



# EFTBA Veterinary Newsletter 5



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September 2011

- *Equine genetics/genomics for the thoroughbred breeder*

## Welcome to EFTBA's veterinary newsletter

As the new Chairman of the EFTBA since mid May this is my first opportunity to introduce our Veterinary newsletter. I believe that this newsletter is yet another example of how the European Federation is fulfilling its aims of educating and informing breeders throughout Europe.

Latest developments in anything can be misunderstood, and I am delighted

that Hanspeter Meier has chosen to look at the new field of genetics in this latest newsletter. I thank him for his enthusiastic editorship and for the invaluable advice and help of all the Veterinary Advisory Committee of the EFTBA

*Rhydian Morgan-Jones*

Chairman, EFTBA

## Equine Genetics/Genomics

After two newsletters each with economic and medical aspects, this and the next issue will deal with another most important field of our endeavours – with genetics or genomics respectively, the latter the technical term in our days. This change of definition is the expression of the development in the last years and is a distinct sign for a completely new aera. TB-breeders always had a great interest in this field, but the traditional knowledge on e.g. population-genetics just isn't good enough anymore. Immune and especially molecular genetics did develop tremendously and finally, epigenetics made this subject even more fascinating. This fascination and most important findings, for instance in regard to the research in diseases with a genetic predisposition, led to a load of articles, publications, books, semi-nars and advertisements on genetics or genomics which one just can't fail to notice. However, this demanding sub-

ject certainly finds our interest, as soundness is the indispensable prerequisite for good performane. Moreover, we already do have some basic knowledge on the principles of genetics as we already do parentage testing for the Stud Book for many years. In another box of Pandora on the shelf of equine genomics is the research for markers for performance, the youngest subject in this field, but probably one that affects us also seriously. But before we try to lift the lid of this box, we really have to delve into history and basic things of all these subjects. Knowledge will prove to be power once again.

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**“Many thanks to Mrs. Eva-Maria Bucher-Haefner, Moyglare Stud Farm, for her valued sponsorship of this newsletter.”**



Profound Beauty (Danehill) owned and bred by Moyglare Stud.



## Equine Genetics/Genomics and the thoroughbred breeder

### Introduction

The newest book on genetics in Thoroughbred Breeding is the one of Matthew Binns and Tony Morris (2010), the men you can't ignore. It is very worthwhile reading – even if one comes across the sentences in its preface: *“Neither at home nor abroad was the Thoroughbred understood. The breed had been established in ignorance, and though it was generally recognised that pedigree was important, and increasing emphasis was placed on correct identification of individuals, the problem of how to interpret pedigree was universal”*. These remarks may not really make us proud, but nevertheless please carry on reading. Otherwise you just may fall into the trap of self-selection bias and please remember the learning theory that the selection-mechanisms of our brain are dependent on feelings mainly. We forget easily what doesn't worry or please us and therefore just appreciate the didactic trick of these prolific authors.

An explanation for the poor recognition of our endeavours by Binns and Morris (2010) can easily be found: We breed racehorses successfully already for centuries, but the beginnings of modern genetics, e.g. the discovery of Mendelian's laws happened only about 150 years ago. At this time there was already quite some tradition and the empiric knowledge of our ancestors must be considered quite remarkable. The TB-breeders did lead the way for all the time, not only in breeding horses but also in domestic animals generally. Of course, the means were much simpler than in our days, but the existing ones generally were used efficiently. The principle was very simple - but also pretty efficient. By selecting best performing animals, one automatically selected also for physical and mental soundness.

Our ancestors did understand this general principle, admittedly with only poor scientific background, just by means of observation and sort of population-genetics. They did learn by experience and empiry did exist for quite some time already as shown e.g. by the British vet Miles (189?) at the end of the nineteenth century. In the chapter *“Breeding the Race Horse”* he wrote *“Above all things, it is essential that both mares and stallions should be free from “constitutional infirmity”; by which term is understood a tendency to defects in the wind, and of their legs and feet to give way in training. The most eminent authorities on human pathology have agreed as to hereditary transmission of certain diseases and defects, such as scrofula, gout, insanity, etc., and guided by their discoveries, able veterinarians, both foreign and British, have shown that the horse is subject to the same law of nature. This opinion, which is founded on reason, common sense, and experience, existed in the days of the Caesars, and is beautifully expressed by Horace in the following lines:*

*Fortes creantur fortibus et bonis.  
Est in juvenvis est in equis patrum  
Virtus; neque imbellem feroces  
Progenerant aquilae columbam.*

*The strong and brave is created by the powerful and  
courageous. In young bulls and horses  
is the strength of the fathers; and the wild eagle doesn't  
produce a gentle pigeon.*

On top of that, and at exactly the same time (1892/1893), the Royal Dublin Society stated that *“... mares to receive nominations must be passed free of any hereditary disease by the Society's Veterinary Surgeon”*, and in Volume Two of its Register of Thoroughbred Stallions (1893) it was stated that all the Registered Stallions had to *“... be declared free from all hereditary diseases (e.g. sidebones, roaring, nervous disorders and bone defects as navicular disease and spavin)”* (Lewis 1980).

There obviously always have been efficient endeavours for improving the breeding of horses and remarkable people with good awareness of rational breeding more than a hundred years ago. A another good, younger example has to be the Italian Federico Tesio with his famous words *“The Thoroughbred exists because its selection has depended not on experts, technicians or zoologists, but one piece of wood: the winning post of the Epsom Derby”*. Binns and Morris (2010, p. 99) feel: *“This was Tesio the philosopher, another side of Tesio the creator of Nearco, Ribot and other champions, and this statement could not be taken literally.”* Contrary to this, in my opinion, Tesio learned this as a practitioner, as an astute, analytical observer and I much more agree with the opinion of Blott and Tate (2011) that *“Thoroughbred breeders have an intuitive understanding of genetics*

from seeing the results of generations of matings which have produced today's elite athlete".

Therefore I wouldn't be so critical of breeders of earlier times as Binns and Morris (2010), as the simple principle of asking highest performance seems to be the most comprehensive selection criterium.

Improving the health and welfare of the performance horse certainly is the primary goal of breeders, very simply because soundness is the basis of the potential for good performance. For ever we wanted to breed "horses sound in wind and limb", but we also know for a very long time that many and severe diseases do have a genetic predisposition. In the past, we tried to study these predicaments mainly by means of the already mentioned population-genetics. However, in the last decades, research in molecular genetics made enormous progress which hopefully will allow us to breed even sounder horses. News about these fascinating achievements did also reach our customers (agents, vets and purchasers) who already are interested in examining the DNA of our horses. A basic knowledge of this demanding field therefore should be favourable for any breeder and the summary of the basics on equine clinical genomics seems to be most helpful for this aim.

### The beginnings of genetics

Early TB-breeders certainly can't be blamed for not knowing much about genetics – for the very simple reason that this definition was used for the first time by William Bateson in 1906 only. He did so by working on the studies and the laws of heredity of the Austrian Augustinian monk Gregor Mendel. Between 1856 and 1863, Mendel inseminated artificially pea plants and presented his findings orally in 1865. His experiments led him to make two generalizations, the Law of Segregation and the Law of Independent Assortment - in other words that an organism can be understood as a mosaic of traits which can be inherited independently from each other and be combined in a new pattern. That did prove that genetic information is made up by single genes, and by the way also supported Charles Darwin's theories of selection.

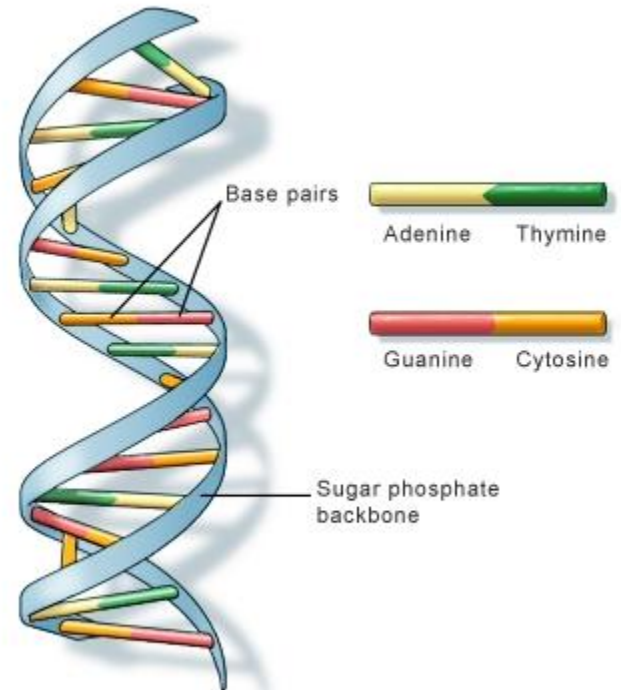
Thomas Morgan Hunt proved already that chromosomes are the carriers of genes in 1910, and in 1944 Oswald Avery showed that the DNA is the proper molecule carrying the genetic information.

### DNA (deoxyribonucleic acid) (fig. 1)

The chemical components of the DNA (base, sugar, phosphate) were discovered in 1919 by Pheobus Levene and its structure by James Watson and Francis Crick in 1953, in the year of Pinza's and Gordon Richards (first) Derby win.

The DNA is built as a helix, a spiral-like and absolutely genial structure which we also know as the scaffold for the wool of sheep, the collagen in tendons and many other tissues in nature. In tendons, the collagen-helices

are mainly responsible for elasticity and shear-strength and in the DNA-molecule, the helix allows the arrangement of an unbelievable number of base pairs (figure 1). A twisted rope-ladder may also serve as explanation for this structure, with the base pairs (of adenine, cytosine, guanine and thymine) as rungs.



U.S. National Library of Medicine

Fig. 1 tiny part out of a DNA-molecule (scheme)

The DNA is a very large molecule which is wound around proteins. In cells of man, the biggest molecule contains 247 millions of base pairs and stretched out would be as long as 8.4 cm !

The sequence of these four different bases A, C, G and T are similar to a code and this code contains the genetic information for the biologic development of cells.

Please note that the letters A, C, G and T are routinely used to talk of these bases and while reading studies on genomics, you may see long rows of these letters, just about like a secret language. But one can get used to it as easily as to black type in a pedigree. Just do it and make sure that you don't get confused with other abbreviations, where single letters are also used, e.g. for genomic studies on the ability to be tame in rats (TT) or being a sprinter as a horse (C:C) (Albert et al. 2009, Anon. 2011). They are completely different definitions.

For the understanding of all the mechanisms of the DNA and its engineering, it is also important to know that the paired bases do not stick together, they do not quite come in contact. In fact they are held together by hydrogen bonds only, by a weak electrical attraction between

partially negative atoms of one side with the partially positive atoms on the other. This has the great advantage that only little effort is required to pull the two halves apart (almost like a zipper), what allows both easy replication (copying of the DNA) and for transcription, the reading of the DNA – what we are especially interested in with this newsletter.

### **Where are we today**

Considering the urgent necessity to get acquainted with today's literature on genetics and genomics, every breeder, especially a seller, must be tempted to consult articles on these subjects. However, there is a very big chance that one is put off right away by the most peculiar language of the researchers in this field. But please do not back off, get used to it and just remember what other people may think of our language, e.g. to abbreviations which readily are understood by all of us (EFTBA, AEI, GAG, EBF, FRBC, etc.).

A very useful article to become familiar with the field of clinical genomics with a vision of improving the health and the welfare of the domestic horse is the review of Brosnahan et al. (2010). The objective of this review is to introduce breeders to the rapidly evolving field of clinical genomics, where a consortium of veterinary geneticists and clinicians has worked together under the umbrella of *The Horse Genome Project* for 15 years. The genome of the domestic horse has now been sequenced (Wade et al. 2009) and this fact holds the potential to transform the way animals are selected for breeding – and for a change must make us very proud, because the individual chosen for the sequencing was the TB-mare *Twilight*.

The genome sequence has enabled the development of new genome-wide tools and resources for studying different things, e.g. inherited diseases of the horse, phenotypic informations from historic TB horses (Campana et al. 2010) and markers for performance (e.g. Harrison and Turrion-Gomez 2006, Hill et al. 2010).

To date (Brosnahan et al. 2010), researchers have identified 11 mutations causing 10 clinical syndromes in the horse, but this figure will increase rapidly. Testing is commercially available for all but one of these diseases. Future research will probably identify the genetic bases for other equine diseases, produce new diagnostic tests and generate novel therapeutics for some of these conditions (Brosnahan et al. 2010).

The impact of genomic study is far-reaching, encompassing not only the obvious identification of specific disease-causing mutations but also expanded knowledge of normal physiology and insights into the evolution of the horse (Brosnahan et al. 2010).

### **A very brief history of horse genome research**

According to Brosnahan et al. (2010), by the mid-20th century equine genetics, was already a dynamic field of study, although the information about the horse genome was sparse. At that time, research investigated mainly the genetic bases of physiology, coat colour and disease in the domestic horse. Knowledge of the horse genome has progressed rapidly from a point less than 20 years ago, when few genes had been characterised. Moving into the 1980s and early 1990s, efforts were underway to identify genetic causes for several important diseases of the horse including e.g. severe combined immunodeficiency (SCID) of Arabian foals and hyperkalaemic periodic paralysis (HYPP) of Quarter Horses.

The Horse Genome Project (HGP) was formed in 1995 by a group of equine geneticists and clinicians from 22 laboratories in 12 countries for the purpose of undertaking large-scale studies to characterise several aspects of the genome of the horse. In 2006 the horse was selected by the US National Human Genome Research Institute of the National Institutes of Health to become one of the mammalian species on a priority list to be sequenced.

Sequencing began at the Broad Institute at MIT early in that year and, by January of 2007, a draft sequence was completed. The horse sequence consists of  $2.6 \times 10^9$  base pairs spread across 31 autosomes and the sex chromosomes (Brosnahan et al. 2010). About 20'300 genes have been identified thus far, a number similar to that found in other mammals (Wade et al. 2009).

With the draft sequence in place, the work of gene identification and genome annotation is on-going and refinements to these complex tasks will continue for years to come.

Today's researchers now have convenient access to genomic data as they continue to elucidate mechanisms of basic physiology, to pursue genetic bases for both single gene and complex diseases and to ascertain whole-genome effects on fitness (Brosnahan et al. 2010). In the meantime we already did hear of quite a few studies on performance markers (e.g. [www.equinome.com](http://www.equinome.com); [www.thegeneticeage.net](http://www.thegeneticeage.net)).

### **Genetic diseases of the domestic horse**

With this newsletter we only want to look at the very valuable research in regard to the cause of diseases. Other aspects will be dealt with in a further issue.

However, almost all of the hitherto investigated genetic diseases do not refer to the TB and we only want to get acquainted with the principles. A good explanation for this fact are the results of a study in American Quarter Horses (AQHs), where Tryon et al. (2009) evaluated the frequencies of inherited diseases in subgroups of AQHs. Five genetic diseases of AQHs were investigated in 651 elite performance AQHs, 200 control AQHs and 180 control American Paint Horses (APHs). As we would expect, the racing and barrel racing subgroups were at the least risk of carrying the genetic diseases tested. - A

convincing proof that testing for performance also tests for soundness - what the TB-breeders did right from the beginning and for centuries.

### Simple genetic diseases

Simple or monogenetic diseases may be defined as those caused by mutation of a single gene and inherited in a Mendelian pattern (Hardy and Singleton 2009). Virtually all of the equine genetic diseases fully characterised to date fall into this category, with 11 identified mutations causing 10 clinical syndromes. Although they are relatively few in number, these diseases have had a discernible impact on the fitness of major breeds. Commercial testing is available for all but one of these mutations to facilitate identification of carriers, confirmation of clinical cases and management of the alleles within breeding populations. Most of these disorders have been identified through a candidate gene approach based upon knowledge of similar inherited syndromes in man or mice (Brosnahan et al. 2010).

A review of confirmed genetic diseases of the horse has been published recently (Finno et al. 2009). Most of these diseases are noted below, just for interest and information, as they don't play a role in TBs:

Hyperkalemic periodic paralysis HYPP (AQH, Paint)  
Polysaccharide storage myopathy PSSM (AQH, QH-related Warmbloods, Draughts)  
Malignant hyperthermia (AQH)  
Glycogen branching enzyme deficiency GBED (AQH)  
Severe combined immunodeficiency SCID (Arabian)  
Junctional epidermolysis bullosa JEB (American Saddlebred, Belgian French draughts)  
Hereditary equine regional dermal asthenia HERDA (AQH)  
Overo lethal white syndrome (OLWS), Ileocolonic aganglionosis (Paint)  
Lavender foal syndrome (Arabian)

### Hyperkalaemic periodic paralysis

We will occupy ourselves with just one of these diseases, in an exemplary manner for all of them, just to show how complex the situation is and that we don't only encounter medical problems.

Our choice is the Hyperkalaemic periodic paralysis (HYPP), a disease of the AQ and Paint horse with clinical signs of myotonia, muscle fasciculations, third eyelid prolapse, weakness, respiratory distress and recumbency. Severity of signs may range from asymptomatic to daily episodes to death.

HYPP is a disease of skeletal muscle caused by a C (Cytosine) to G (Guanine) substitution in the voltage-gated sodium channel (SCN4A) gene on ECA 11. This results in a phenylalanine to leucine substitution in the alpha subunit of the channel, affecting resting membrane potential such that the channel fails to deactivate in response to increasing potassium after initial depolarisation. Continuous depolarisation of myocytes ensues, manifesting clinically as transient paralysis. The mutation is inherited in

an autosomal co-dominant pattern. (Brosnahan et al. 2010). Sounds extremely technical, doesn't it ? But just don't worry. We only want to show with this example how advanced this research is. In these days, it is very detailed, and as you know, attention to detail makes the difference between success and failure and is the common theme that aligns the great professionals. For the breeder, principal knowledge is good enough and for details please seek advice of your vet.

Ongoing management of animals experiencing repeated episodes should include dietary changes to reduce potassium intake and medications.

The HYPP allele probably has been perpetuated in the Quarter Horse population due to the desirability of the associated muscular phenotype in halter competitions. A recent study reported that while only 1.5% of the Quarter Horse population at large is affected, over one-half of elite halter horses carry the mutation (Tryon et al. 2009). Additionally, 4.5% of the American Paint Horse population also possesses the deleterious allele (Tryon et al. 2009). Efforts intended to reduce the allele frequency in the Quarter Horse breed include exclusion of homozygotes from the American Quarter Horse registry since 2007, but affected animals may still be bred at the discretion of their owners.

HYPP status can be determined by genetic testing and further information can easily be obtained from the AQHA website: <http://www.aqha.com> (> HYPP).

The detailed information from this association's homepage can also be considered exemplary for the open-minded approach to deal with genetic diseases. For instance, since 1998 already, in case one finds on the registration certificates of foals the disclosure: „This horse has an ancestor known to carry HYPP, designated under AQHA rules as a genetic defect. AQHA recommends testing to confirm presence or absence of this gene.”

### Other genetic diseases

Several additional diseases do exist but are not mentioned here; they can be found on the website [www.omia.org.au/home](http://www.omia.org.au/home) (> horse). There it is obvious that quite a number of problems are related to the colour of horses, something which we TB-breeders never ever selected for.

### Prospects for the future

In the coming years, the field of medical genomics may contribute much more to equine veterinary medicine than the simple identification of disease causing mutations (fig. 2). The union of well defined medical questions with cutting-edge genomic technologies will enable deeper investigation into physiology, patho-physiology, pharmacology and many other facets of medicine and disease (Brosnahan et al. 2010).



Fig. 2: Automated DNA Sequencer (courtesy of Prof.T.Leeb, Bern)

### SNP chips

Another set of tools that will greatly facilitate future research efforts are SNP chips (fig. 3). These permit evaluation of genetic variation across the entire genome in single tests and, furthermore, facilitate dissection and identification of different forms of complex diseases. The SNP Chip supports additional strategies for identifying genes contributing to complex conditions such as family and association studies. In the former, affected animals, their parents and other relatives comprise the test popu-

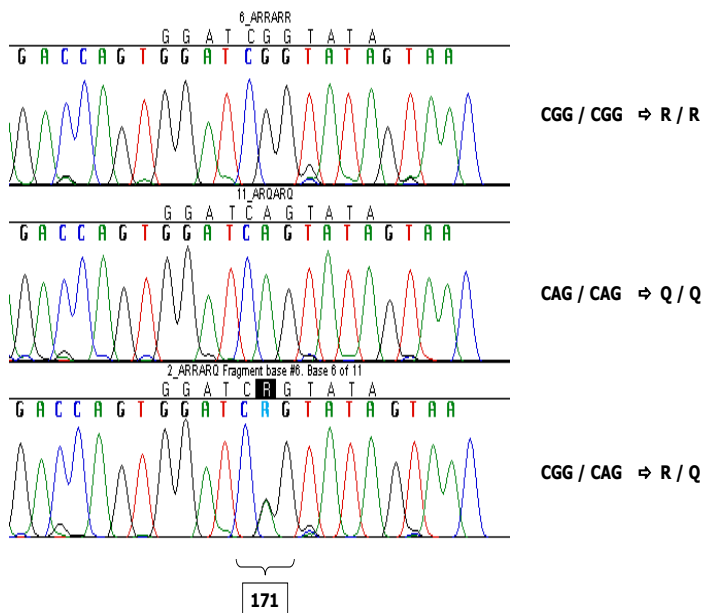


Fig. 3 Analysis of a mutation: Three sequences of three genotypes with one SNP in a gene which produces proteins with different amino-acids (R = Arginine, Q = Glutamine) (courtesy of Prof. T.Leeb, Bern)

lation, while, in the latter, cohorts of affected and non-affected unrelated individuals are tested. A 56,402 element equine SNP chip was produced and evaluated in 2008, and both Brooks et al.( 2010) and Brosnahan et al. (2010) did describe it as becoming widely used in investigations of inherited diseases of the horse. In 2011, there is already a 70'000 SNP Chip available from Neogen (GeneSeek) (Leeb 2011).

### Conclusion

Throughout history, man has bred the horse to accentuate both its physical beauty and its incredible athletic ability. We appear to have moulded a species with a relatively low, but by no means insignificant, number of inherited diseases. The Horse Genome Project has provided a genome sequence and powerful tools to help us continue to unravel its mysteries (Brosnahan et al. 2010).

As stewards of the future health and welfare of the domestic horse, it is imperative that researchers, clinicians, breeders, breed registries and owners work together to achieve maximum benefit from each new discovery. We must ask ourselves whether there are ways to harness this knowledge not simply to eliminate genetic disease but to breed horses that are sounder and healthier than in the past. The possibilities seem limited only by our imagination and our commitment to a species that has contributed immensely to centuries of human work and leisure activities.

Charles Darwin proposed that species evolve through random mutation and natural selection, with the fittest individuals surviving to reproduce. As we artificially select animals to breed, fitness must be our ultimate goal (Brosnahan et al. 2010).

### Appendix I

#### Allele

The different forms of a given gene that an organism may possess. For example, in humans, one allele of the eye-color gene produces green eyes and another allele of the eye-color gene produces brown eyes.

#### Chromosome

A package for carrying DNA in the cells. The DNA is wound up and bunched together into a compact structure. Different species of plants and animals have different numbers and sizes of chromosomes (man 46, horse 64, donkey 62, mule 63, zebra 44).

#### DNA

The deoxyribonucleic acid is a molecule as in fig. 1, a double stranded helix which is made of four types of bases and the sequence of these units carries the genetic infor-

mation, just as the sequence of letters carries information on a page.

**Expression array**

The expression array is another type of multiplexed, miniaturised hybridisation device. Expression arrays contain oligonucleotide probes for the expressed genes of an organism.

Expression arrays are used to assess gene activation by providing a semi-quantitative estimate of the amount of mRNA encoding specific genes in a tissue sample, based upon hybridisation of fluorescently labelled cDNA. Current equine expression arrays contain probes for nearly all of the estimated 20,000+ horse genes. (Brosnan et al. 2010)

**Gene**

A segment of DNA. Genes are like sentences made of the "letters" of the nucleotides. Between them they direct the physical development and behavior of an organism. Genes are like a recipe or instruction book, providing information that an organism needs so it can build or do something (e.g. "how to make an eye").

**Genetic engineering**

When man changes an organism by adding new or deleting genes from its genome

**Genetics**

The study of genes and heredity; traditionally refers to classic Mendelian principles of inheritance.

**Genome**

The complete set of genes in a particular organism.

**Genomics**

The branch of genetics concerned with the global characterisation of all of the genes and non coding DNA sequence of organisms.

The term 'genomics' has supplanted that of 'genetics' as research focus has shifted from single genes and their protein products to considerations of how the products of multiple genes interact to produce complex traits and how genes are regulated.

**Microsatellite**

Highly repetitive lengths of noncoding DNA involving multiple repeats of shorter segments of nucleotides (e.g. a di-, tri- or tetra-nucleotide).

These genetic markers often display length polymorphism based on the number of repeat units. Determination of variation at microsatellite loci is

widely used as a measure of polymorphism in a population and to identify nearby coding genes that determine traits of interest.

**Mutation**

An event that changes the sequence of the DNA in a gene

**Nucleotides**

They form the rungs of the DNA helix and are the repeating units in DNA. They are the four types A, C, G and T and it is the sequence of these nucleotides that carries information.

**Pleiotropy**

The participation of a single gene in 2 or more unrelated processes; mutation of such genes therefore may produce seemingly unrelated effects in several organs, tissues, or cellular functions (e.g. horses with white spotting phenotypes that are also deaf).

**Polymorphism**

Genetic variation; usually refers to genes in which there are 2 or more alleles (slightly different forms of the same gene) circulating in a population.

**SNP chip**

A single nucleotide polymorphism (SNP, pronounced snip) is a DNA sequence variation occurring when a single nucleotide - A, T, C or G - in the genome differs between members of the same species. Mammalian genomes contain millions of SNPs dispersed widely throughout the genome. A SNP chip is a miniaturised molecular device consisting of thousands of single stranded DNA oligonucleotide probes bound to a glass support. Each probe can be used to interrogate the DNA sequence at a single SNP locus using DNA hybridisation. SNP chips have become the method of choice for assessing variation across the genome; they are widely used in association and family studies designed to identify genes influencing traits of interest.

## Appendix II

### Websites relevant to horse genetics (according to Brosnahan et al. 2010) in addition to those mentioned in the text

Horse Genome Project (HGP) University of Kentucky  
<http://www.uky.edu/Ag/Horsemap/>

NIH Horse Genome Resources  
<http://www.ncbi.nlm.nih.gov/genome/guide/horse/>

Horse Genome Project (NIH)  
[http://www.ncbi.nlm.nih.gov/sites/entrez?term=txid9796\[orgn\]&cmd=search&ab=genomeprj](http://www.ncbi.nlm.nih.gov/sites/entrez?term=txid9796[orgn]&cmd=search&ab=genomeprj)

Horse Genome Browser Gateway (UC Santa Cruz)  
<http://genome.ucsc.edu/cgi-bin/hgGateway>

Ensembl Horse Database  
[http://www.ensembl.org/Equus\\_caballus/index.html](http://www.ensembl.org/Equus_caballus/index.html)

Horse Genome Project  
Bacterial Artificial Chromosome (BAC) Resource (Hannover, Germany)  
<http://www.tiho-hannover.de/einricht/zucht/hgp/index.htm>

American Association of Equine Practitioners (AAEP)  
Statement on Genetic Defects  
[http://www.aaep.org/statement\\_updates.htm](http://www.aaep.org/statement_updates.htm)

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**Readers are very welcome to ask questions or for further information if something doesn't make sense.**

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**EFTBA say a warm thanks and to Tim Richardson who has been Chairman of the EFTBA Veterinary Advisory Committee over the past few years.**



**And an equally warm welcome to Des Leadon, the new Chairman.**