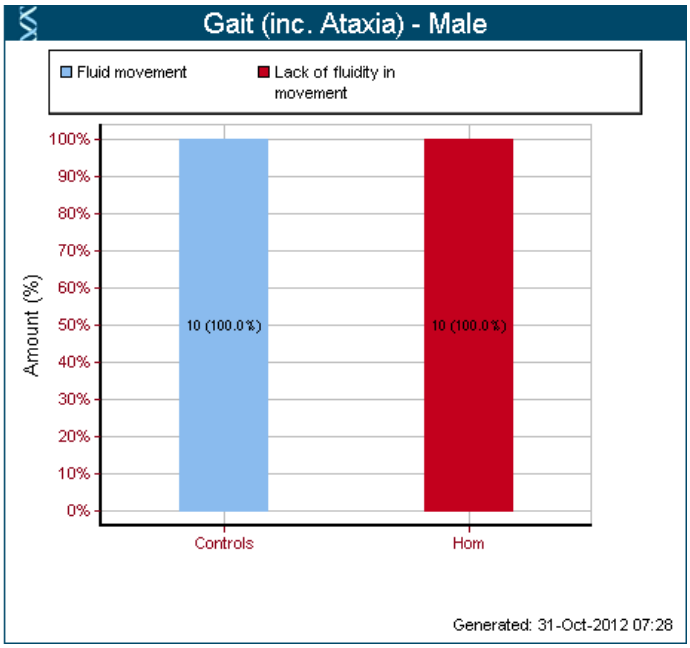
Modified SHIRPA



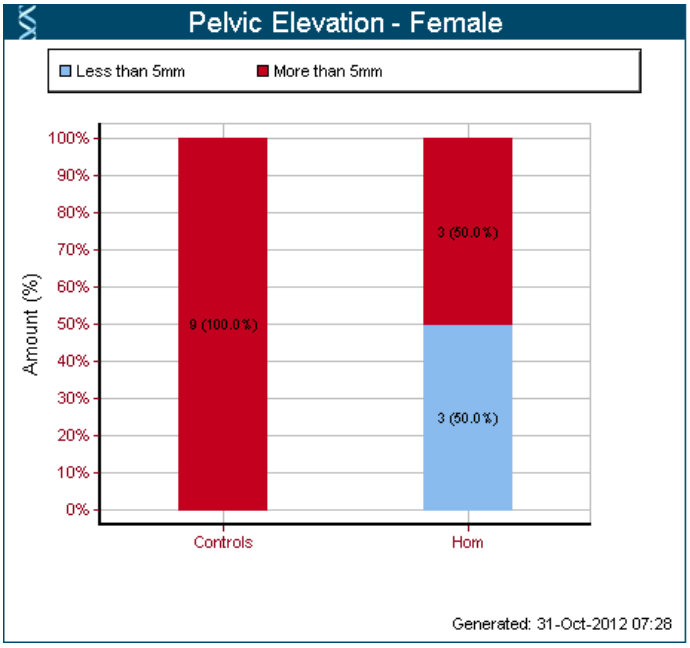


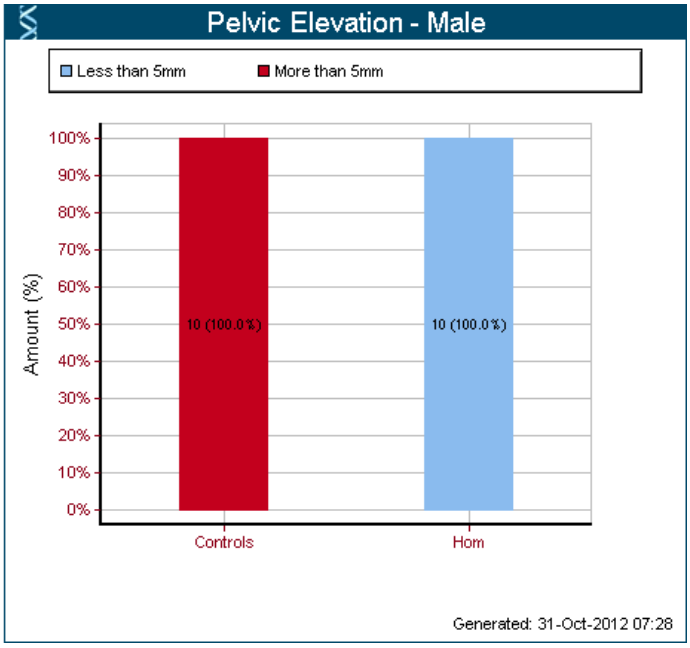
Males - Tremors [MP:0000745]





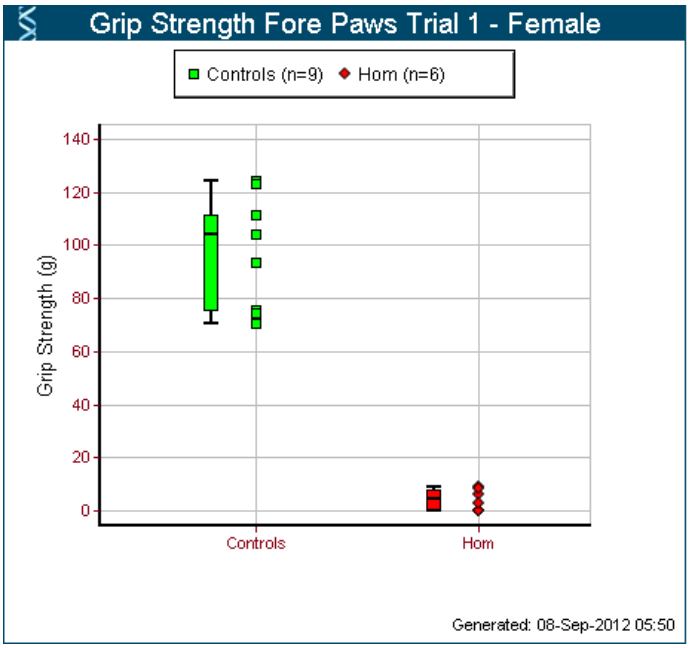
Males and Females - Abnormal gait [MP:0001406]

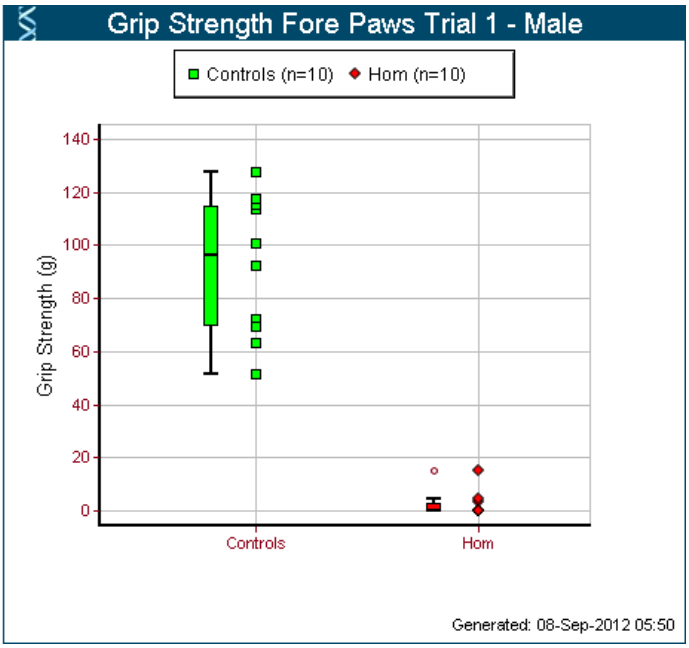




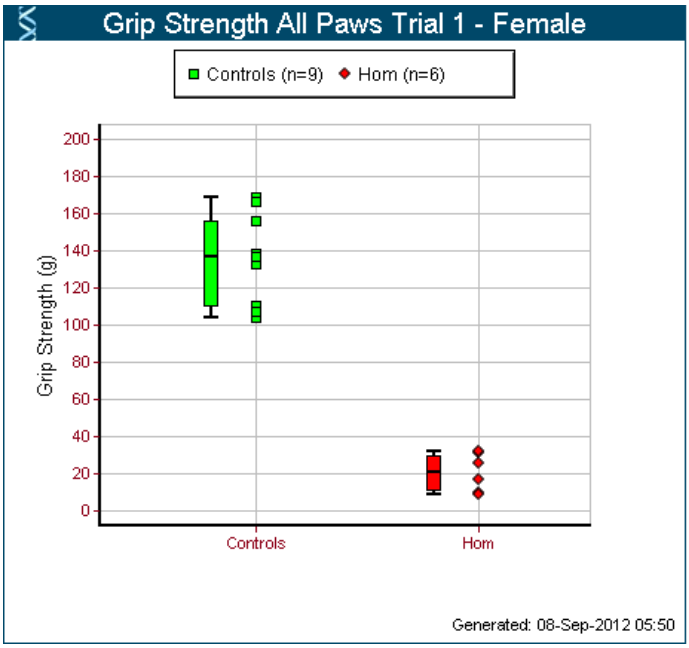
Males and Females - Abnormal gait [MP:0001406]

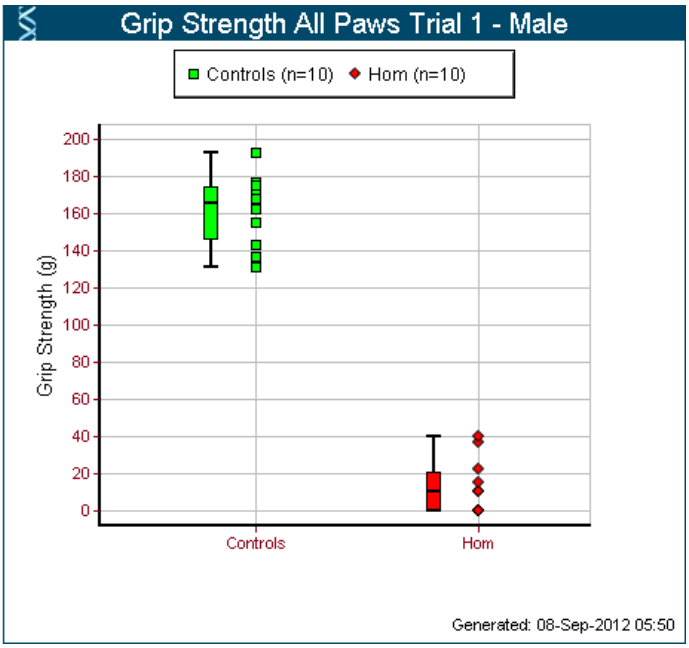
Grip Strength





Males and Females - Decreased grip strength [MP:0010053]





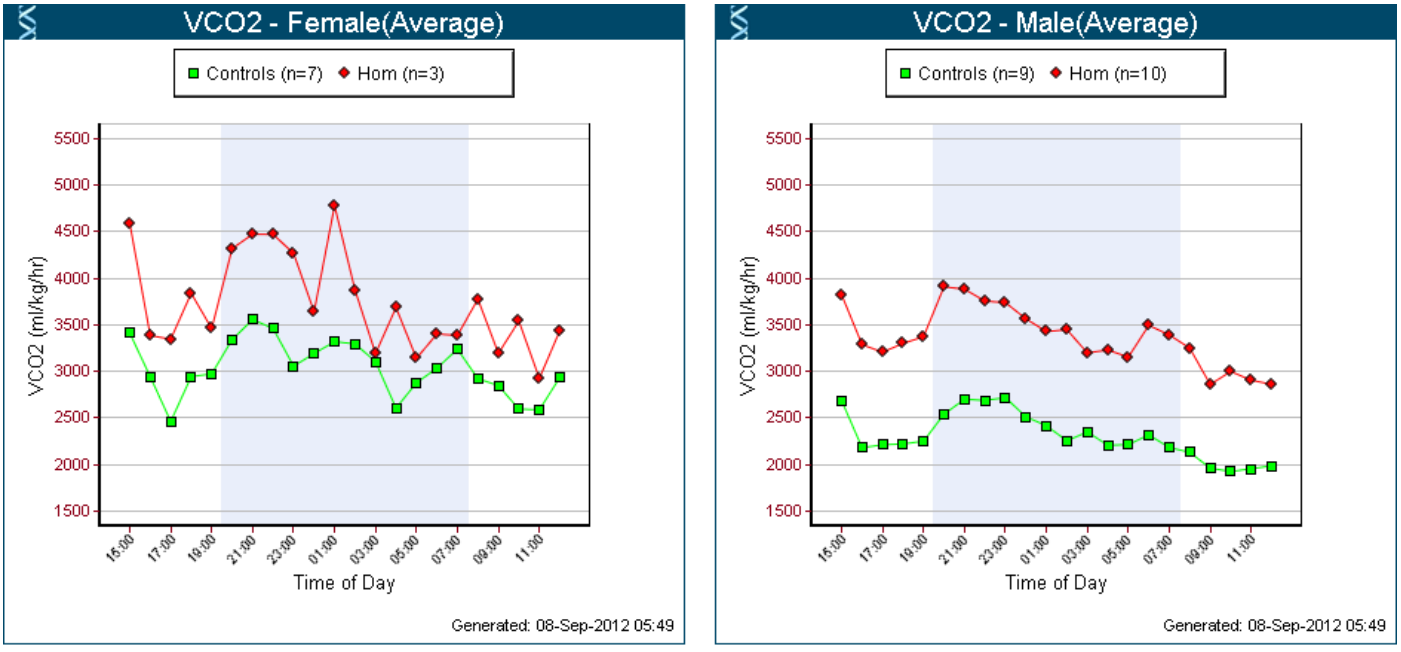
Males and Females - Decreased grip strength [MP:0010053]

Dysmorphology Images

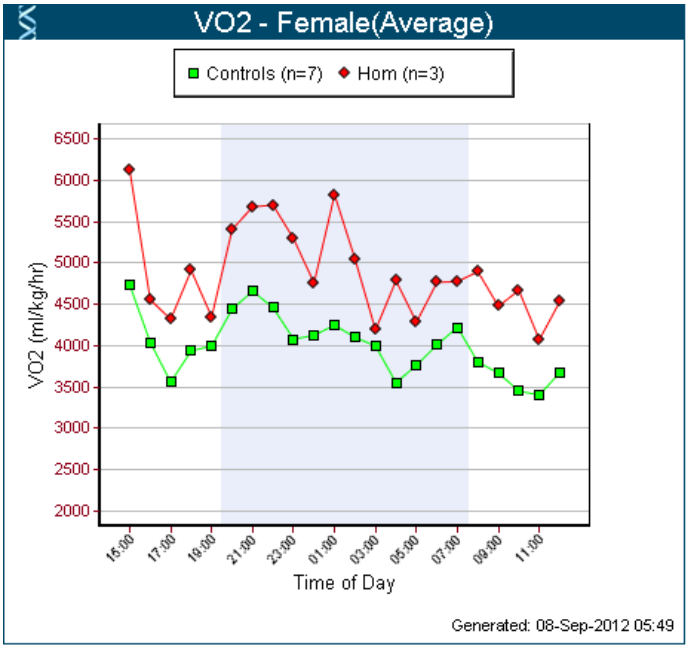
a b

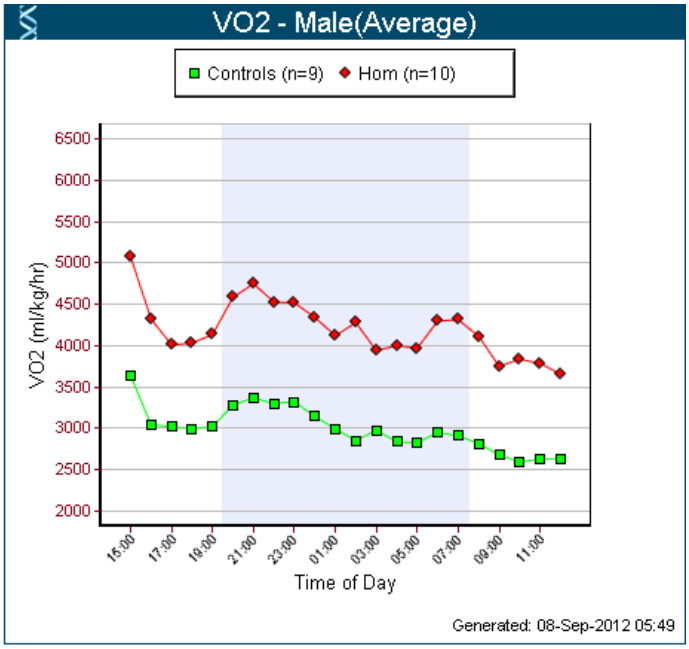
Figure 1. Ventral view of wild-type (a) and homozygous (b) mice showing abnormality in hind paw morphology (abnormal autopod morphology [MP:0000572]) in homozygotes (indicated by yellow arrows).

Indirect Calorimetry

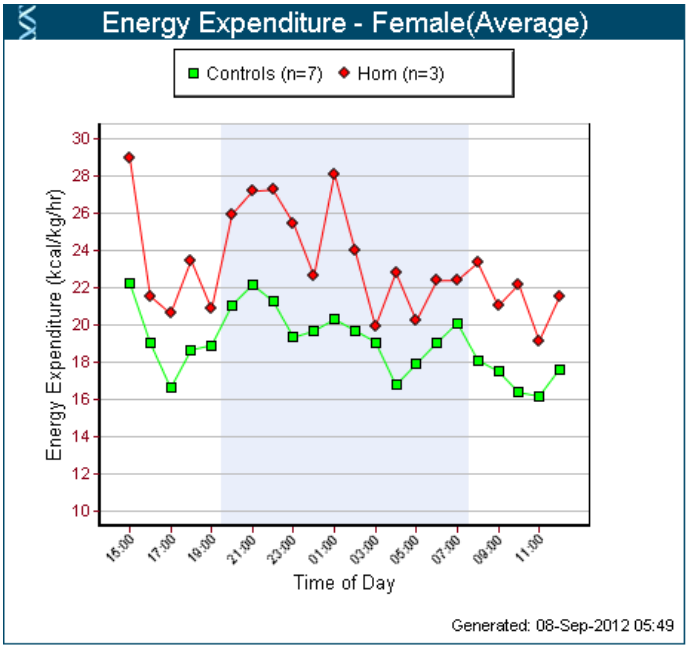


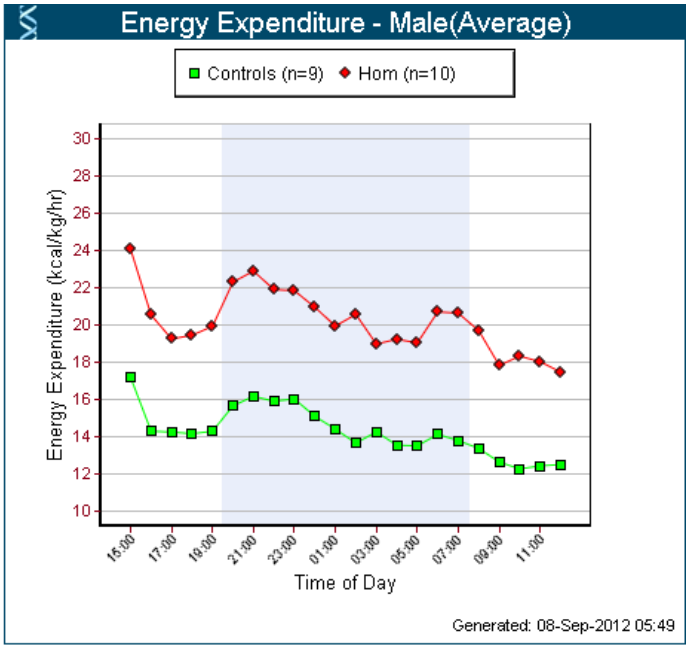
Males and Females - Increased carbon dioxide production [MP:0008963]





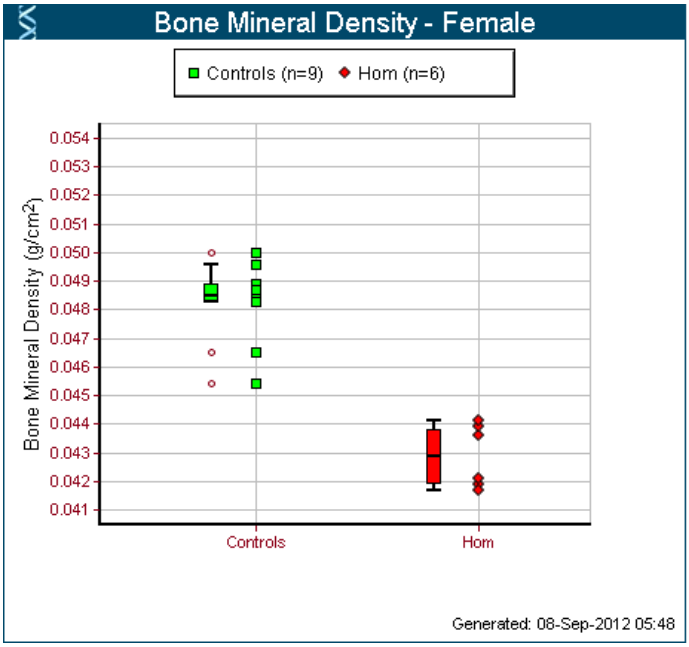
Males and Females - Increased oxygen consumption [MP:0005289]

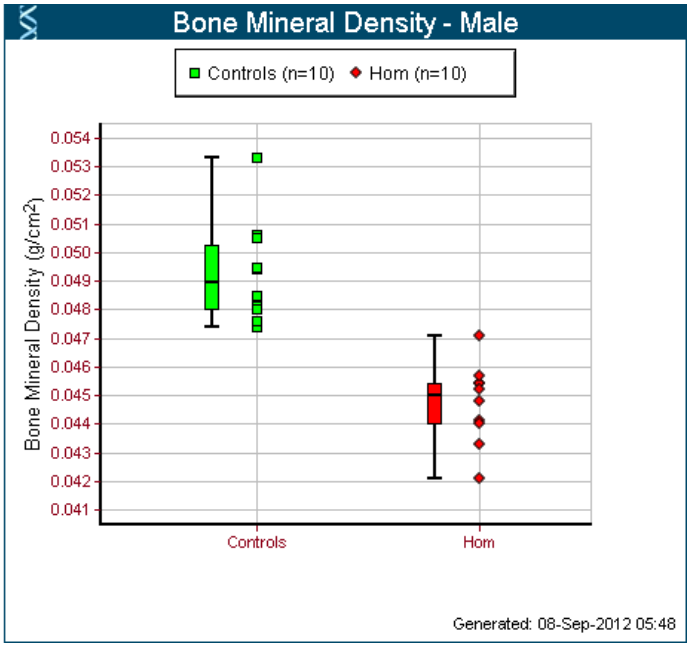




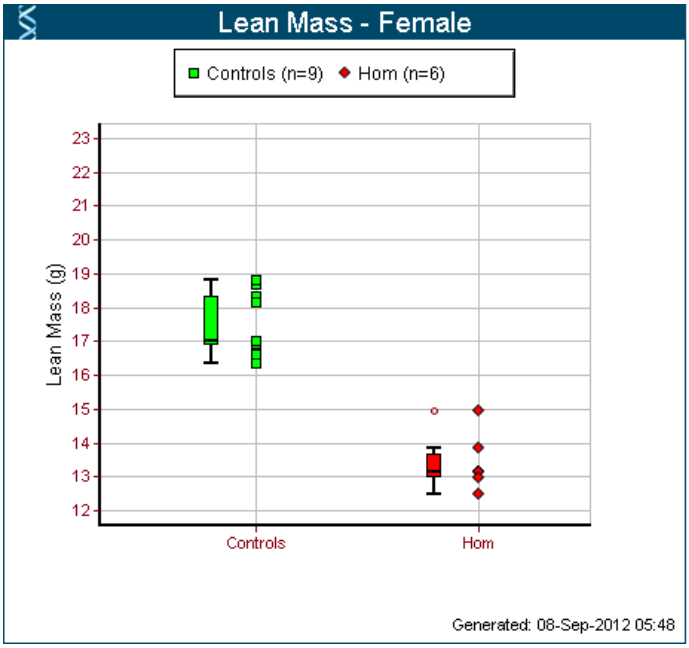
Males and Females - Increased energy expenditure [MP:0004889]

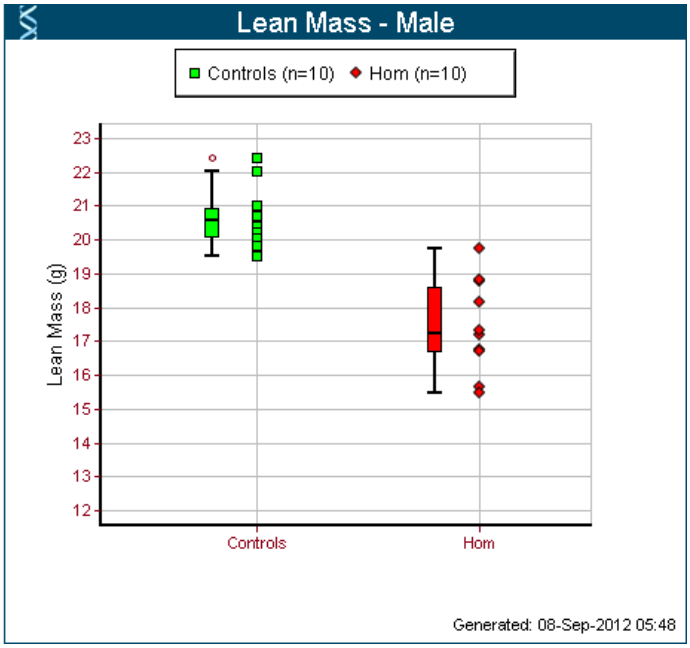
Body Composition (DEXA)





Males and Females - Decreased bone mineral density [MP:0000063]

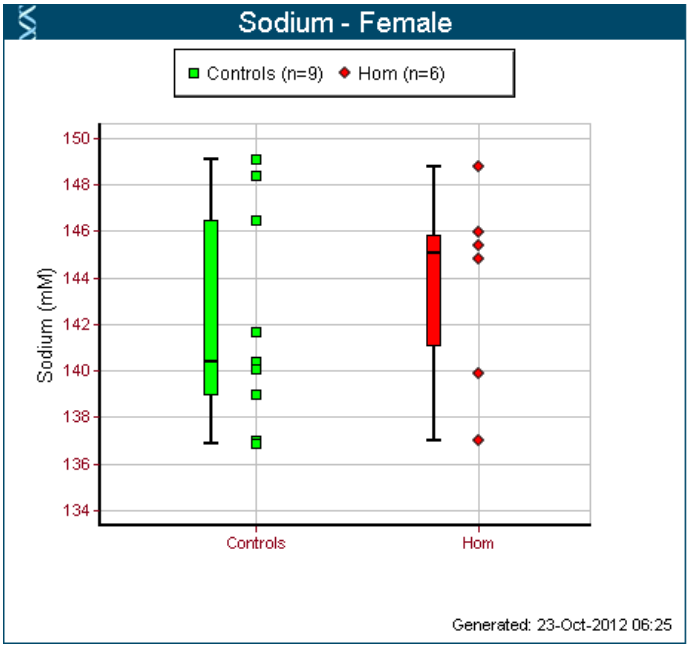


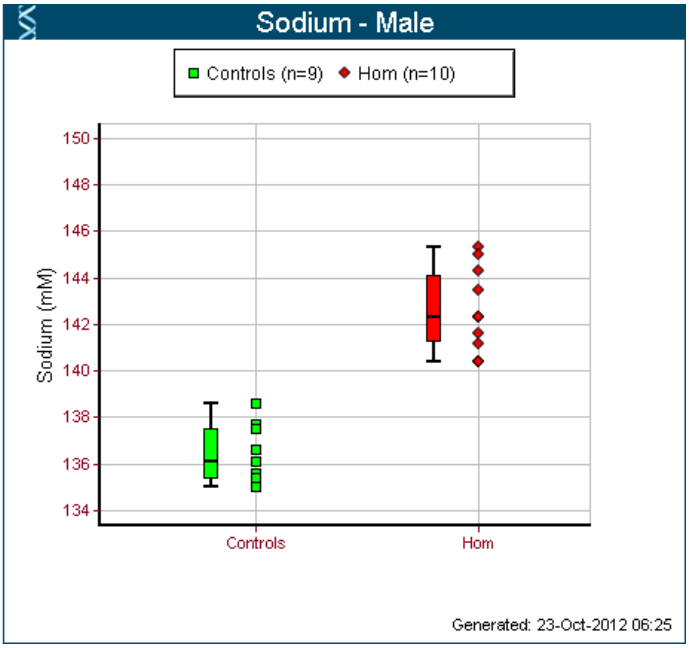


Females - Decreased lean body mass [MP:0003961]

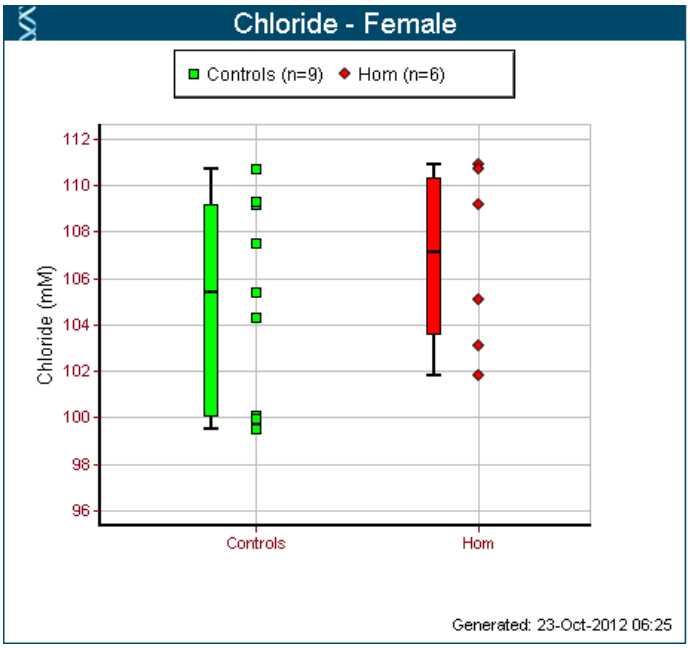
Ex vivo phenotyping

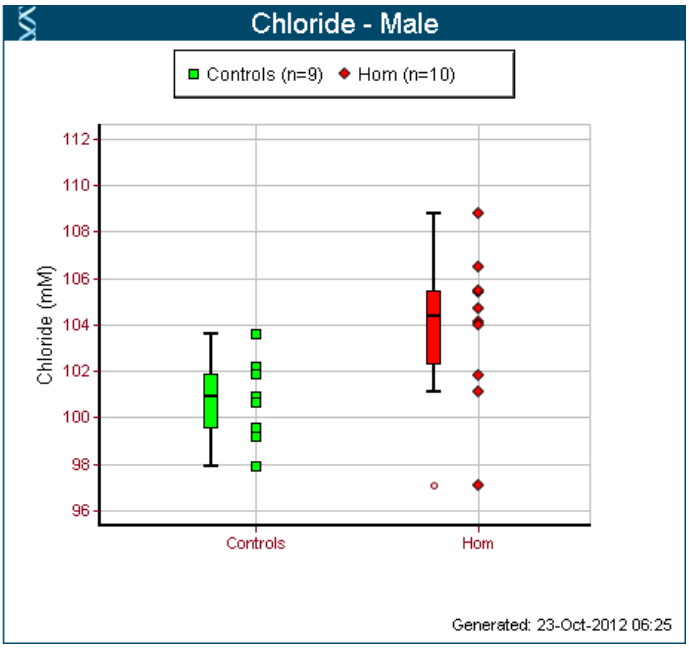
Plasma Chemistry



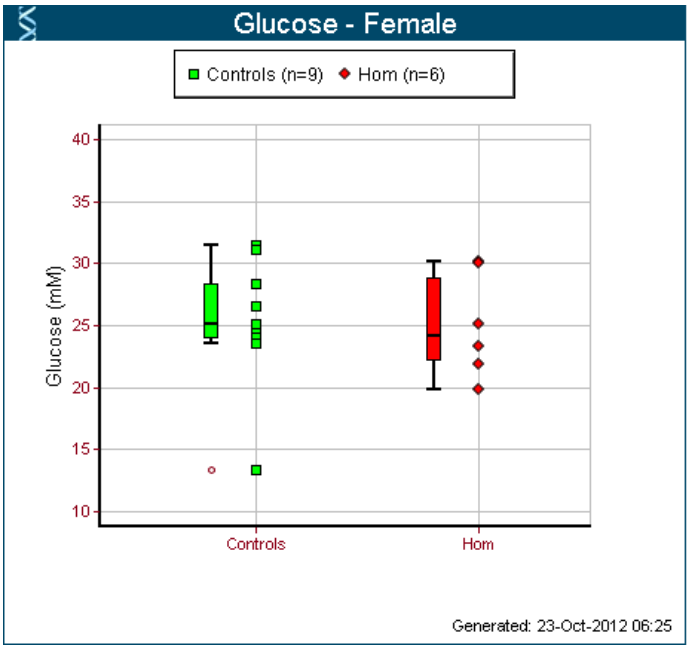


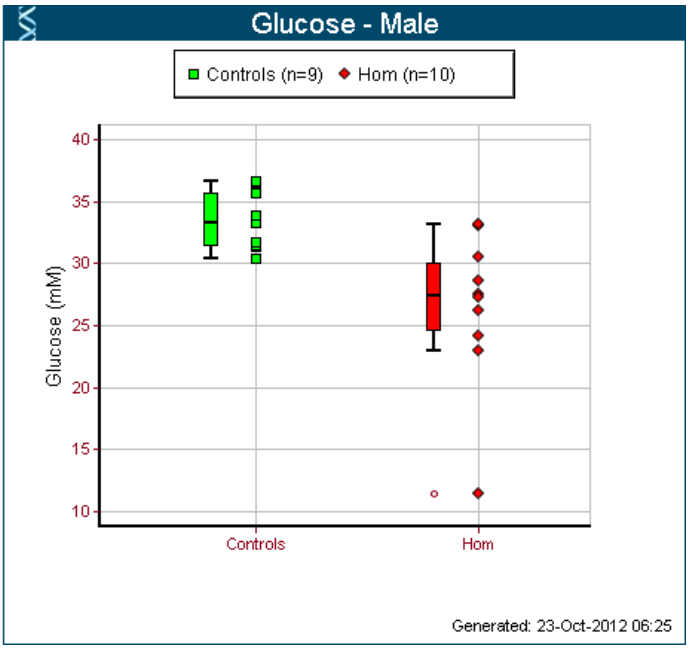
Males - Increased circulating sodium level [MP:0005633]



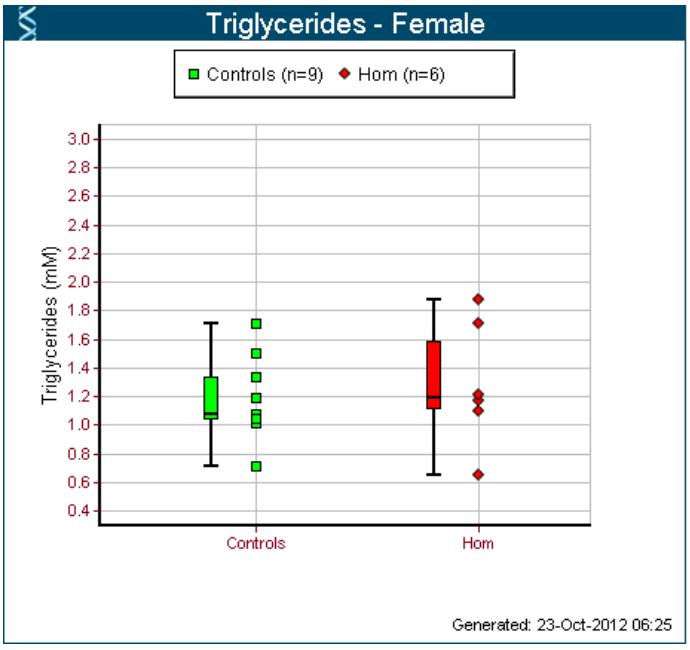


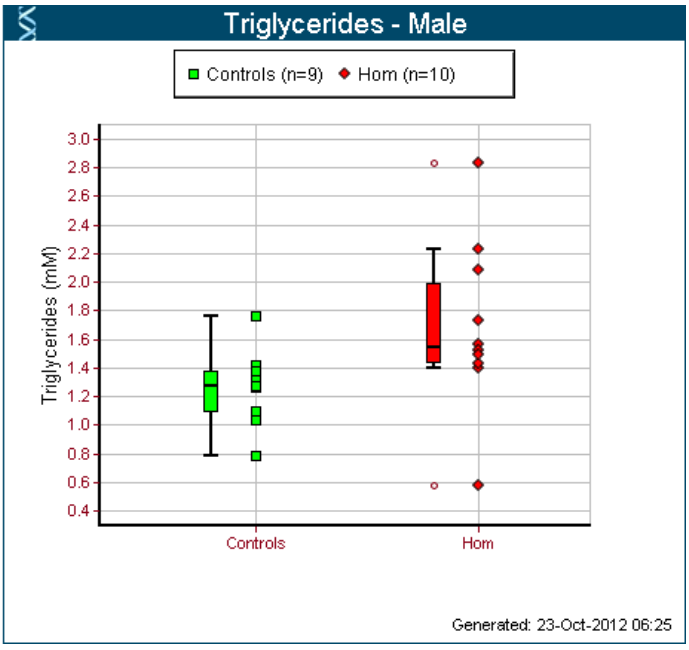
Males - Increased circulating chloride level [MP:0003019]



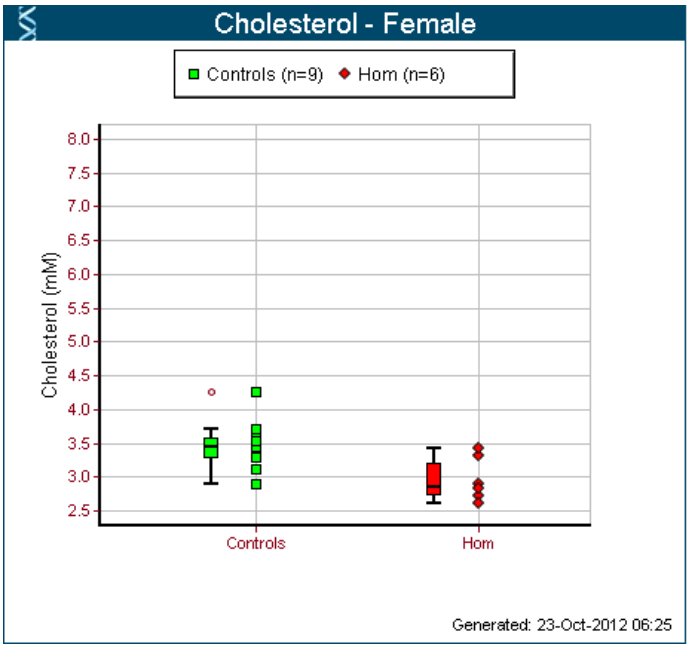


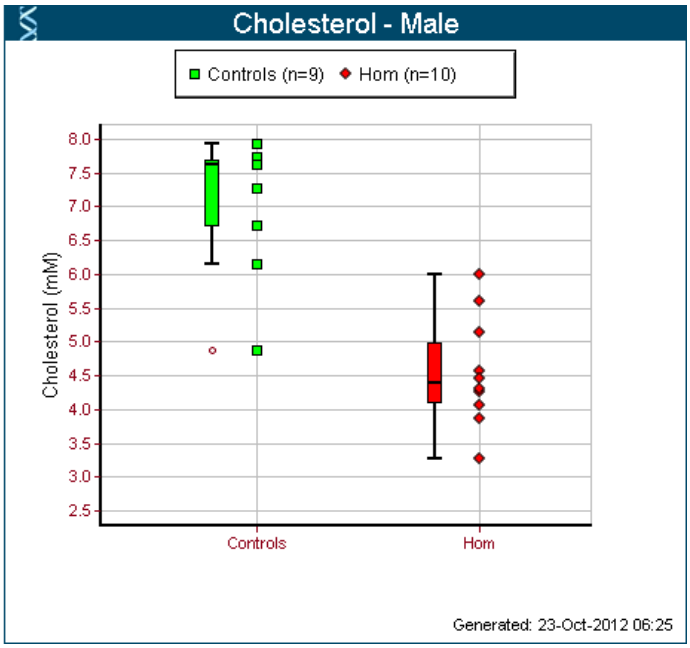
Males - Decreased circulating glucose level [MP:0005560]



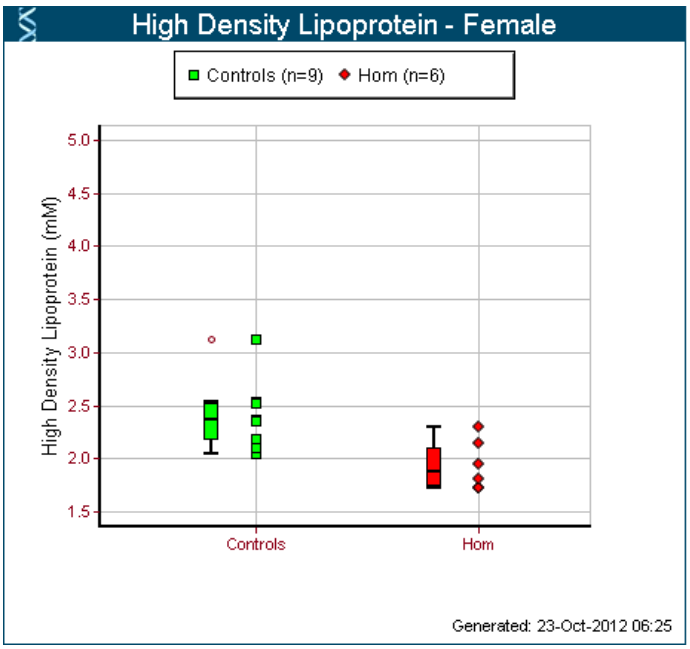


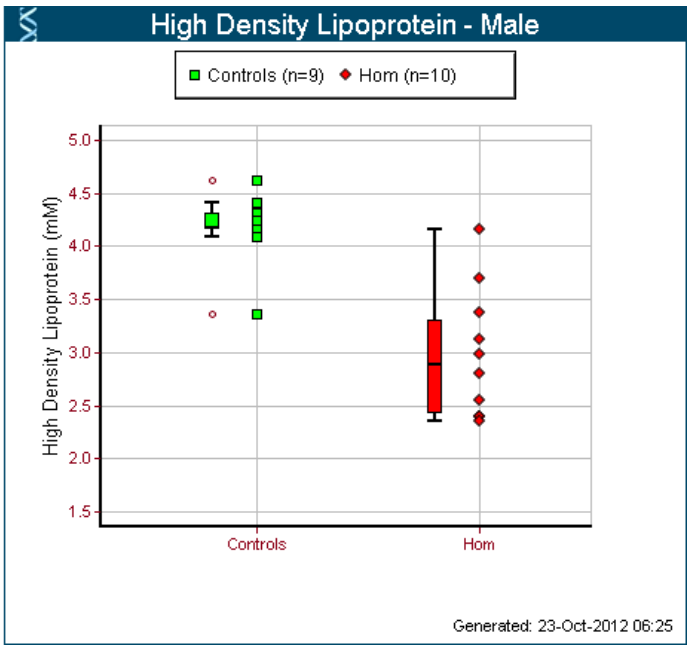
Males - Increased circulating triglyceride level [MP:0001552]



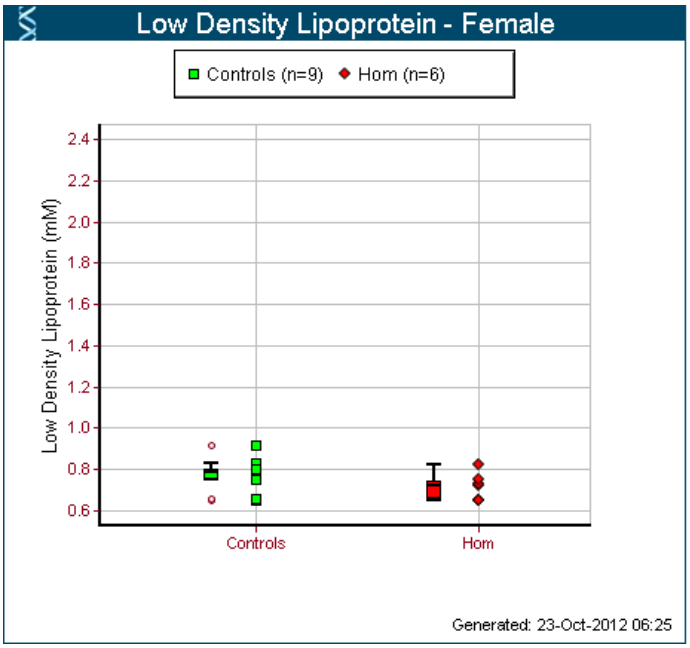


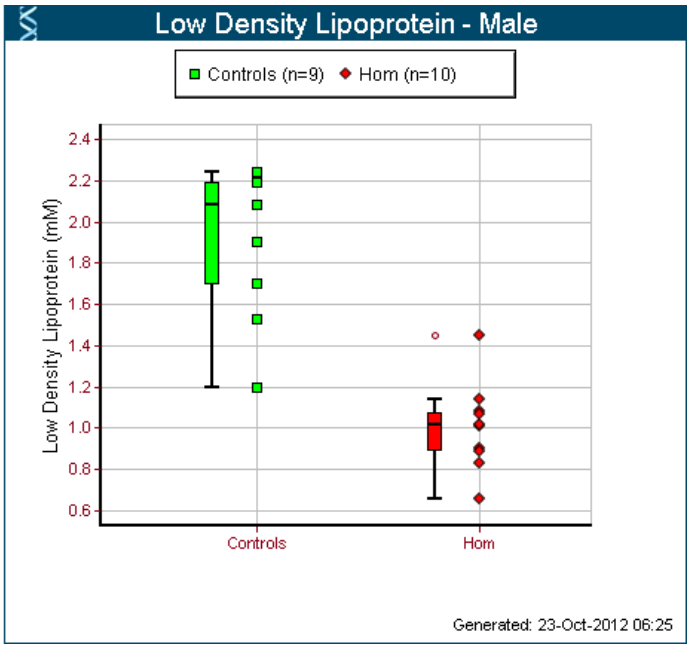
Males and Females - Decreased circulating cholesterol level [MP:0005179]



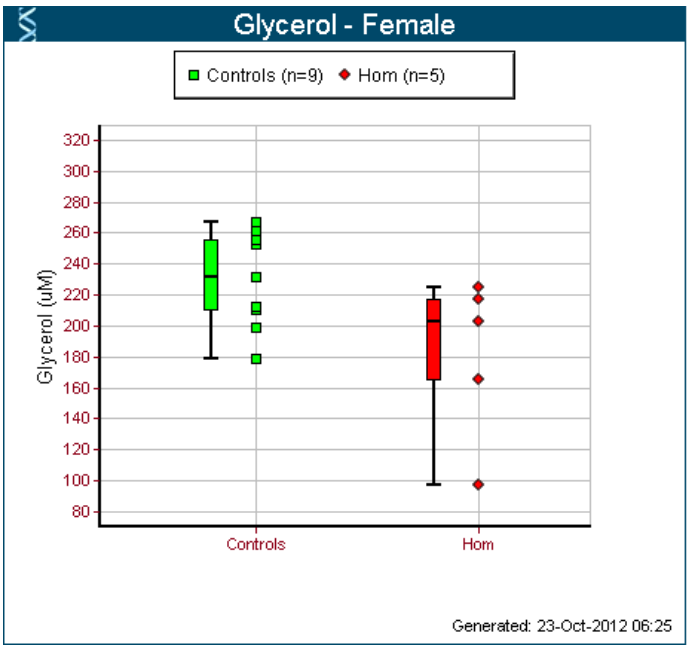


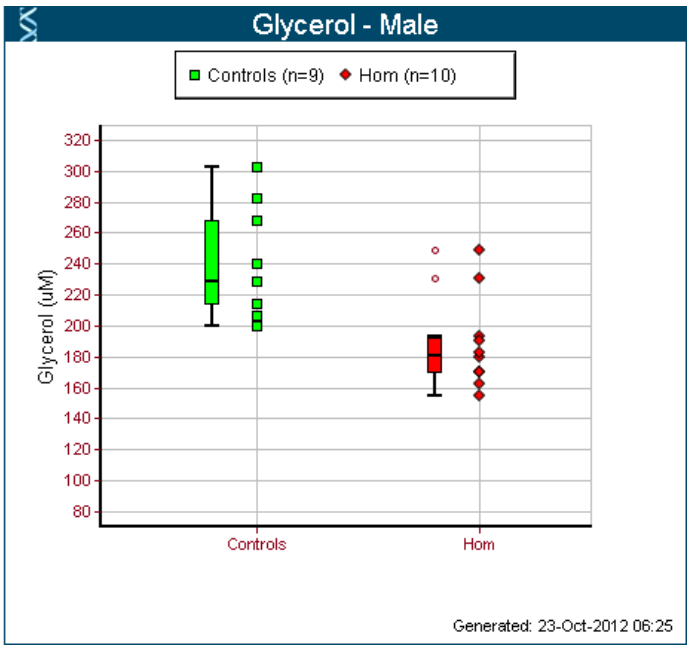
Males and Females - Decreased circulating HDL cholesterol level [MP:0000186]



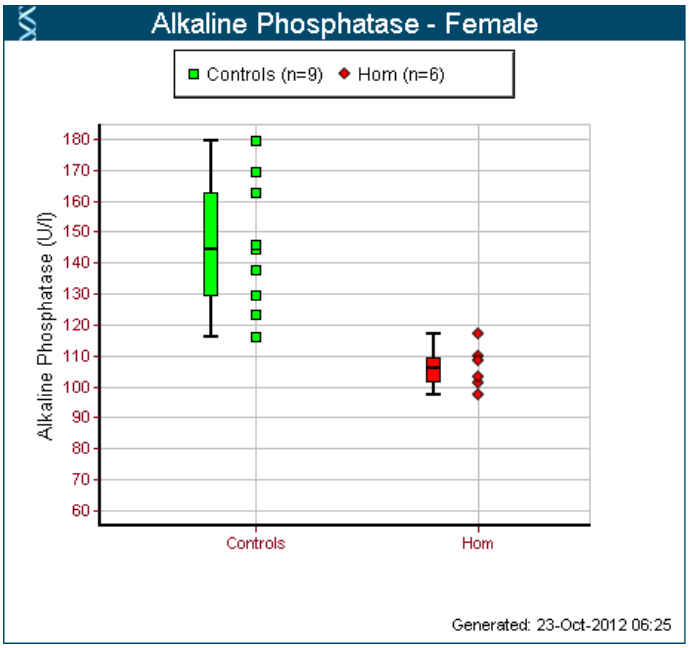


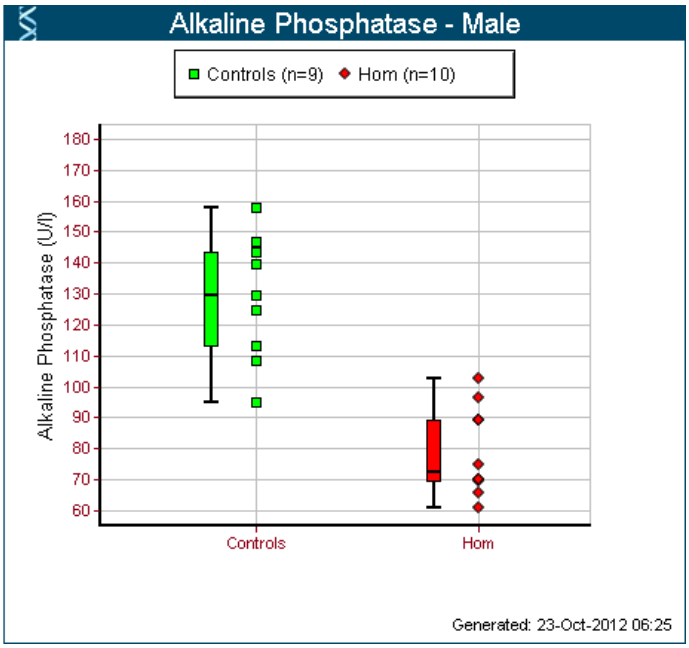
Males - Decreased circulating LDL cholesterol level [MP:0000183]



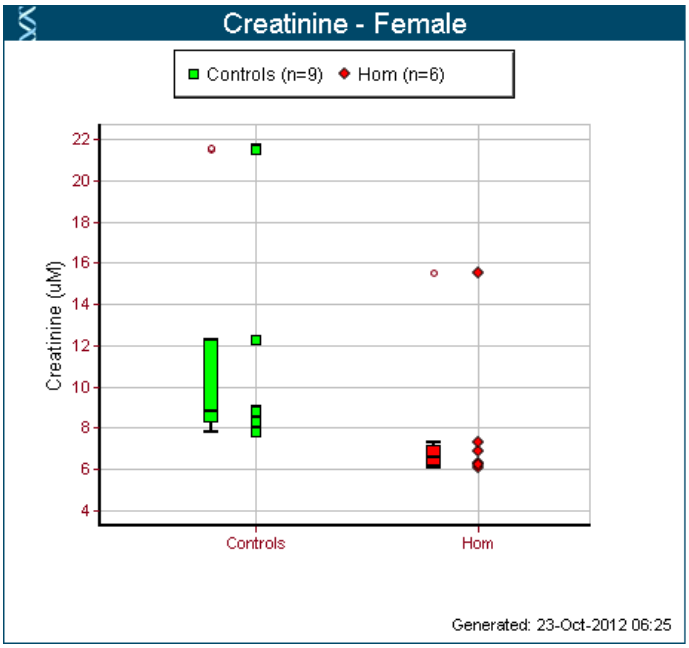


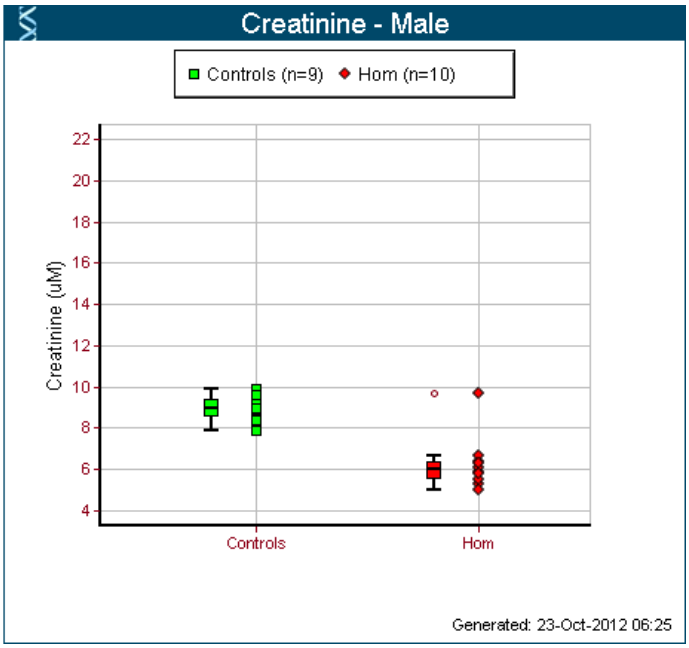
Males - Decreased circulating glycerol level [MP:0003442]



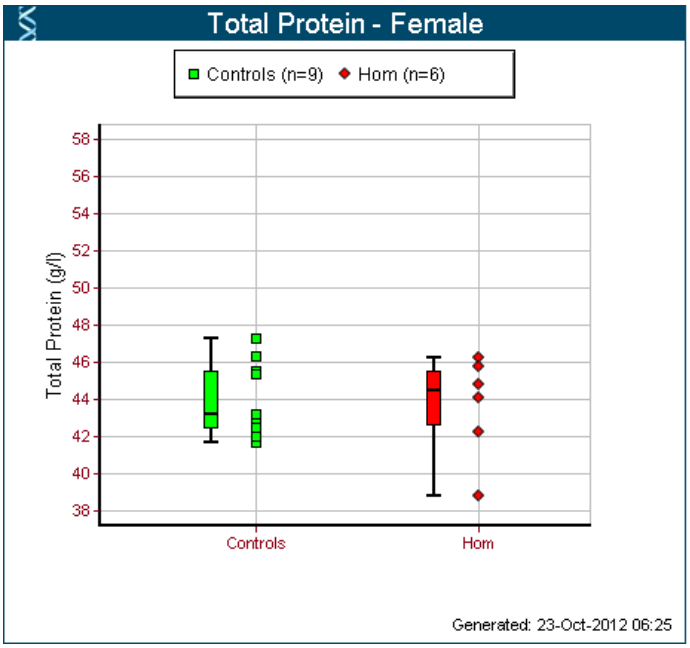


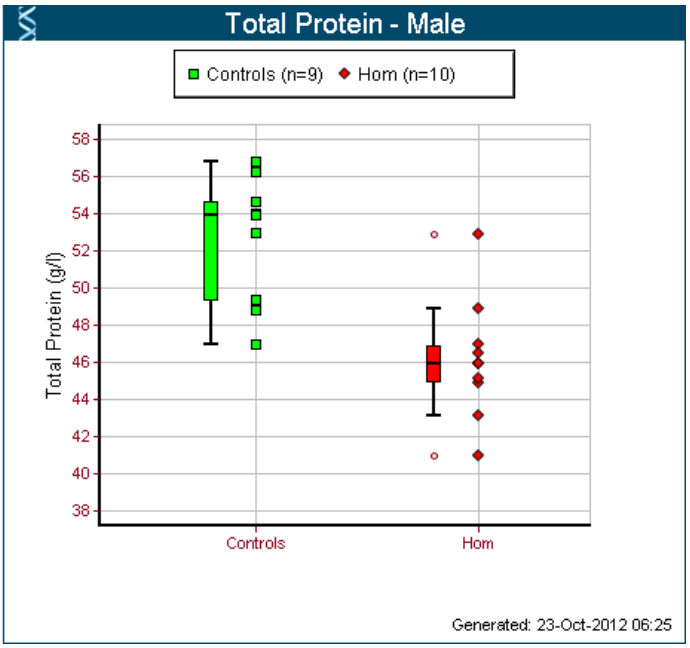
Males and Females - Decreased circulating alkaline phosphatase level [MP:0002966]



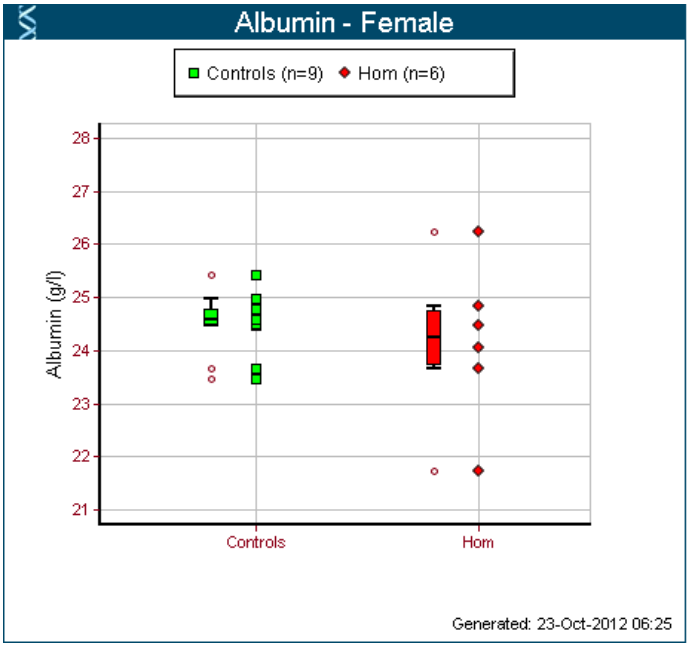


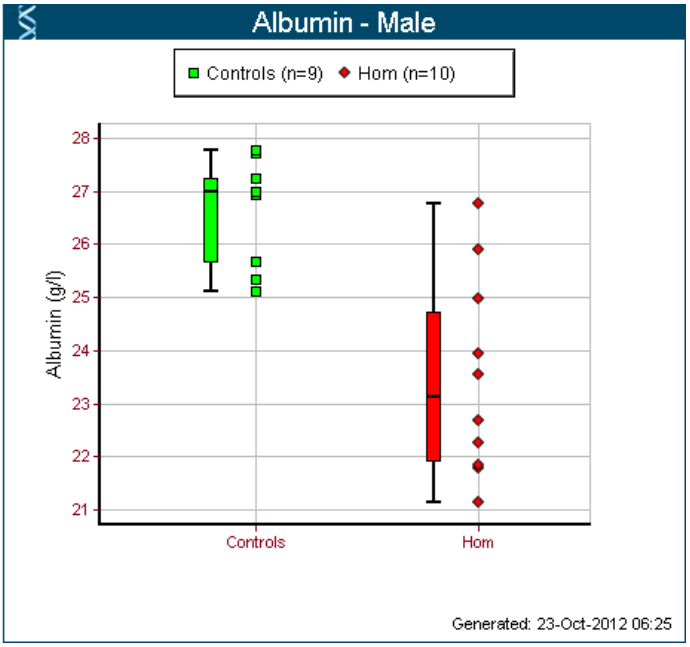
Males and Females - Decreased circulating creatinine level [MP:0005554]





Males - Decreased circulating total protein level [MP:0005567]





Males - Hypoalbuminemia [MP:0005419]

Necropsy observations

Small skinny mice with wasted muscles - skeletal muscle atrophy [MP:0009417].