HAPLOTYPE Test tracing as explained by Leah Brault, VGL Lab at UC Davis and contributed by Beth Minnich : (27 Dec 2009)

The basis for haplotype tests is that a particular mutation has a common ancestor. This ancestor is the horse in which the original mutation first arose. There are genetic markers scattered throughout the genome, and this ancestor had particular alleles at the markers in the area of CA. So, for example, if the horse had the CA mutation arise on one chromosome, and he had alleles ABCDEFGH in that area, the genotype looked something like this (overly simplified version):

A--B--C--D--CA--E--F--G--H (chromosome 1)
a--b---c---d---N---e---f---g---h (chromosome 2)

These markers are all close together and the concept is that they will "travel" together as they are passed on. Therefore, when this horse passes on its CA allele, it will pass along ABCD(CA)EFGH, and when it passes on its normal allele, it will pass on abcd(N)efgh. Then, whenever offspring pass on the CA mutation, they too will pass on ABCD(CA)EFGH. The mutation moves with these associated markers through generations.

When UC Davis first started looking at KNOWN carriers of CA (known based on production of affected foals,) and KNOWN CA affected foals (known based on diagnosis), they noticed that every affected foal was AA BB CC DD EE FF GG HH, and every carrier horse was A_ B_ C_ D_ E_ F_ G_ H_. Most of these early foals were pretty closely related, and so it wasn't a huge surprise - the assumption was that they were getting it from a great-grandsire or something. But, as more and more affected foals (based on diagnosis) were sent to the lab for testing, who didn't have common ancestors with the first group of foals until nine or ten generations back, they saw that ALL of these foals were also AA BB CC DD EE FF GG HH. That told the researchers that CA has a single ancestral source in the Arabian breed, one that is very, very old. These affected foals are of a variety of bloodlines, including Egyptian, so the CA mutation must predate the division of these "nationality/geographic" subgroups, since they all carry the same marker alleles.

When testing is done, the lab is looking for these alleles--ABCDEFGH. I believe they have found about 40 markers that travel with CA and they test for 15 (so the A-H example is

simplified). Although it isn't possible to determine an overall % accuracy for the test, the research shows a very high degree of success. Theoretically, there could be another source of CA in the Arabian breed (meaning a different haplotype would be involved) or there is a very slight possibility of the halplotype they are testing for exisitng in a "normal form" in some horses. I'm not aware of any of these theories playing out as reality, but yes, theoretically it is possible. However, something we DO know is that when two carriers are bred together, there is a 25% probability of having an affected foal - so which odds do you want to go with?

In terms of test results - ALL of the confirmed affected foals tested so far have had two copies of the CA haplotype. They have NOT yet seen a confirmed affected foal that did not carry two copies of these markers. So, the presence of these markers is certainly very indicative of CA. Occasionally a horse is tested with an "odd" haplotype...perhaps it has ABCD, but not EFGH. In these cases, the result is listed as "undetermined". As they continue to narrow the CA region down further and further, some of these "undetermined" cases are being resolved and it is becoming very rare among the rare to get an "undetermined" result now.

In the end, Arabian breeders need to decide whether the very small chance of error is worth it when making breeding decisions. Also of note, people who are testing now (directly through UC Davis, not necessarily through one of the European labs) will NOT need to send another sample when the direct test becomes available. The lab will automatically re-test and let owners know if they obtained a different result.

The indirect CA test is a very valuable tool for breeders, especially for those working with known CA lines. The choice is there to use or not to use....with the primary goal being not to produce affected foals. IMO, that is where the focus should be.....no more affected foals.

Addendum to Haplotype Testing - dd. 20 feb 2010

From: "Genetic Disorders: From Knowledge to Action": A Free Symposium with Dr. Cecilia Penedo, Veterinary Genetics Laboratory, University of California at Davis, director of research that identified genetic markers for Cerebellar Abiotrophy (CA) and developed the marker-based test.
According to Dr. Penedo:
Of all the cases tested by UC Davis using the haplotype method, UC Davis has had 100% accuracy on the carrier status of CA affected neocropsied foals. Out of 999 cases tested , they have had 6 horse samples show normal alleles on one chromasone (N) and partial or

incomplete on the second chromasone. (U). These cases have been designated as Undetermined (U) and are considered *Inconclusive* because the carrier status can not be totally excluded with 100% confidence. Of the six, four have been retested at a later stage when more data had been collected and these have been identified with confidence.