Equine Incontinentia Pigmenti

***Rachel Towers, Angus Clarke, David Millar, Elise Glen, Ana Topf, Judith Goodship**
International Centre for Life, Newcastle University. Institute of Medical Genetics, Cardiff University
University of Glasgow student number: 0800480 Course: Medicine Email: 0800480t@student.gla.ac.uk

Aims

To establish whether a mutation in the equine IKBKG gene is causing Incontinentia Pigmenti in a family of horses by analysing mRNA and DNA level and sequence. Understanding the condition in the horse may provide opportunities for research into the condition in humans and perhaps new therapies in the future.

Introduction

Incontinentia Pigmenti (IP) is an X-linked dominant, recessive lethal ectodermal dysplasia caused by mutations in the human IKBKG gene[1]. NEMO, the protein product of IKBKG has a key regulatory role in inflammation, immunology, cellular proliferation and cell survival[1].

IP signs and symptoms in humans

- Evolving skin lesions [vesicular, verrucous, hyperpigmented and atrophic stages]
- Alopecia & unusually textured hair
- Scarring
- Nail abnormalities
- Abnormal dental development
- Ocular abnormalities

A family of horses is exhibiting signs consistent with IP including a family history suggestive of an X-linked dominant, recessive lethal condition (figure 1). The condition has not previously been identified in the horse.

Positive family history!

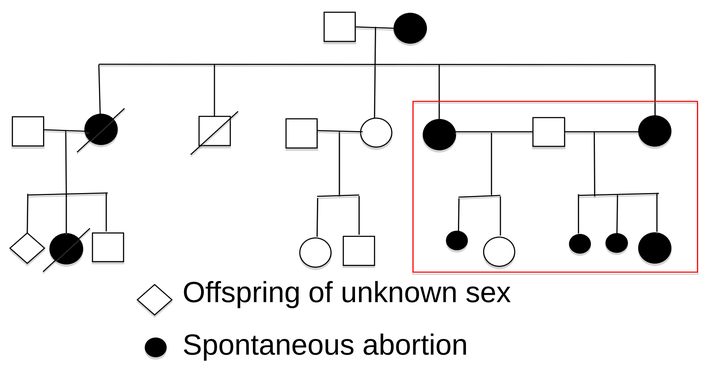
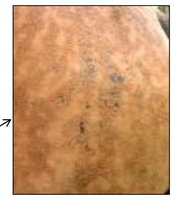
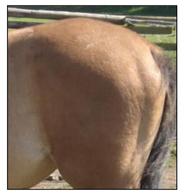


Figure 1. Family tree of affected horses. The 4 female horses within the red box and an unrelated horse have been studied.

Results

Horse clinical features mimic IP in humans!


Hyperpigmented stripes and scars following Blaschko lines


A normal coat


Abnormal hoof and coronet


A normal hoof[2]


Gaps between teeth

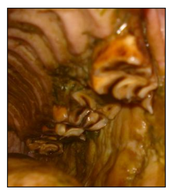

Missing teeth. Pointed, uneven teeth

Figure 2. Some clinical features in affected horses.

Exonic sequencing; No abnormalities found.

Intronic sequencing; Common human deletion not present.

Limitations; Inaccuracies in reference sequences (different NCBI & ensembl predicted sequences). There are 398 unknown bases in the DNA reference sequence.

Results

cDNA sequencing; mRNA from unaffected horse IKBKG gene identified (sample 1), including a novel exon not present in the incomplete reference DNA.

- Novel exon found!

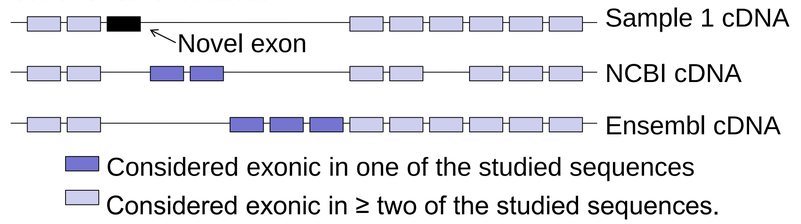


Figure 3. Accurate cDNA sequence with novel exon (sample 1 cDNA) and the differences between predicted reference sequences, which complicated the analysis of this gene.

Q-PCR; The level of IKBKG mRNA expression in abnormal compared to normal skin varied between horses.

- mRNA expression in abnormal skin increases with age!

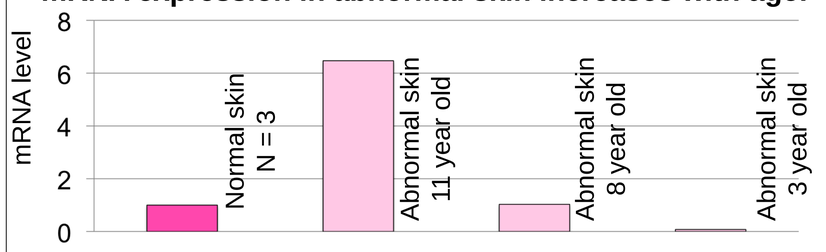


Figure 4. Level of IKBKG mRNA expression in affected horses.

X-inactivation or IKBKG up-regulation over time may occur as expression in abnormal skin increases with age. Is there a mutated protein elsewhere in the same biochemical pathway?

Conclusions

- The involvement of the IKBKG gene in the cause of IP in horses is inconclusive; sequencing of affected horses mRNA is still underway due to technical laboratory difficulties.
- A novel 119 bases were found in the mRNA, this probably represents a previously unidentified exon, this more accurate mRNA sequence should aid future research into this horse gene.

References: 1. Aradhya S, Woffendin H, Jakins T, Bardaro T, Esposito T, Smahi A, et al. A recurrent deletion in the ubiquitously expressed NEMO (IKK-gamma) gene accounts for the vast majority of incontinentia pigmenti mutations. Hum Mol Genet. 2001;10(19):2171-9

2. Horses with Amie. [Online]. [Updated 2010; cited July 18]. Available from: http://www.horseswithamie.com/horsehealth/founder.htm