History of Boxer ARVC in the UK

By Bruce Cattanach

Boxer cardiomyopathy, now known as ARVC, came to light in the UK around 2000 through the observation of numbers of Boxers of various ages fainting or dying with ventricular arrhythmias, some with and some without clinical signs, occasionally extending to congestive heart failure. This was as first described by Neil Harpster in American Boxers several years earlier to define Boxer cardiomyopathy, and later by Kate Meurs. Collation of these UK cases, with pedigrees, quickly showed that the condition was inherited as dominant, as deduced by Kate Meurs, but of more immediate practical value, they showed that the disease occurred only within three family groups leaving the remainder of the breed effectively free of the disease. This discovery could be made in the UK with its relatively small confined Boxer population (the show section) and allowed the root sources in each family to be traced back through ARVC-producing individuals. Without accusation, but just as fact, I can say that the sources of ARVC in each family could be identified as American imports. These were all closely related, and all basically derived from one kennel, the same kennel in which Neil Harpster had identified ARVC. Thus all our ARVC cases had one or the other of these imports in their pedigrees. We can conclude that our UK ARVC is the same disease as that in the States. Our ARVC-free section effectively did not have the source dogs in their pedigrees; they were of more Continental European origins. These findings allowed a breeding control scheme to be developed in the UK which allowed breeders to selectively breed away from ARVC. An open publication of names of all dogs deduced to carry ARVC was a key component. The scheme, with names, was endorsed by the Boxer Breed Council in 2008. Since then the incidence of ARVC has declined sharply in the show section of the breed to the point that no new cases have been detected for several years. They still occur in the pet and commercial sections which could not really use the scheme.

During the course of this time an international veterinary group, acronym LUPA, was offering funding to detect genes for diseases in dogs, and this included ARVC in Boxers. The UK responded via Jo Dukes-McEwan and together with another cardiologist, Paul Wotton, I was called in to help collect blood samples for a LUPA-funded GWAS screen. Part way through this Kate Meurs came out with her paper reporting that striatin was the gene responsible for the disease. This caused great excitement. I immediately wrote to Kate asking her if she would like to try out her test on blood samples from my three family lines and deduced normal populations, and she eagerly accepted. But, disastrously, striatin POS and striatin NEG dogs were found in both my affected and normal groups. Even from the breeding evidence of the time and since soundly verified, I could see there was a major problem, but Kate's interpretation was that my striatin NEG cases must have some other form of cardiomyopathy or were not adequately diagnosed, and my normal group was untested by any means (other than by breeding records). Jo Dukes-McEwan subsequently had Kate screen a much larger collection of Boxers, most of which had been veterinary tested to Kate Meurs' specifications, but with the same result (published paper to be found on my website, steynmere.co.uk); we had a seemingly insoluble problem.

The LUPA ARVC investigation had been terminated following publication of Kate's paper but I was eventually able to find a Canadian human cardiologist, Robert Hamilton, who was eager to find the gene for human ARVC and was willing to take on my supposedly inadequately typed material for the purpose. Initially this was a winner because my 'inadequate' material immediately identified a hot spot for DNA markers on chromosome 17 and in exactly the same region as found by Kate. The data were in full accord. And more precisely, as also seen by Kate, there were two peaks in this region with striatin lying in the smaller one. All was still in accord. But further exhaustive efforts to find another gene in the region that could be responsible for the disease was unrewarding.In frustration, I turned back to the striatin data on our UK dogs and applied some genetic thinking. Why did the striatin data not fit with the disease and normal phenotypes? Here one should first point out that not all of Kate's animals accorded with her interpretation; some of her ARVC cases were striatin NEG and some of her normal controls were striatin POS, so our findings were not totally different from hers. But I had one advantage for genetic investigations; I had the mass of the pedigree and breeding information based on over 200 cases from our three (now only two) affected families with the rest of the breed serving as normals. So, how did our 'exceptions' fit with these? The greatest discord was in our normal group where the majority were striatin POS. Although almost none of these have been Holtered, no dogs affected with ARVC have been found in this group even to this day. There is therefore no possibility that the gene for ARVC could be in this population. So here we do have total discord. However, in complete contrast, in one of our families, the striatin typing was in complete accord with Kate's expectation; all affected cases were striatin POS. But in the other family typed for striatin there was discord again, with some ARVC cases being striatin POS and others striatin NEG. Could there be a second gene for ARVC? Initially this seemed to be a possibility as the first family tended to have a different, early onset, severe form of ARVC (average under 4 years) whereas in this other one the disease tended to be milder and manifest itself in dogs of around 7 years of age or later.

A look at the pedigrees and some elementary genetics provided the answer. The striatin POS and striatin NEG dogs in the second family group were often closely related and so were therefore unlikely to have different cardiomyopathies. But the pedigrees showed something else that is critically important; one could see evidence of 'switches' from one association to the other (striatin POS to striatin NEG, or vice versa) among these close relatives, and these switched striatin types were then inherited as such. In other words, we had family groups in which the disease and striatin NEG were associated and so inherited, as also others in which the disease and striatin POS were associated and so inherited. The switching constitutes the classical genetic evidence for recombination between two equivalent parental chromosomes in the germ cells. This is a normal and actually essential occurrence for all chromosomes. But a separate causal ARVC gene close to striatin is indicated. To explain this, imagine one parental chromosome carrying the striatin mutation (Str) alongside/associated with this ARVC mutation (Arvc) such that the two genes tend to be inherited together (Str – Arvc), and the other parental chromosome having the normal form of striatin ($+^{Str}$) and the normal form of the ARVC gene($+^{Arvc}$), thus ($+^{Str}$ - $+^{Arvc}$). But recombination between the two will allow the striatin and ARVC mutations to separate and switch partners. The result will be striatin POS – normal (Str - $+^{Arvc}$) and striatin NEG – affected ($+^{Str}$ - Arvc) individuals (I describe only one chromosome for simplicity). In effect, one association generates the other. This is standard normal genetics that applies to all genes on all chromosomes. Recombination can thus account for the finding that both normal dogs and dogs with ARVC can be either striatin POS or striatin NEG.

The basic conclusion is that the ARVC disease gene is not striatin itself, but simply lies close to it on the same chromosome and the normal recombination process provides the switch from one association to the other. An off the record estimate of the incidence of striatin – ARVC recombination/switching could be 4%, with the two mutations being inherited together or staying apart 96% of the time. This is the main genetic message of the published paper: "A pedigree-based genetic appraisal of Boxer ARVC and the role of the Striatin mutation": (http://veterinaryrecord.bmj.com/cgi/rapidpdf/vr.102821?ijkey=0UH8NRSls1UFxBv&keytype=ref). The close linkage further helps define the location of the true ARVC gene but does not identify it. My hope is that the findings will trigger further research upon this region such that even if the ARVC gene cannot be recognised, DNA markers that are tightly enough linked to it will serve the same role.

A second message from this study is of more veterinary interest. In one family, many of the affected dogs showed the early onset severe form of cardiomyopathy often called Boxer dilated cardiomyopathy, DCM. A revelation was that many of these dogs were homozygous (double dose) for the striatin mutation. Such dogs were also found in the other family, but less frequently, so that the overall average age of onset was later. It would seem that the striatin homozygosity, together with the ARVC gene, worsens the disease to cause the extreme DCM effect. This could suggest that striatin and the gene for ARVC interact genetically, as they might as striatin does affect the cardiomyocyte. But since ARVC seems to be triggered by a range of factors such as stress, exercise, myocarditis, and concurrent heart conditions such as SAS and heart-base tumours, it seems more likely that anything that damages the heart may exacerbate ARVC expression.

A final point will be appreciated by everyone who breeds any kind of animal. Genetic disease does not appear randomly throughout a breed. It occurs in family groups. Pedigree studies can highlight these and help define genotype (the genetic makeup), rather than just phenotype (the effect), which is determined for ARVC by Holter testing. Pedigree studies therefore provide a valuable extra tool for aiding research to find genes.

Looking to the future, whereas it might be considered that the exclusion of striatin as the causal gene for ARVC is a step backwards, I see the new evidence as a step forward, as it should trigger further searches for the causal ARVC gene or for DNA markers that would remove the difficulties experienced with striatin and help breeders deal finally with this desperate Boxer disease. To this end I would hope to make available whatever surplus DNA we have from our UK dogs for this further research.

About the Author:
Dr. Bruce M. Cattanach has been a noted breeder/exhibitor of boxers in England since 1949 under the Steynmere prefix. Ch. Steynmere Night Rider had a strong influence on boxer bloodlines in the UK in the 1980s and was the sire of his BIS all-breed winner Ch Garnet Gelert of Steynmere, while his grandsire, English Ch. Steynmere Summer Gold - imported to the US as an adult - appears in many North American pedigrees through his descendants, Chs. Berena's Gemini Splashdown and Tribute to Fa Fa. Dr. Cattanach is a geneticist by profession and has specialized in the cause and analysis of genetic defects. Until his retirement, Dr. C. was Director of the Medical Research Council Mammalian Genetics Unit Harwell in the UK. In the 1960s he also worked on the genetic effects of radiation in the USA and Harwell thereafter. On his return to the UK in 1969, he took a Cherokee Oaks bitch back to the UK to restart his Steynmere breeding program.

Dr. Cattanach was instrumental in eradicating the crippling, hereditary neurological disease, Progressive Axonopathy (PA), from British Boxers in the 1980s, and later worked with British cardiologists and breeders to lessen the (then) widespread incidence of Aortic/Subaortic Stenosis in British Boxers. Later, he played a prominent role, along with British cardiologists, in eliminating ARVC from the show section of the breed in Great Britain and has continued to genetically research ARVC since 2009. Most recently he has been concerned with Juvenile Kidney Disease (JKD/JRD).