Intra-allelic Genetic Heterogeneity of Hypertrophic Cardiomyopathy in the Maine Coon Cat 1,2Mia Titine Nyberg, 2J¢rgen Koch, 1Michael Christiansen 1Statens Serum Institut, Artellerivej 5, 2300 Copenhagen S, Denmark, 2Faculty of Life Sciences, University of Copenhagen, Dyrlaegevej 16, 1870 Frederiksberg C, Denmark Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium characterised by unexplained concentric hypertrophy and is an autosomal dominant genetic disease. In the Maine Coon cat the prevalence of HCM is high and the disease expresses the same clinical characteristics as seen in humans. Thus, the Maine Coon may therefore be a good spontaneous animal model of human HCM. The MYBPC3 gene encodes the cardiac myosin binding protein C (MyBP-C) and is associated with mutations causing HCM in humans. Recently, the mutation A31P in feline MYBPC3 has been associated with HCM in Maine Coons. We screened exon 3 of the feline MYBPC3 gene in a cohort of Maine Coon cats to examine whether feline HCM exhibits intra-allelic heterogeneity. Two-hundred-and-four Maine Coon cats with a median age of 2.2 years, (24 had HCM and 19 were clinically suspected of HCM) were genotyped for the A31P variant. Exon 3 of the feline MYBPC3 gene was identified from a feline heart cDNA library. Primers were defined and mutation screening performed using capillary electrophoresis SSCP and DNA sequencing. Two different SNPs were identified in Maine Coon cat, the known A31P with a minor allele frequency of 0.20 in controls and a novel A74T with a minor allele frequency of 0.13 in controls. The odd ratio (OR) for having HCM was 16.2 (95%-confidence interval (cfi): 4.3 - 61.0) for homozygosity for the A31P variant and 7.6 (95%-cfi: 2.7 - 21.7) for homozygosity for the A74T variant. These ORs probably underestimated the significance of the alleles as the cat cohort was young. Feline HCM in Maine Coon exhibits intra-allelic heterogeneity with at least two disease associated genetic variants. Both code for amino acid substitutions in the poorly characterised C0 part of the MyBP-C protein. However, the two variants are responsible for less than 50% of HCM cases in young Maine Coons. Thus, the feline model of human HCM is more heterogeneous than previously believed and it must be expected that mutations in other genes contribute to the causation of disease, just as is the case in human HCM. The genetic characterization of the Maine Coon HCM model will probably lead to the establishment of feline models for HCM caused by many different genetic variants and this will greatly increase the utility of the model as it will enable us both to understand the pathophysiology of different genetic variants, the function of different genes, and to link this information to clinical characteristics.