Research Update: The Hereditary Basis of Adult Onset Deafness in the Rhodesian Ridgeback Breed

(Report given by Clayton Heathcock at the Annual Meeting of the Rhodesian Ridgeback Club of the United States; Topeka, KS; 29 October 2013)

An inherited deafness has been clinically documented in Rhodesian Ridgebacks. Affected dogs appear to show normal hearing early in post-natal development, but ultimately these dogs lose their hearing, with complete loss by 1 year of age. Anecdotal observations from breeders and owners suggest that hearing loss occurs as early as 4 months in some affected dogs, and that males exhibit an earlier onset deafness than affected females. Over almost 15 years, breeders and owners of affected dogs have submitted cheek, saliva, and blood samples to the Laboratory of Dr. Mark Neff in support of a genetic study.

Research in Dr. Neff's lab at UC Davis established that this defect is indeed genetic, and that the mode of transmission from parent to offspring follows a simple Mendelian autosomal recessive pattern of inheritance. This means that any sire or dam that has previously produced affected progeny must be a carrier of the causal mutation.

The UC Davis research further showed that the defect maps to a single chromosomal region, and that all carriers and affected dogs have inherited exactly the same DNA sequence in this region. **This means that the mutation that causes the deafness occurred once and only once, and that all affected dogs are descendants of a single common ancestor.** It is not known how long ago this ancestor lived, and it is possible that the mutation occurred prior to the development of the breed in the late nineteenth century.

Research has continued in Dr. Neff's laboratory at the Van Andel Institute in Michigan. In the past year, Dr. Neff's team has sequenced the entire genome (that is, 2.4 billion letters of genetic code) from two affected Ridgeback dogs that are distantly related. Using the prior mapping results as a lens, the team has mined all the sequence variants within the mapped interval that was found in these dogs. The filter used to enrich for the causal mutation requires that candidate variants be:

> **homozygous** (the causal mutation must be inherited from both the sire and dam, and thus be found on both gene copies) and

private (the causal mutation is expected to be unique among the other dog genomes that the team has sequenced, and Dr. Neff's team has done complete genome sequences of about 30 dogs of other breeds).

The analyses of these sequence data sets have identified roughly 7,000 candidate variants that fit the pattern expected for the causal mutation. It should be noted, however, that current computational programs identify with high confidence two types of mutations (single nucleotide polymorphisms and short insertions/deletions). Two other less common types of mutations are more difficult to detect. Therefore, it is still possible that the exact mutation is NOT being detected. Even if the causative mutation IS among the variants detected, the current list is still too large to study comprehensively.

The approach being used to narrow down the list of variants and identify the lone mutation that is actually causal is to type the variants on a large number of Ridgebacks. Any variant that does not fit the required inheritance pattern can be excluded from further study. For instance, any variant that is present on both gene copies in a **non-affected** dog can be effectively ruled out. Also, any variant that is not homozygous in an **affected** dog can also be eliminated.

It should be noted that there are instances where strict adherence to the pattern might not be obeyed, even for the causal mutation. But this still represents the most logical approach to identify the single ancestral mutation that causes adult onset deafness in the Rhodesian Ridgeback.

To advance this project, a team of generous donors from the RRCUS community have provided a gift to support DNA sequencing and analysis, and to subsidize DNA testing of a large number of Rhodesian Ridgeback dogs. In the coming weeks, Dr. Neff and his associate Dr. Alison Ruhe will be launching a DNA testing study in collaboration with **projectDog**, a non-profit laboratory in California. The goal of this work is two-fold -- to identify the rare, exceptional dogs that will enable the list of putative variants to be refined, while at the same time providing breeders and owners with information that could be helpful in avoiding crosses that are at-risk for producing affected dogs. Please understand that the information from this typing phase will be imperfect. Dr. Neff will deal with this uncertainty by separating test results into two classes:

The first class will he those that are high confidence outcomes -- highly likely to be affected, highly likely to be a carrier, or highly likely to be clear.

The second class will be results that will be uniquely informative to the research, but difficult to interpret for the breeder/owner. These outcomes will represent test results where some but not all the candidate mutations are found in a given dog. Researchers will follow up with the owners of these dogs to help explain the uncertainty of the outcome, and to have the dog tracked for health and breeding outcome. **These rare exceptional dogs hold the key for pinpointing the truly causal mutation.**

Once enough dogs like this have been studied, test results can be re-interpreted. It is hoped that all participants will ultimately be provided with a definitive result.

Finally, Dr. Neff has indicated that the gene responsible for adult onset deafness in the Ridgeback is highly likely to be responsible for a similar deafness in humans. Specifically, human genetics literature suggests that THIS human deafness affects infants before they learn how to speak, thus sentencing these children to a lifetime of challenges in communicating. It is hoped that a successful conclusion of this research will enable Rhodesian Ridgeback breeders to improve the health of future generations of dogs, and beyond this, have important implications for improving human health as well. Dr. Neff and his team have expressed deep appreciation for the long-term commitment and patience by the Ridgeback community, and for the continued support of this important research.