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Diseases of the older horse from a genetic point of view

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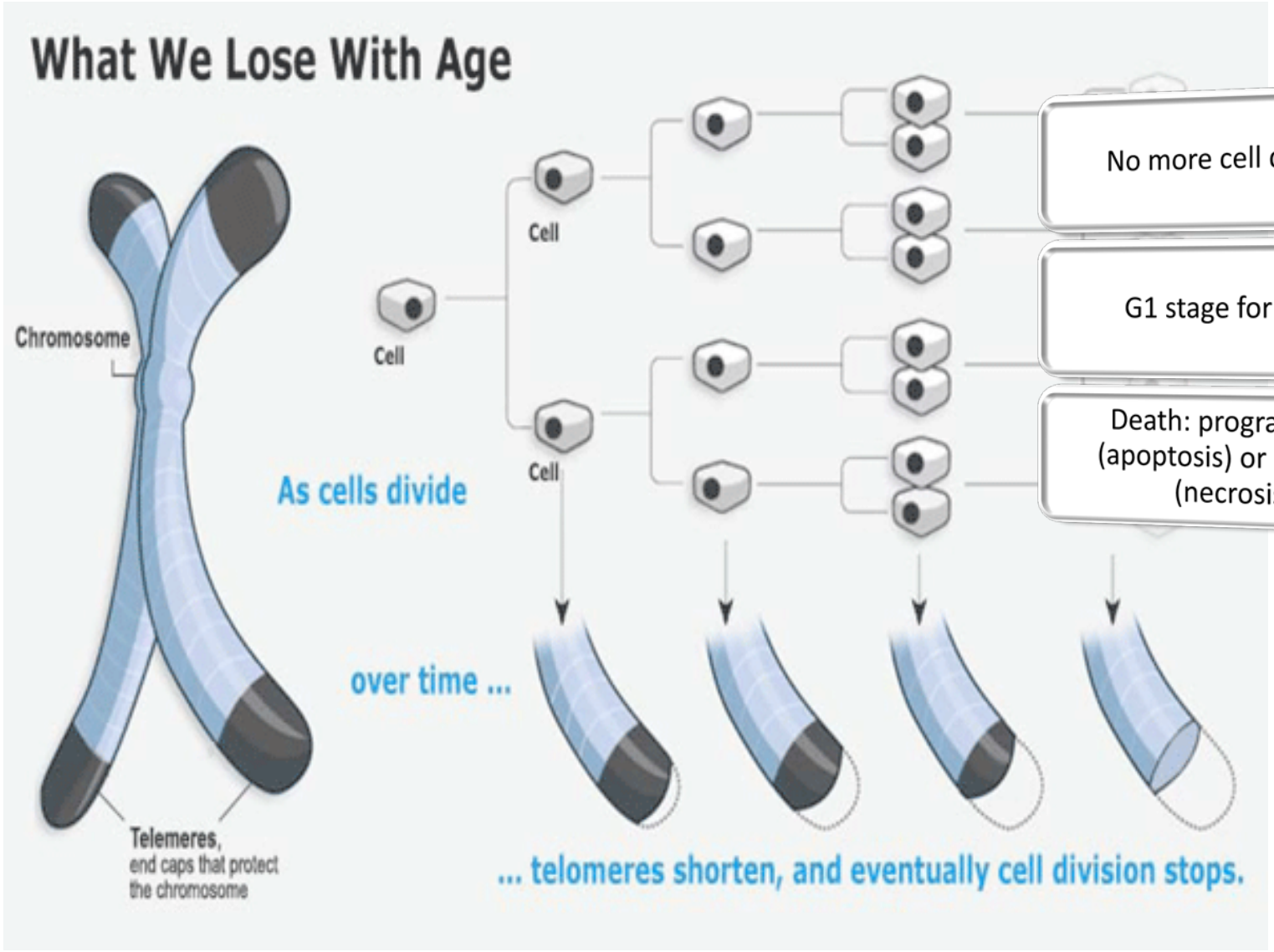
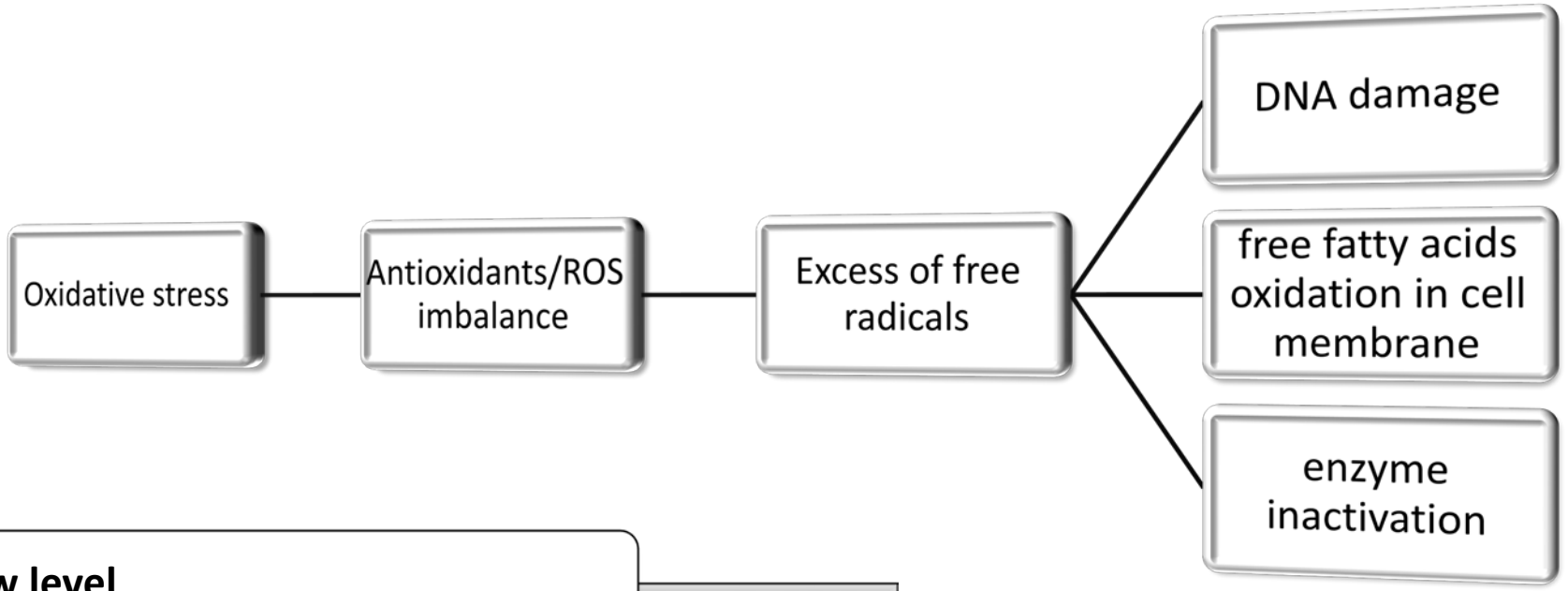
Replicative senescence



http://www.viewzone.com/telomerase.telomere.gif

Cell senescence



Low level

- Adaptation: transient or permanent growth arrest (senescence)

High level

- Necrosis or apoptosis

Hansen et al. 2015 Ageing Res Rev,
Bree et al. 2002 Biogerontology

Late-onset genetic disorders

Accumulated mutations

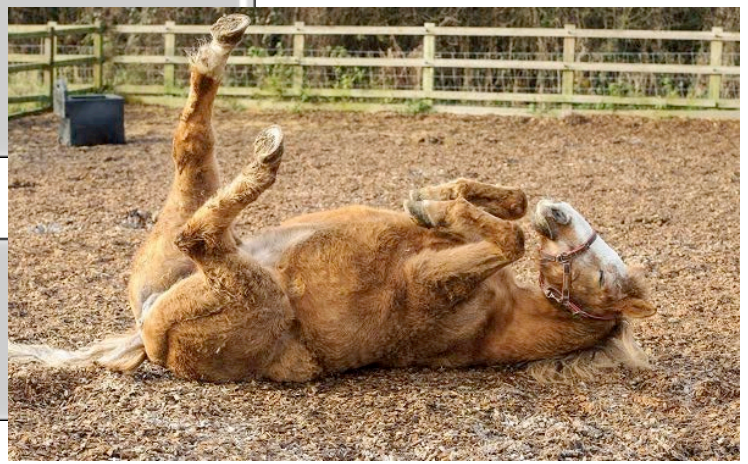
- Intrinsic failures of the replication (somatic mutations)
- Mutagens: expression of so far dormant genes

Accumulated gene products

- Accumulation of disease agents
- Lack of vital substances
- Gradual process, unnoticed for years

Genetic modifiers

- Timing regulated by other genes



Orchid, lived ~50

http://www.horsechannel.com/images/horse-news-article-images/orchid-oldest-horse-1.jpg

Zhaurova, 2008 Nature Education

Why horses get so old?

Unless they are eaten before…

- They are often companions, quite expensive
- It takes ~ 3-5 years until they mature
- Training can take 10 years or more
- Valuable stallions
- From molecular point of view
  - High rate of DNA repair
  - Low rate of free radical production

Pamplonaet al. 1998, MacRae et al. 2015

Geriatric horses

- > 20 years old
- Decline in:
  - Dental health
  - Body condition
  - Muscle tone
  - General well-being
- Increased susceptibility to infectious diseases
- Decreased responsiveness to vaccination

Shayne, lived 51

http://i.dailymail.co.uk/i/pix/2013/03/06/article-2288910-1878B1B7000005DC-258_634x824.jpg

Geriatric horses

Horse ageing involves changes in the immune system

- Genetics
- Nutrition
- Environment
- Organ-specific

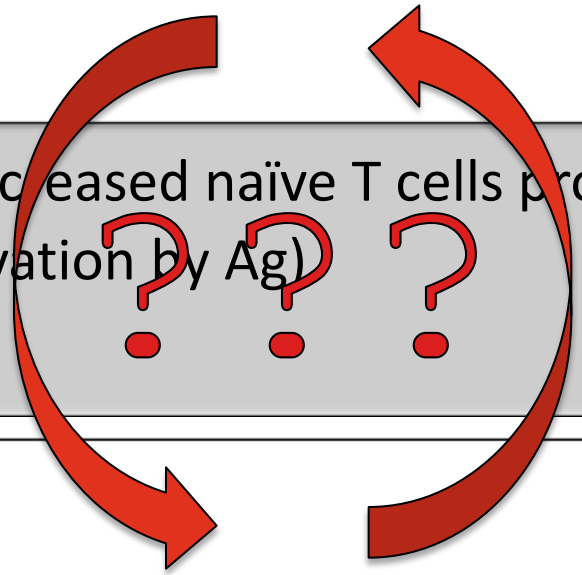
Twiglet, 46

http://i.dailymail.co.uk/i/pix/2012/09/26/article-0-1536F678000005DC-704_634x445.jpg

Age-related phenomena

Immuno-senescence

- Thymus involution – decreased naïve T cells production
- Clonal exhaustion (activation by Ag)
- Aging of resting T cells



Inflamm-ageing

- Increased pro-inflammatory (Th1) cytokine production
  - (IL6, TNFA, acute phase proteins)
- Disability and mortality in chronic diseases (chronic MØ activation)
- Adipose tissue contribution

Hansen et al. 2015 Ageing Res Rev
Horohov et al. 2010 J Comp Path

Age-related diseases

Monogenic, "solved"

- Melanomas in grey horses

Complex, unsolved

- Cushing's disease
- Horse asthma

} mature horses

Grey horses

- Autosomal dominant
- More common in some breeds, e.g. Lipizzans
- Appears gradually
- >70% of >15 years old develop melanomas

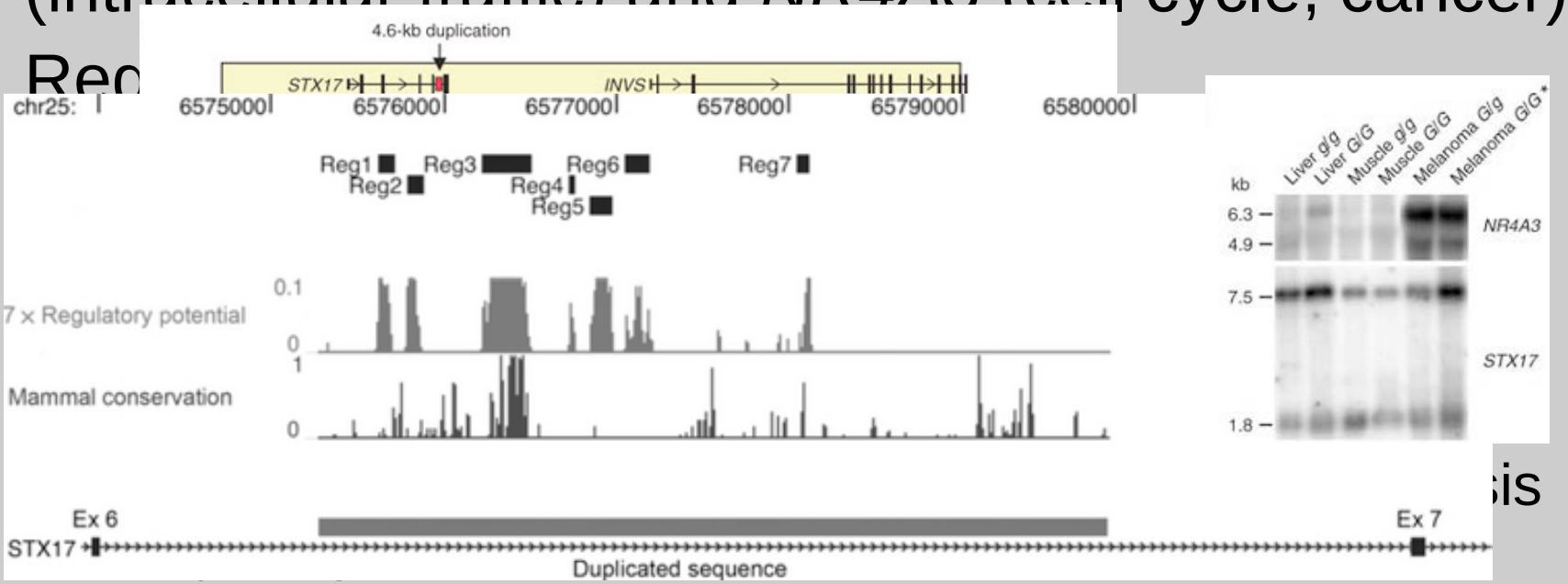
- Not UV-induced
  - dark skin
  - regions well protected from UV

http://www.lipica.org/it/#

Grey horses

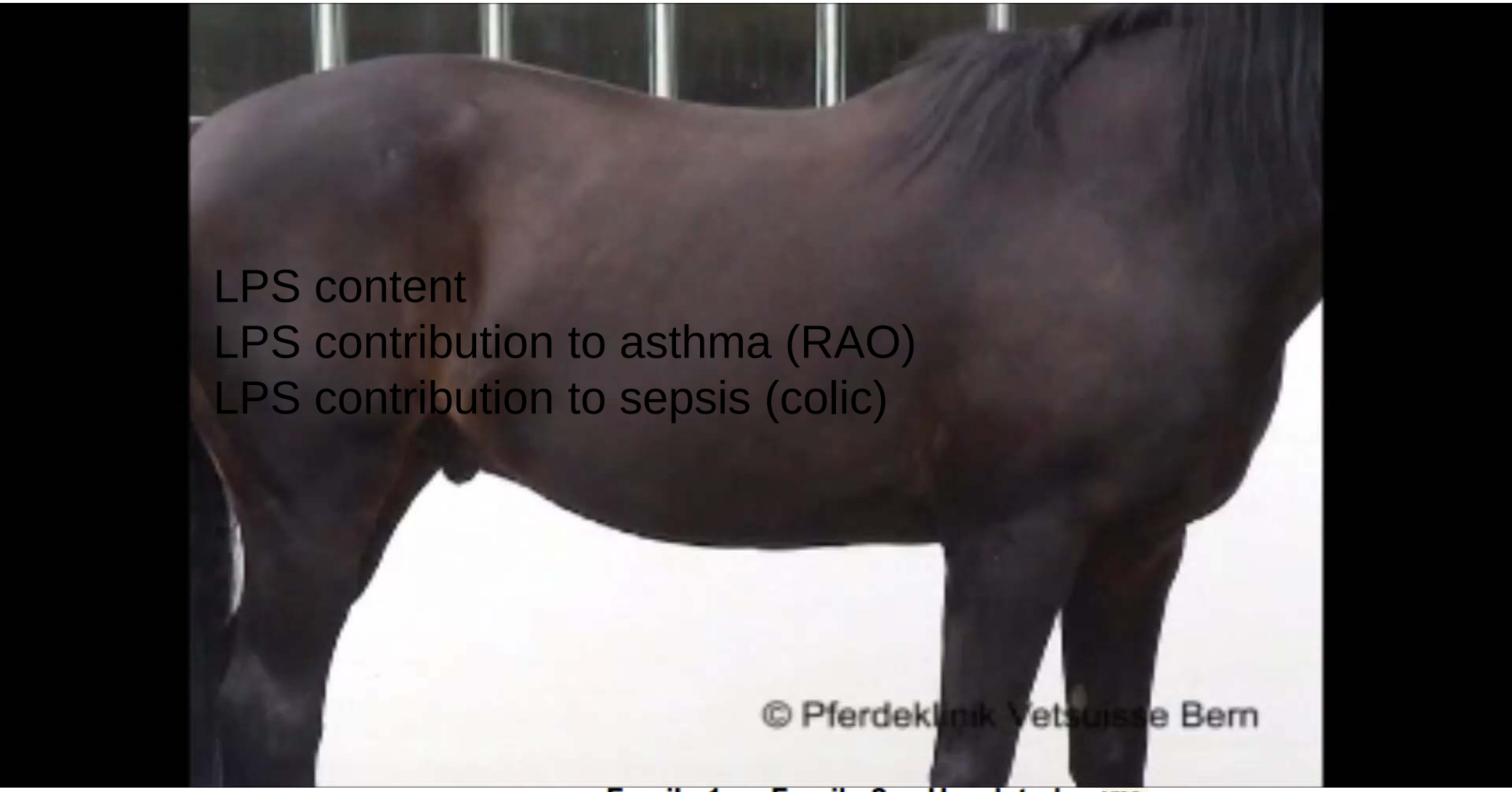
Melanocyte-specific mutation

- 4.6-kb duplication in *STX17* intron 6
- cis-acting regulatory mutation affecting *STX17* (intracellular traffic) and *NR4A3* (cell cycle, cancer)
- Rec
- is



Sundstrom et al. 2012, Pigment Cell Melanoma Res
Rosengren Pielberg et al. 2008, Nat Gen

Horse asthma, RAO



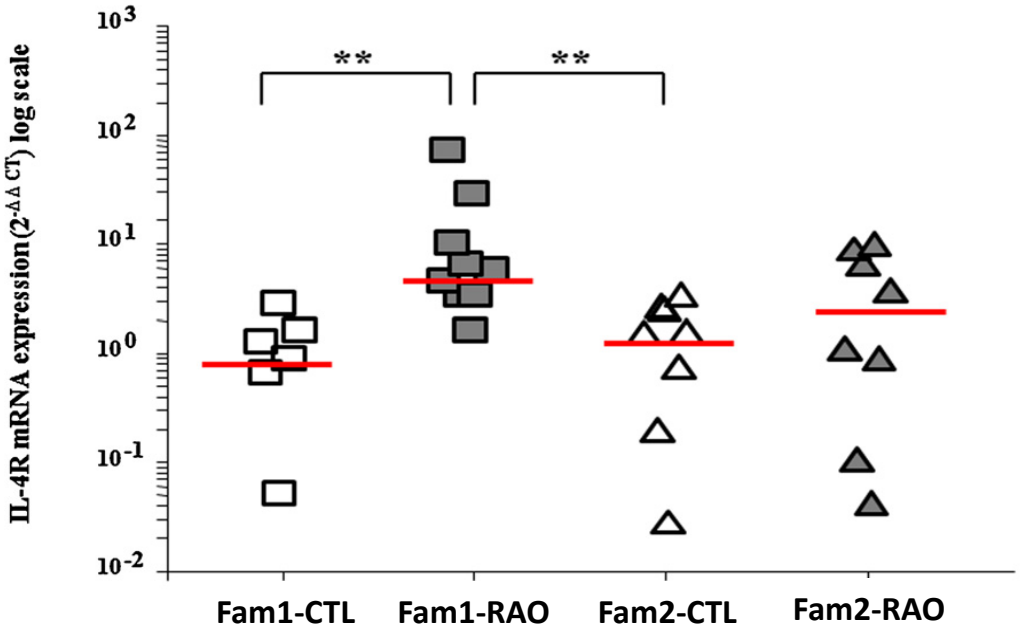
Family 1 Family 2 Unrelated

Bründler et al., 2011 2001

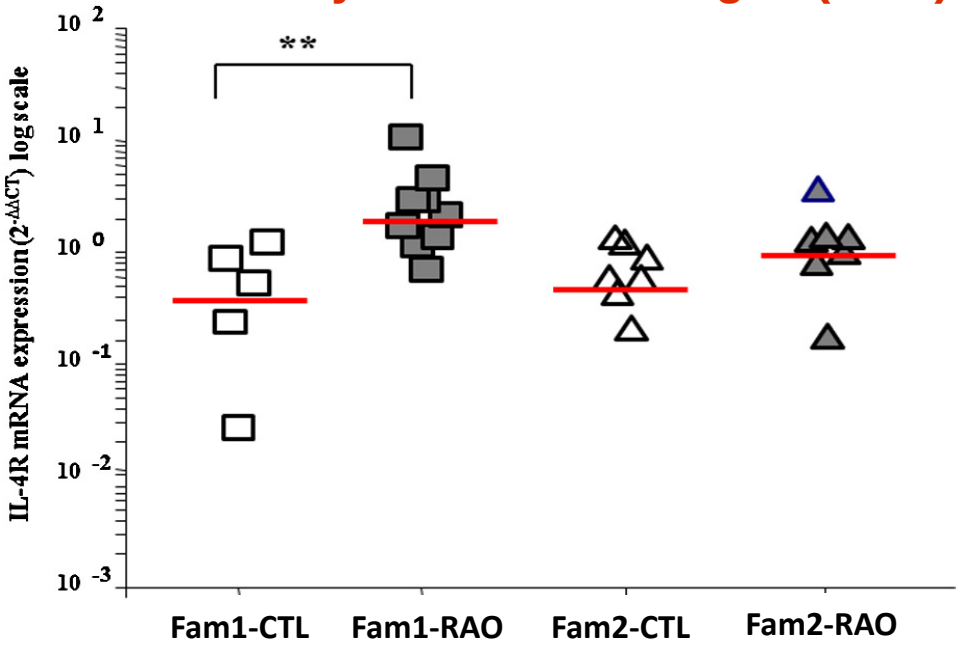
Quantitative RT-PCR

In vitro stimulated peripheral blood mononuclear cells (PBMCs)

hay dust extract (HDE)



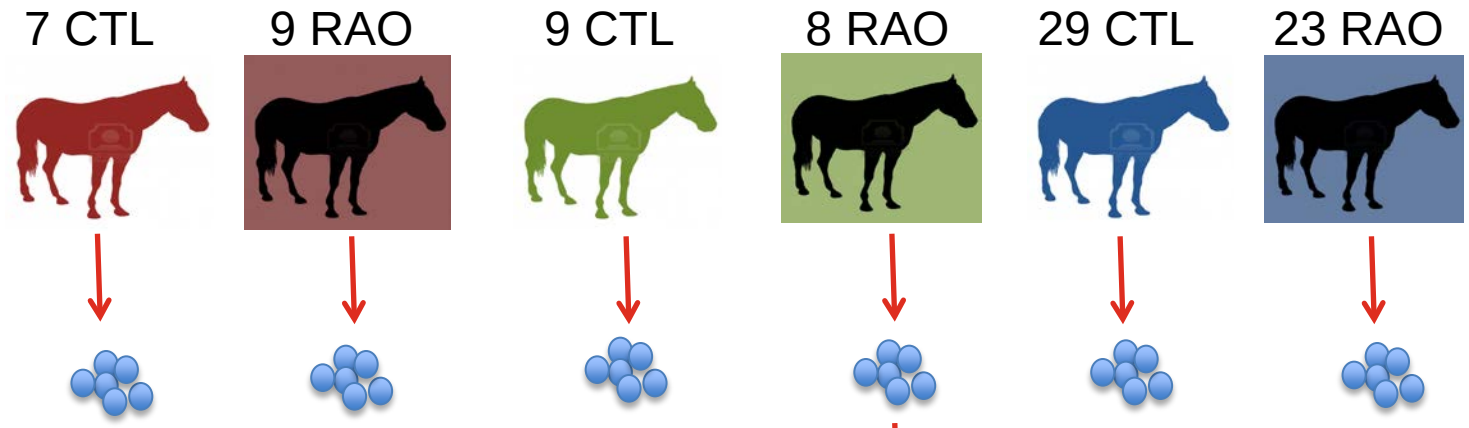
recombinant cyathostomin antigen (RCA)



CTL – control; RAO – RAO-affected; Fam - family

Lanz et al., 2013

In vitro study with PBMCs



24h

8 x 10^6 cells

Mock **LPS** **HDE** **RCA**

Mock – no stimulating factor

lipopolysaccha
dry dust extra
recombinant

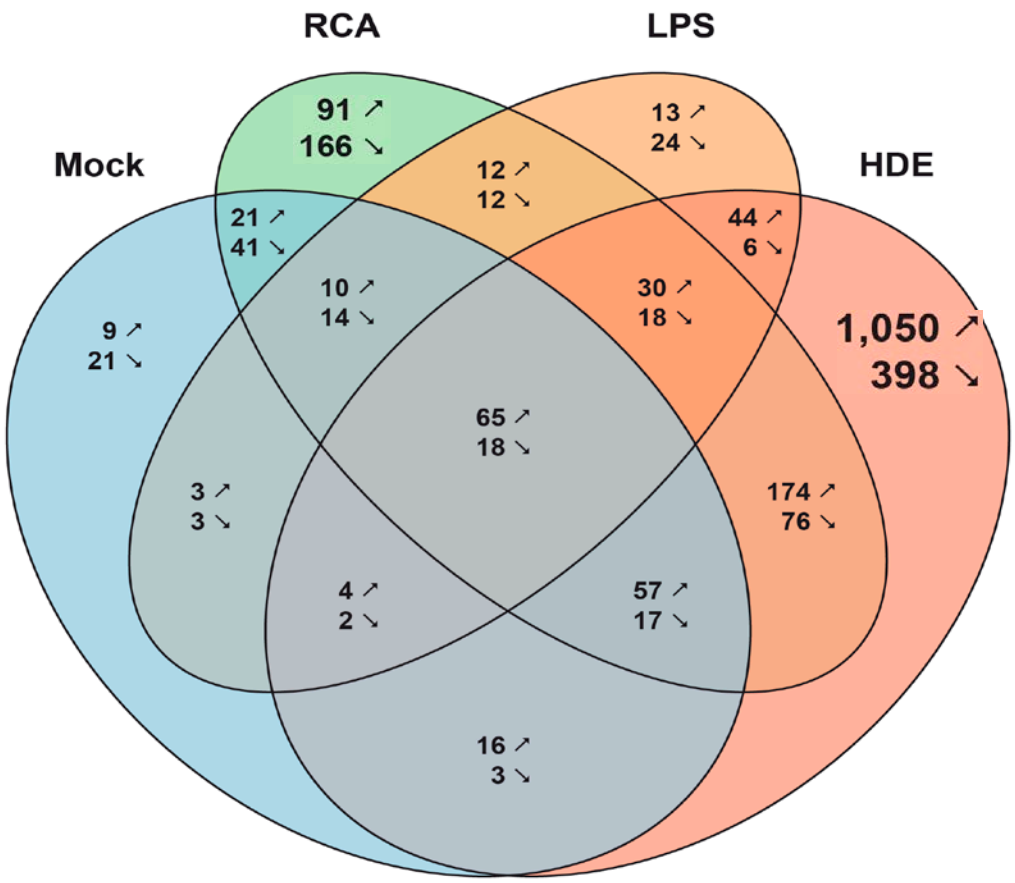
TNF-rela
protein

antigen)
on pa

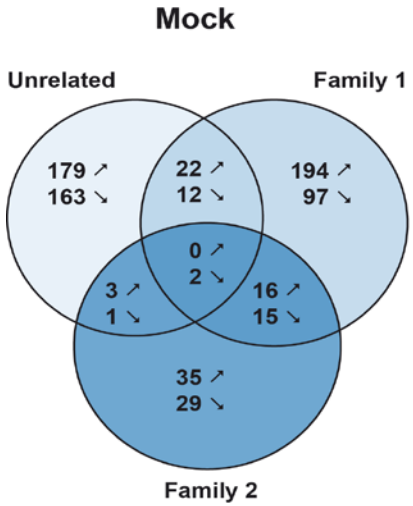
n h

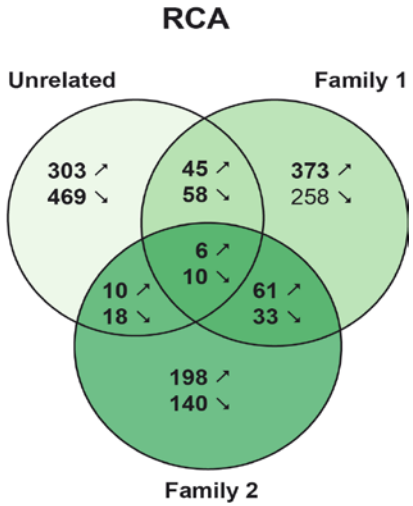
ntigen

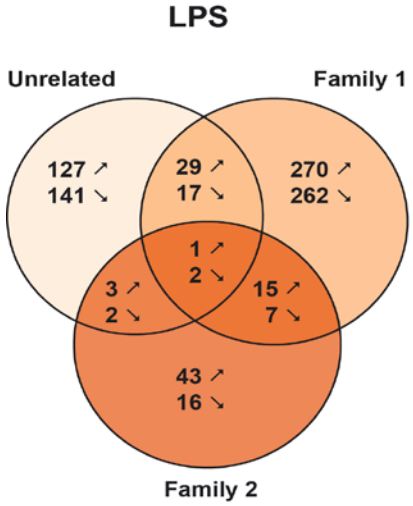
DE analysis in PBMCs

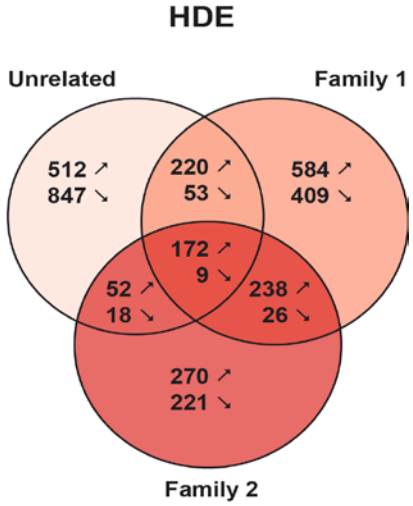


↗ upregulated
↘ downregulated

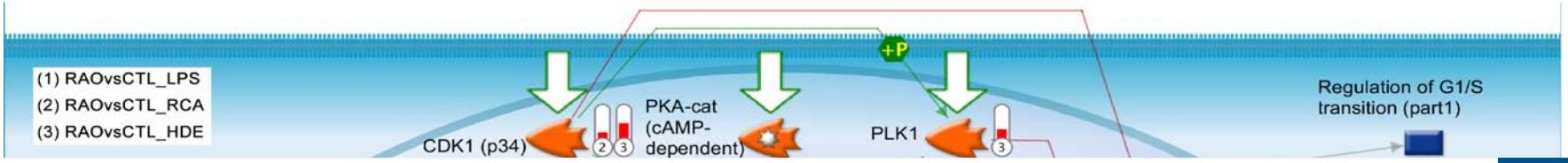








Pacholewska et al. (2015) PLOS One



Developmental Cell
Article

CellPress

APC^{Cdc20} Suppresses Apoptosis through Targeting Bim for Ubiquitination and Destruction

Lixin Wan,[1] Mingjia Tan,[2] Jie Yang,[2,3] Hiroyuki Inuzuka,[1] Xiangpeng Dai,[1] Tao Wu,[4] Jia Liu,[1,5] Shavali Shaik,[1] Guoan Chen,[6] Jing Deng,[7] Marcos Malumbres,[8] Anthony Letai,[7] Marc W. Kirschner,[4] Yi Sun,[2] and Wenyi Wei[1,*]

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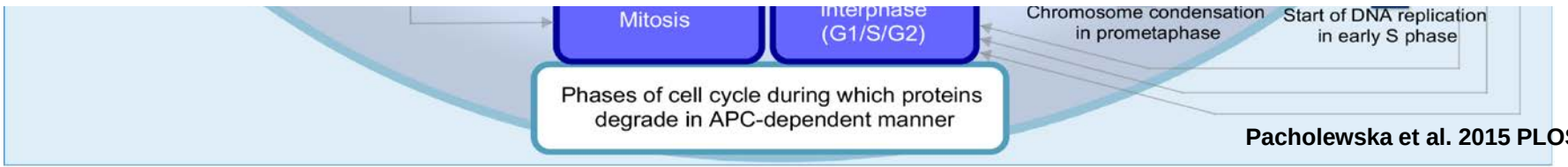
*Correspondence: wwei2@bidmc.harvard.edu
http://dx.doi.org/10.1016/j.devcel.2014.04.022

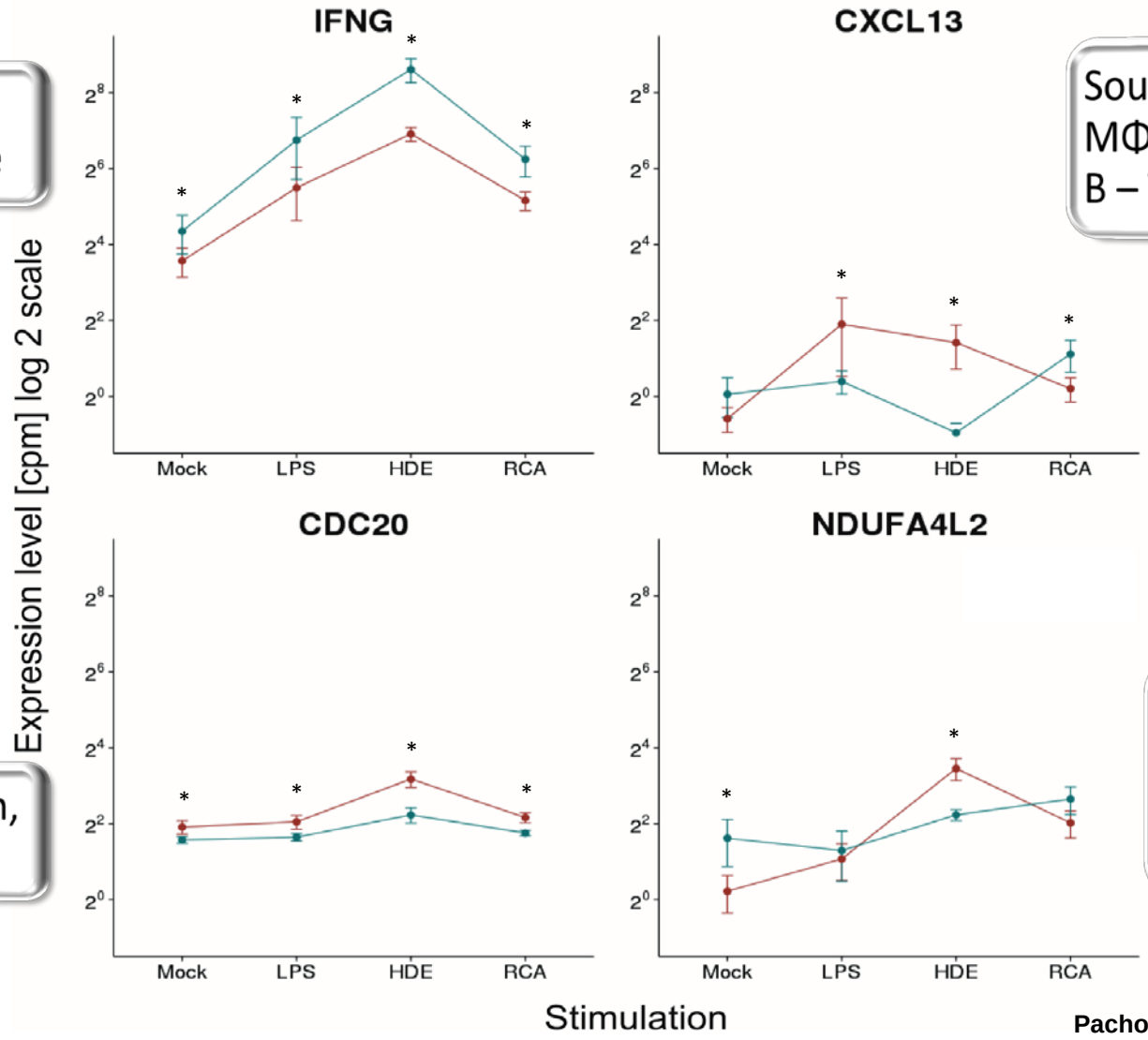


Pacholewska et al. 2015 PLOS One

RAO-relevant genes

Innate response,
Th1-type response

Cell cycle regulation,
anti-apoptosis



Source: activated MΦ,
B – T-cell interaction

Target for HIF-1,
Reduces ROS,
Hypoxia-induced tissue remodeling?

Pacholewska et al., 2015, PLOS One

PPID (Cushing's disease)

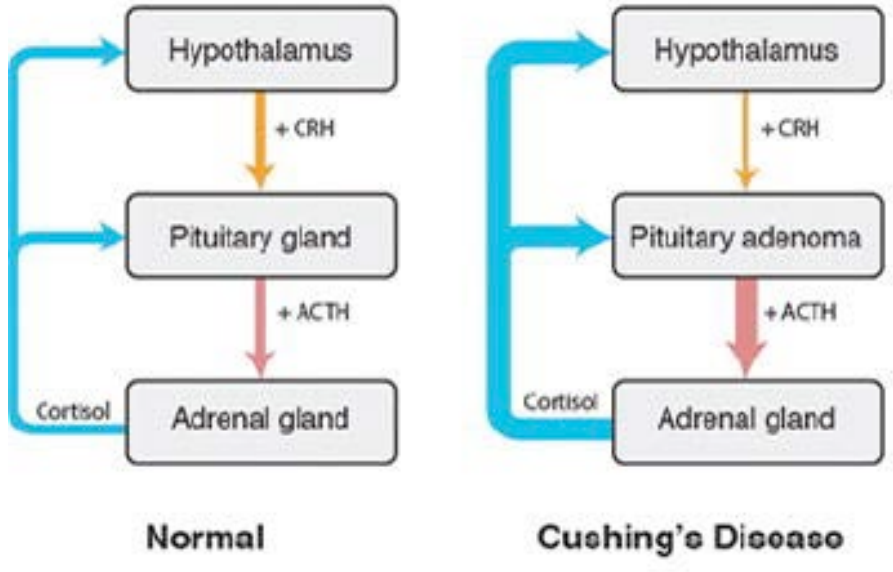
Pituitary Pars Intermedia Dysfunction

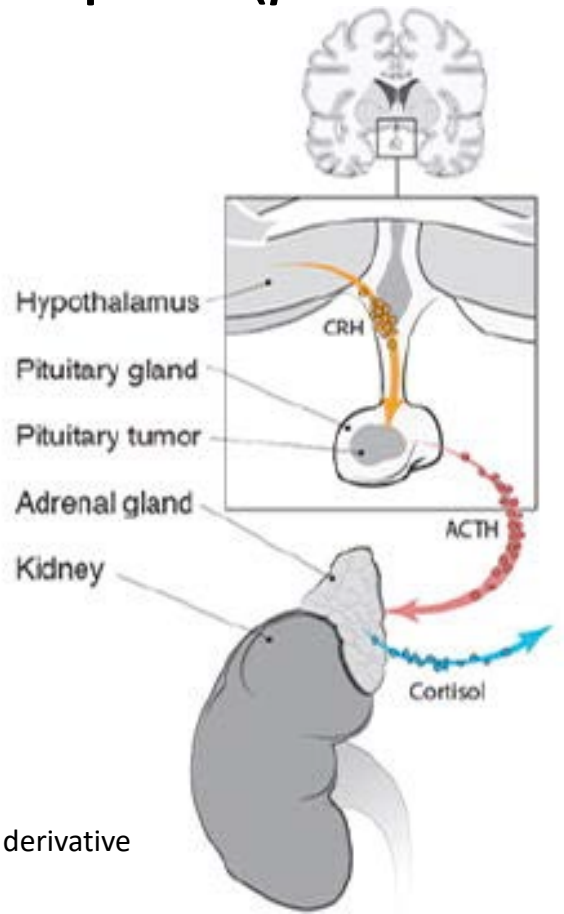
- Hypertrichosis (long curly coat)
- Muscle loss, poor performance
- Abnormal fat distribution
- Laminitis
- Increased sweating, drinking
- Susceptibility to infections

http://www.mayowvets.co.uk/info/images/24_266710.jpg

PPID (Cushing's disease)

- Hormone-secreting tumour of the pituitary gland
- In human and dog: the anterior part (*pars distalis*):
- In
  -
  -
  -





onal

role

CRH – corticotropin-releasing hormone
ACTH – adrenocorticotropic hormone, a pro-opiomelanocortin (POMC) derivative
Cortisol – glicocorticoid involved in response to short periods of stress

al. 2016 *J Neuroserg*
Breuhaus 2011
007 Ageing Res Rev.

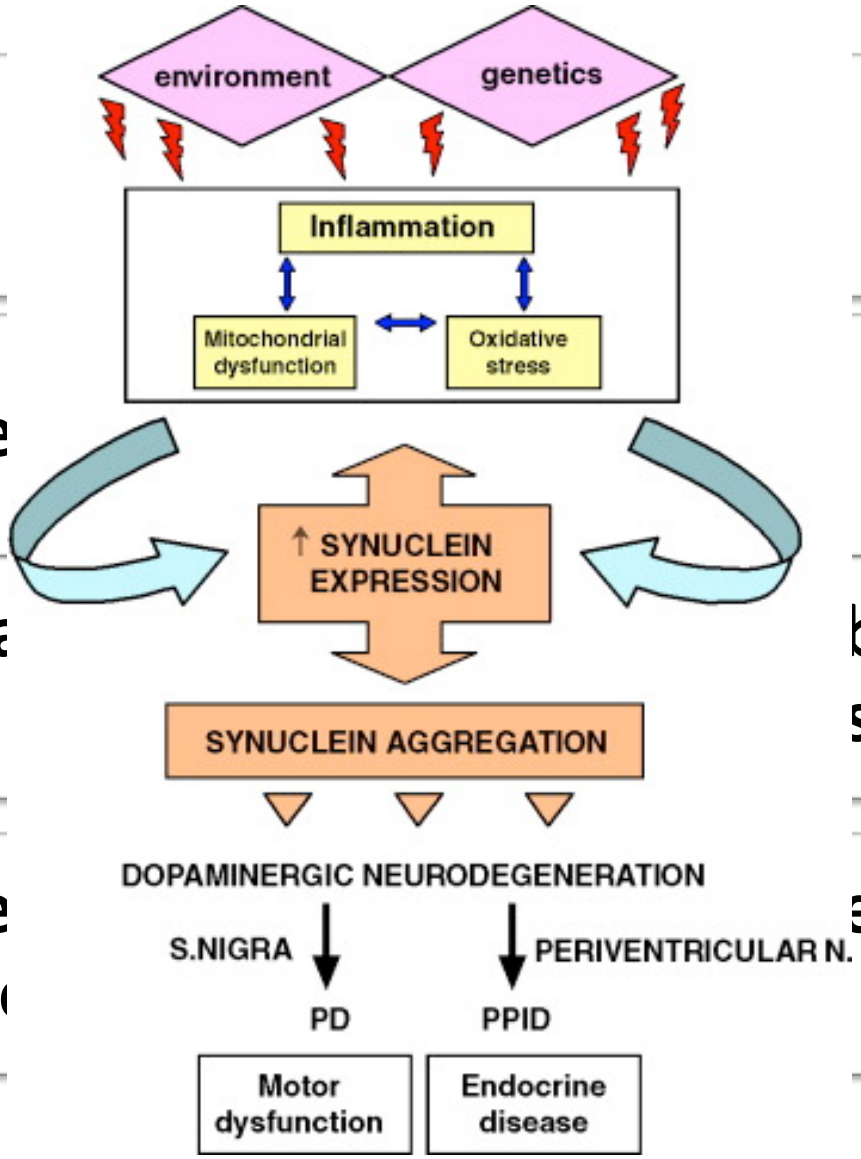
PPID in horses

~ 20% horses >

PPID horses fre

Neurodegenera bitory
dopaminergic i s?

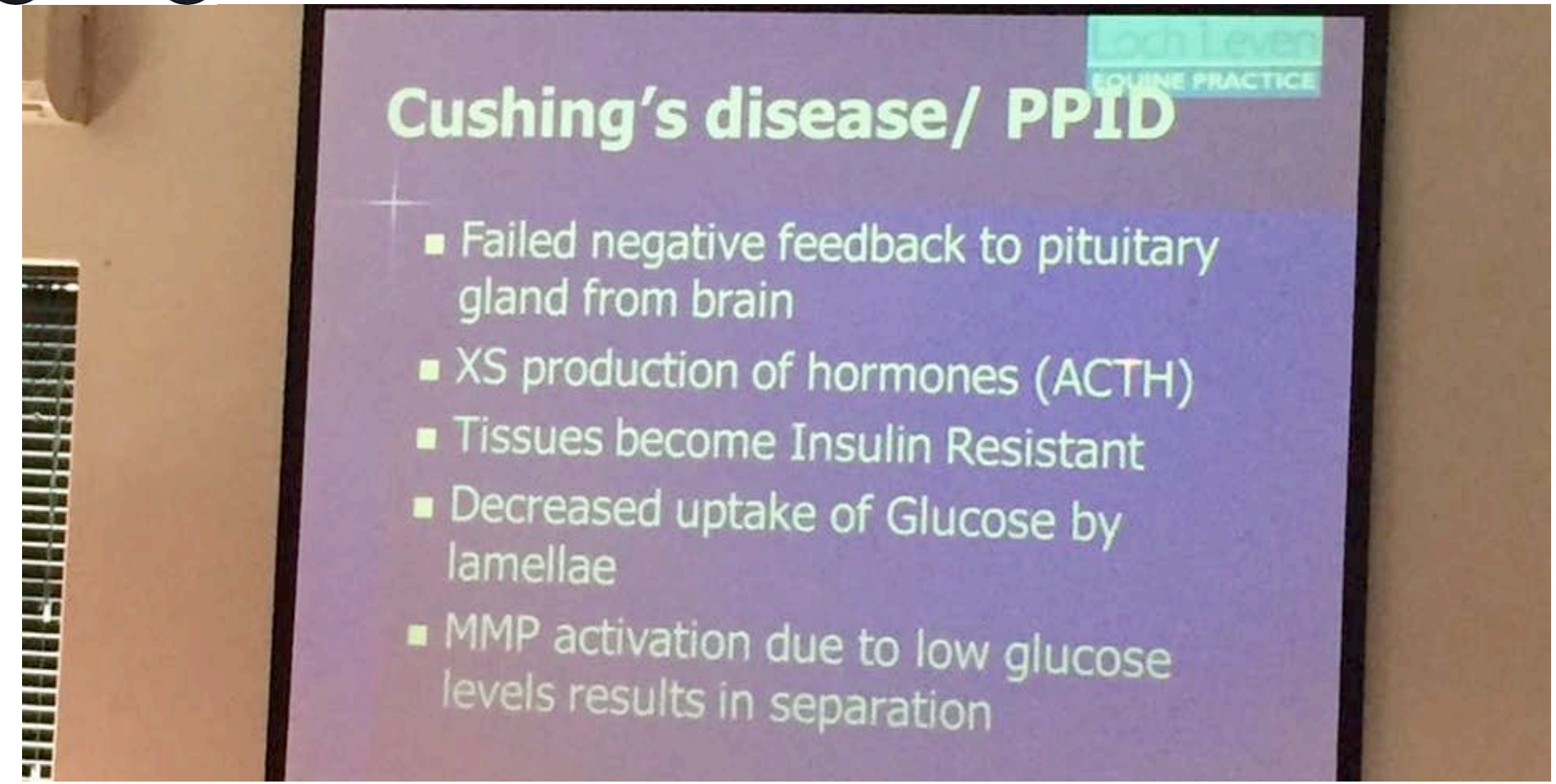
Genetics: more e in human
increases risk f



McGowan, 2013 EVJ
McFarlane 2007 Ageing Res Rev.

VETs with HORSEPOWER
The Iron Run - South Africa 2016

www.facebook.com/VwHPCPD



Jenny Croft from Loch Leven Equine

VETs with HORSEPOWER
The Iron Run - South Africa 2016

Horsepower 2014 Warszawa
Page Liked · 6 July 2014 ·

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Joanna Sak, Jane David and 3 others Top

Pat Adams Impressive line up!
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Short description

We are a group of motorbiking senior level vets who go on tours delivering high level CPD for charities.

http://www.justgiving.com/vetswith-horsepower

Laura, ältestes Pferd Deutschlands

Conclusions

- Some genetic disorders manifest late
- Genetic predisposition ≠ genetic disorder
- Causative mutations are not always within protein-coding genes
- Well maintained horses may not develop the disease predicted
- *De novo* mutations not yet associated with a disease
- Animals with causative/associated mutations should be excluded/restricted from breeding as soon as possible

Thank you
for your attention