# ICCFGG

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Canine & Feline Genetics & Genomics 2022 Program & Abstract Booklet

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## #35 Major Histocompatibility Complex (MHC) allele and three-locus haplotype diversity in canid species

**Lorna J Kennedy**[1], Greger Larson[2], Elaine Ostrander[3], Peter Parham[4], Ronald Bontrop[5], and William ER Ollier[1] Lorna.Kennedy@manchester.ac.uk

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The major histocompatibility complex (MHC) has been investigated in many mammalian species. To date, no substantial level of sharing of alleles and haplotypes has been observed amongst related species. As we describe below, canids are an exception to this finding.

We characterised alleles at three loci in the canine MHC (termed DLA): DLA-DRB1/DQA1/DQB1. Alleles were assigned to haplotypes using an iterative process, by initially identifying haplotypes in homozygous dogs. Finding these haplotypes in heterozygous dogs allowed identification of further haplotypes. We have data for 14,476 domestic dogs, 739 village dogs, (from 13 countries), 1,100 grey wolves and 277 coyotes, from multiple locations. Diversity was assessed based on the numbers of homozygous animals, and the number of major haplotypes found in each group.
We observed 31% domestic dogs were homozygous at all three loci, 9% village dogs, 20% grey wolves and 12% coyotes. There were 181, 122, 57 and 61 haplotypes in each group, respectively; 72 were shared by domestic and village dogs. However, 66% of haplotypes in grey wolves and 72% of those in coyotes were unique to those species. Overall, eight haplotypes were shared between dog/grey wolf, four between dog/coyote, two between dog/grey wolf/coyote, and six between grey wolf/coyote. This level of allele and haplotype sharing is both significant and unexpected. When we included dingo, golden jackal, Ethiopian wolf, and African wild dog, a complicated pattern of shared alleles at each locus emerged.

Previous studies of DLA allele and haplotype sharing were based on relatively small sample sizes within each of the four groups described above. This study provides a unique insight into DLA allele and haplotype distribution in the largest dataset assembled to date.

## #36 Allele drop-out cases in screening of HCM assoicted *ALMS1* gene variant in Italian Sphynx cats

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Hypertrophic cardiomyopathy (HCM) is the most common cardiomyopathy in domestic cats. Several clinical forms have been identified and both classification and differentiation from normal variation are still often difficult. In pure breeds (Maine Coon, Ragdoll, and Sphynx) and random-bred cats

HCM causative variants have been identified and diagnostic tests are widely used, helping practitioners in prognosis and breeders in selection. However, when clinical and genetic screening of known variants have been carried out on different populations, differences in penetrance and expressivity have been reported, suggesting an effect of different genetic backgrounds on HCM onset and development, and supporting the use of both clinical and genetic investigations, for more accurate knowledge, classification, and management of the disease. Since 2006, the Osservatorio Italiano Veterinario Cardiopatie (OVIC) has been storing clinical and genetic data, pedigrees, and tissues (maintained at the "Animal Bio Arkivi", a repository of the University of Milan, Lodi, Italy) and promoting periodic analysis of data collected for genetic consulting, in partnership with University and service labs. Screening has been recently conducted on the identified HCM-associated ALMS1 gene variant in the Sphynx breed (Meurs K. et al, 2021) on OVIC present and archive Sphynx samples. Nucleotide variability in flanking regions has been observed using Sanger sequencing. Thanks to clinical data, pedigrees, and trio samples availability, an allele drop-out of the wild-type allele have been identified in cats unrelated in the fourth generation. Allele frequency analysis is showing a fairly wide diffusion of the variant in the Sphynx population bred in Italy.

## #37 Deletion in canine GLRA1 is associated with progressive hypertonia resembling human hyperekplexia

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We observed closely related Miniature Australian Shepherd puppies affected with episodic stiffness and subsequent collapse. The clinical signs progressed within a few months to permanent hypertonia and inability to ambulate. After the exclusion of known variants causing myotonia, we carried out whole genome sequencing and identified a 36-bp deletion in glycine receptor alpha 1 (GLRA1) segregating as a recessive disease in the pedigree. In silico analysis of the variant predicted exon skipping followed by a frameshift leading to a premature termination of the protein translation which would disable the protein function. GLRA1 encodes a glycine receptor subunit, which mediates postsynaptic inhibition in the central nervous system and the variants in the gene are known to cause hyperekplexia in humans. Hereditary hyperekplexia is a rare neurological disease characterized by sudden and exaggerated startle response to unexpected sensory stimulus, e.g. simple and intense tactile or auditory stimuli. This is followed by an episode of general body stiffening with unaltered consciousness. The clinical features in affected dogs were similar, although not entirely identical to human condition. Two other variants in dogs are known to be associated with hyperekplexia, however this is the first likely pathogenic variant in canine GLRA1. The breed will benefit from genetic testing to prevent the disease and control the variant prevalence.