

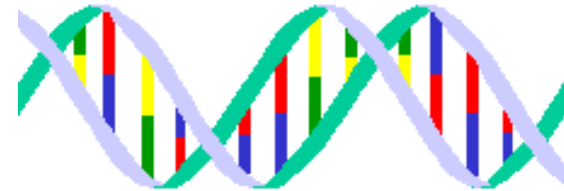
New approaches to dealing with
recessive inherited diseases
and guidance on how to use them

Huw Jones

Biosciences KTN

Recessive Inherited diseases

- Originate from errors in the DNA replication process (*mutation*)



- Only appear when an animal carries two copies of a defect causing genetic
- Common in many species and can take the form of a variety of different types of diseases or defects

Some well know examples



Polydactaly



Spider leg



Bulldog calf



Syndactaly/mule foot



**CVM
BLAD
DUMPS**

They are not always easy to spot

Fell Pony Foal Syndrome - first reported in 1998

Clinical signs

- Weight loss
- Failure to suckle
- Increased salivation
- Dull demeanour
- Opportunistic infections

Diarrhoea (Cryptosporidium)

Nasal discharge (adenovirus)

Glossal ulceration / hyperplasia



Patterns can be seen with records

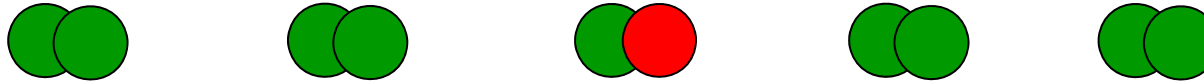
- Apparently 'normal' at birth
 - Age on-set 2-12 weeks
 - Anaemia
 - B-lymphocyte deficiency
 - 100% mortality
-
- Repeated incidence in families
 - Incidence estimated to be up to 15%
 - Similar condition first reported in Dales Foal – 2008



Recessive Inherited diseases

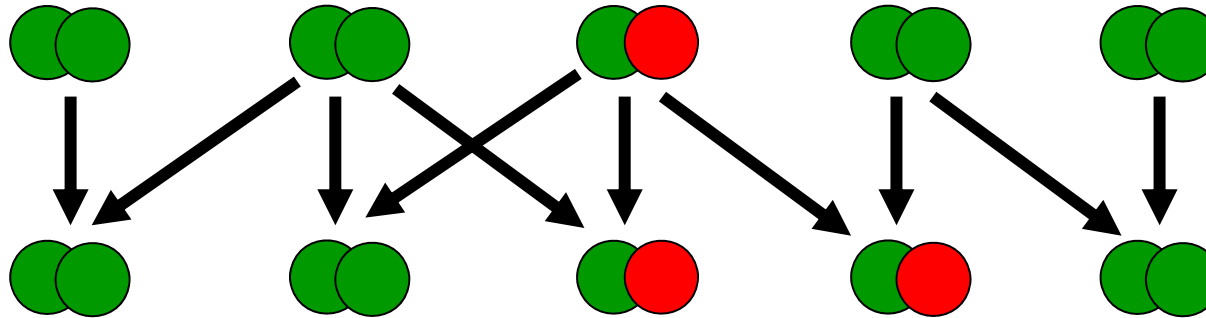
- Originate from errors in the DNA replication process
- Only appear when an animal carries two copies of a defect causing genetic variant
- Common in many species and can take the form of a variety of different types of diseases or defects
- Can appear intermittently – especially in species with small litters – $\frac{1}{4}$ chance if both parents are carriers
- Carriers can multiply unnoticed

Curse Of The Recessive



A new mutation

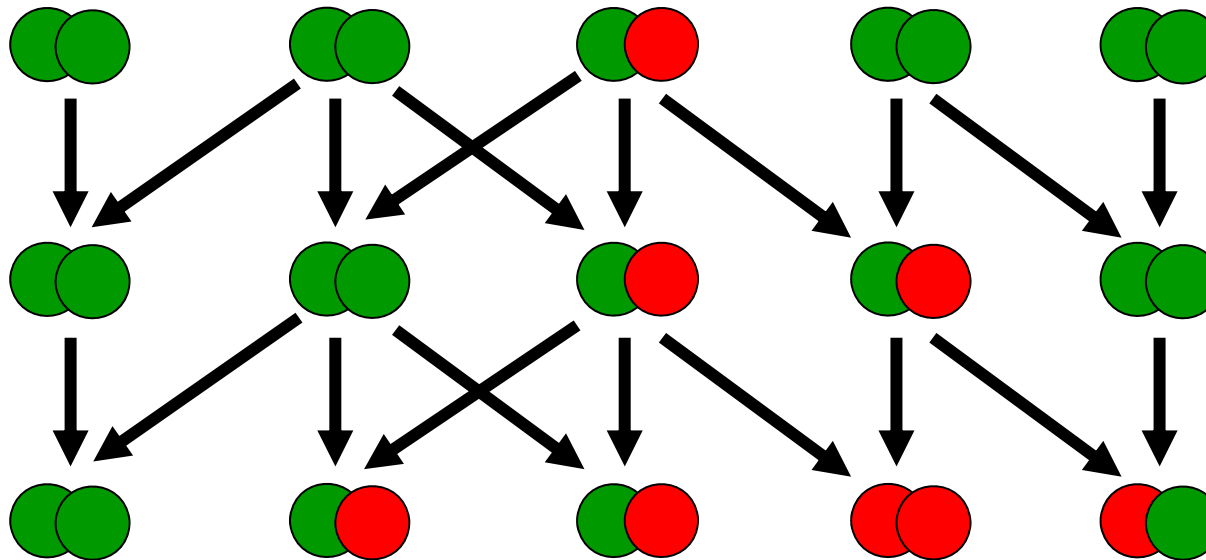
Curse Of The Recessive



**No disease has yet
appeared**

**But more carry the
bad gene variant!**

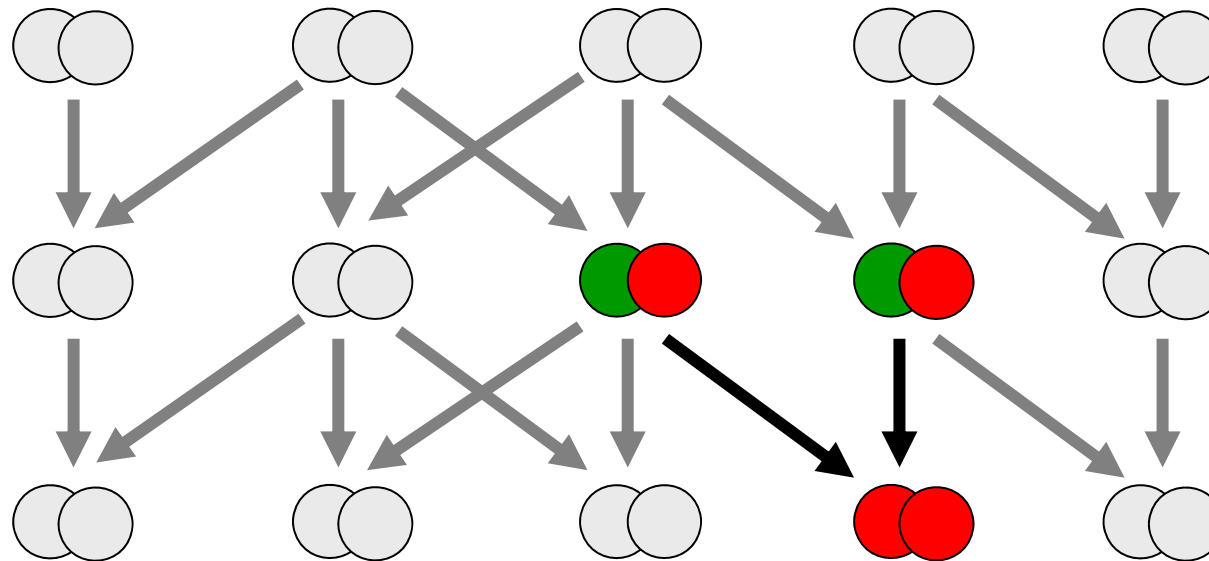
Curse Of The Recessive



Disease appears!

Is it recognised?

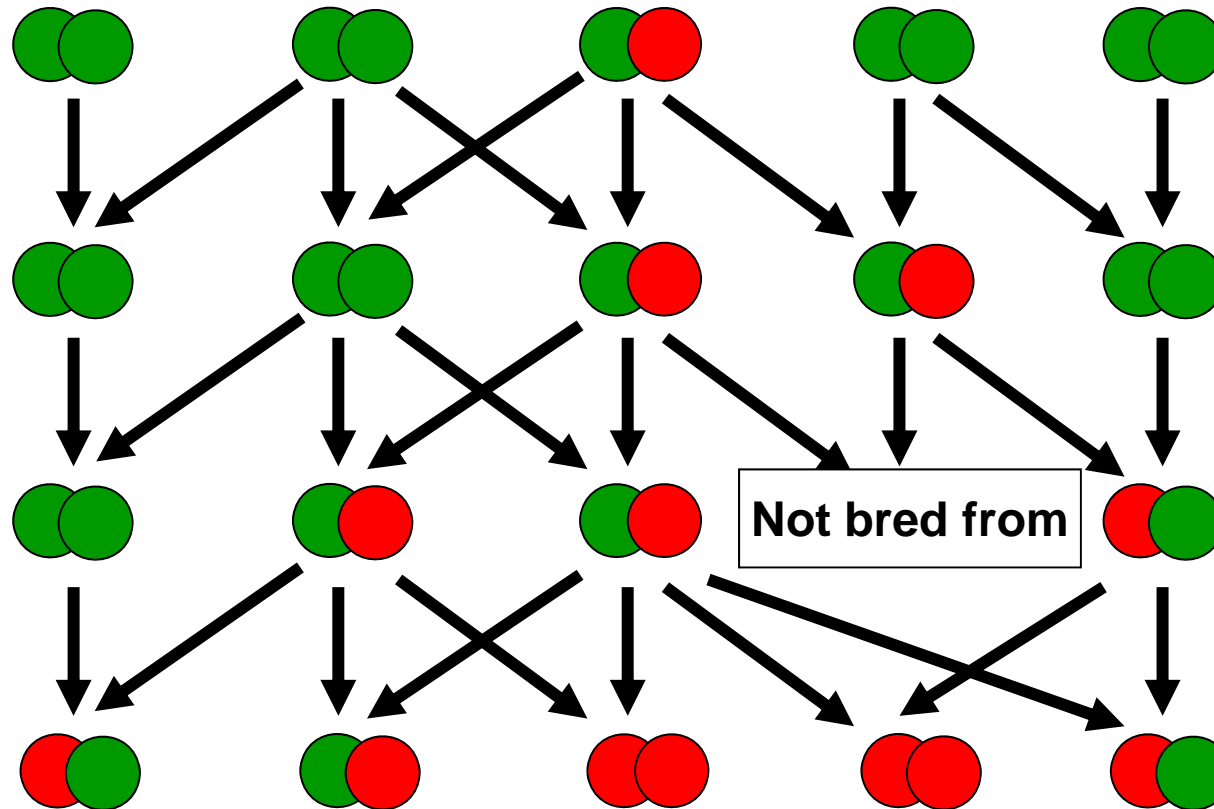
Curse Of The Recessive



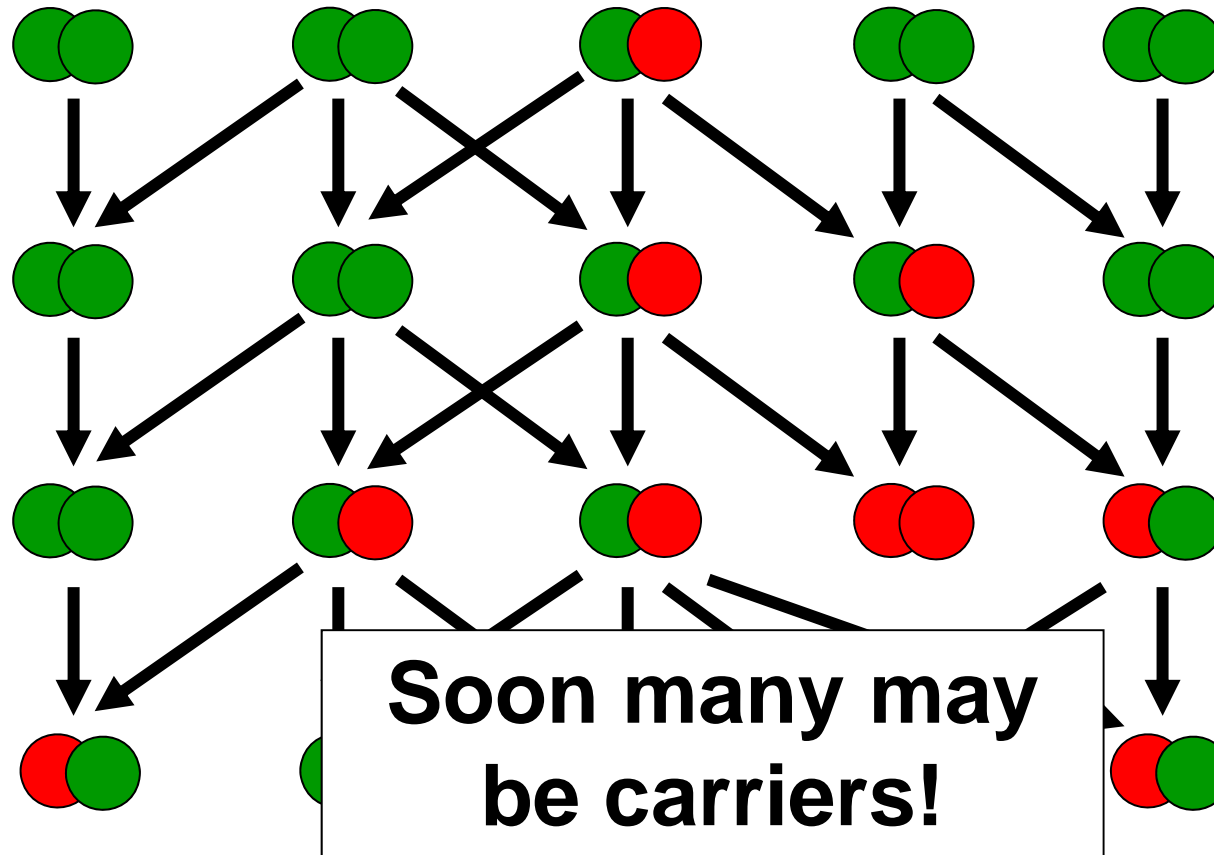
Both parents carriers

Only $\frac{1}{4}$ chance

Curse Of The Recessive



Curse Of The Recessive



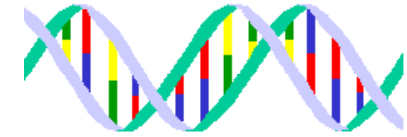
Recessive Inherited Diseases

- Frequency of carriers can multiply quickly if:
 - Rates of inbreeding are high e.g.
 - *Population size is small*
 - *Populations go through a bottleneck*
 - Disease variant is linked to a desirable phenotype
- **Breeders' response may be to ignore or suppress the problem**
 - **only helps to make it worse!**

Managing the problem

- Can be managed or eliminated by using suitable genetic markers
- Historically tests could be developed, but process tended to be expensive and often difficult (*e.g. CVM, DUMPS and BLAD for dairy cattle*)
- But new technologies can help to simplify the process

The challenge



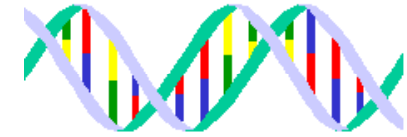
**Animal 1
(affected)**

AATGTGGTCGTCAACTCGTAGCATCAAAAAT
CTAGCTACGACGCATGTCTCTCGTCAAAAATT
GATCTAACGATCA**A**GCCGATCGCCGCATGC
ACGGCTACGTTATAGGACACTATCATTGAA

**Animal 2
(not affected)**

AATGTGGTCGTCAACTCGTAGCATCAAAAAT
CTAGCTACGACGCATGTCTCTCGTCAAAAATT
GATCTAACGATCAA**T**GCCGATCGCCGCATGC
ACGGCTACGTTATAGGACACTATCATTGAA

The challenge



**Animal 1
(affected)**

AATGTGGTCGTCAACTCGTAGCATCAAAAAT
CTAGCTACGACGCATGTCTCTCGTCAAAAATT
GATCTAACGATCA**A**GCCGATCGCCGCATGC

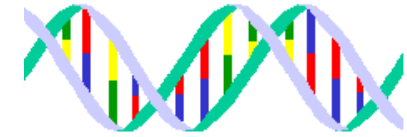
Each sheep genome is
3,000,000,000 bases long!!

**Animal 2
(not affected)**

AATGTGGTCGTCAACTCGTAGCATCAAAAAT
CTAGCTACGACGCATGTCTCTCGTCAAAAATT
GATCTAACGATCAA**T**GCCGATCGCCGCATGC
ACGGCTACGTTATAGGACACTATCATTGAA

**There will be '000s of other differences
between individual animals**

The challenge



**Animal 1
(affected)**

AATGTGG
CTAGCTA
GATCTAA
ACGGCTA



AAAAT
AAATT
CATGC
'GAA

**Animal 2
(not affected)**

AATGTGG
CTAGCTA
GATCTAA
ACGGCTA

AAAAT
AAATT
CATGC
'GAA

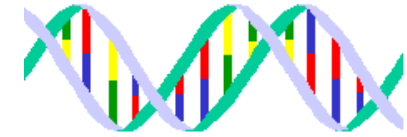
**Full sequencing of large numbers is an
option but ££££££**

A new approach

- *Charlier et al., 2008* - Demonstrated how new genomic tools and methods could be used to identify causatives:
 - more quickly
 - with higher success rates and
 - with relatively small numbers of cases and controls
- Make use of recessive characteristics
- Use of SNP chips to identify a narrow region of interest
- Sequence the narrower region to identify better markers or actual causative change



How SNP chips can help



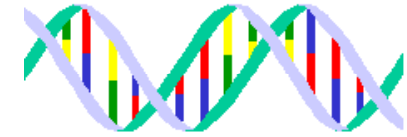
**Animal 1
(affected)**

AAATGGTCGTCAACTCGTAGCATCAAT
CTAGCTACGACGCATGTCGTCAAAATT
GATCTGATCAAAGCCGATCGCCGGC
ACGGCTACGTTATAGGACACTATCATGAA

**Animal 2
(not affected)**

AAATGGTCGTCAACTCGTAGCATCAAT
CTAGCTACGACGCATGTCGTCAAAATT
GATCTGATCAATGCCGATCGCCGGC
ACGGCTACGTTATAGGACACTATCATGAA

How SNP chips can help



**Animal 1
(affected)**

AAATGGTCGTCAACTCGTAGCATCAAT
CTAGCTACGACGCATGTCGTCAAAATT
GATCTGATCAAAGCGATCGCCGGC
ACGGCTACGTTATAGGACACTATCATGAA

**Animal 2
(not affected)**

AAATGGTCGTCAACTCGTAGCATCAAT
CTAGCTACGACGCATGTCGTCAAAATT
GATCTGATCAATGCCGATCGCCGGC
ACGGCTACGTTATAGGACACTATCATGAA

Compare affected, parents and control animals

ID_Hap	889_S	890_S	891_S	892_S	893_S	894_S	895_S	896_S
0AR3_153042045.1	1	1	2	1	2	1	1	2
0AR3_153072398.1	2	1	1	1	1	2	1	1
0AR3_153199019.1	2	2	1	2	1	2	2	2
0AR3_153238355.1	1	2	1	2	1	2	2	1
0AR3_153278443.1	1	1	1	1	1	1	1	1
0AR3_153462015.1	1	1	1	1	1	1	1	1
0AR3_153501802.1	2	2	2	2	2	2	2	2
0AR3_153541443.1	2	2	2	2	2	2	2	2
0AR3_153570088.1	2	2	2	2	2	2	2	2
0AR3_153598690.1	1	1	1	1	1	1	1	1
s47510.1	2	2	2	2	1	1	1	2
0AR3_153687173.1	1	1	1	1	1	2	2	1
0AR3_153703374.1	2	1	2	1	2	2	1	1
0AR3_153758491.1	2	1	2	1	2	1	1	1
s22496.1	2	1	2	1	2	1	1	1
0AR3_154013741.1	1	1	2	2	1	1	1	1
0AR3_154110053.1	1	1	1	1	1	2	1	1
0AR3_154151089.1	1	1	2	2	1	2	1	1
0AR3_154209677.1	1	1	2	2	1	1	1	1
0AR3_154298018.1	1	1	2	2	2	2	1	1
0AR3_154426406.1	1	2	2	2	2	2	1	1
0AR3_154456922.1	2	1	1	1	1	1	1	1
s71507.1	1	2	1	2	2	2	1	1
s64952.1	1	2	1	2	2	2	2	1
0AR3_154597839.1	2	1	1	1	1	1	2	1
0AR3_154650682.1	2	2	1	1	1	1	2	1
0AR3_154661602.1	1	2	1	2	1	1	1	1
0AR3_154707289.1	1	1	1	1	1	2	1	1
0AR3_154771125.1	1	1	1	1	1	1	2	1
0AR3_154796395.1	1	1	1	1	1	2	1	1
s49048.1	1	1	1	1	1	2	1	1
0AR3_154879265.1	2	2	1	2	1	2	1	1
0AR3_154913369.1	1	1	2	2	1	1	1	1
0AR3_154922296.1	1	1	2	2	1	1	1	1
0AR3_154940822.1	1	2	2	2	2	1	2	1
0AR3_155015529.1	1	2	1	1	1	1	2	1
0AR3_155022791.1	1	2	1	1	1	1	2	1
0AR3_155081787.1	1	1	1	2	1	1	1	1
0AR3_155103999.1	1	2	2	1	1	1	2	1
0AR3_155236610.1	1	1	1	2	1	1	1	1
0AR3_155262167.1	1	1	2	1	2	2	1	1
0AR3_155288261.1	1	1	1	1	1	1	1	1
0AR3_155337562.1	1	2	1	2	1	1	2	1
0AR3_155355052.1	1	2	1	2	1	1	2	1
0AR3_155454982.1	2	2	1	2	2	2	2	1
0AR3_155486772.1	1	1	1	1	1	1	2	1
0AR3_155531793.1	1	1	1	2	2	1	2	1
0AR3_155555840.1	1	1	1	1	2	1	1	1
0AR3_155652351.1	1	1	1	2	2	1	2	1
s23658.1	1	1	2	1	1	1	1	1
0AR3_155737327_X.1	1	1	1	2	2	1	2	1
0AR3_155763724.1	1	2	2	2	2	1	1	1
s66272.1	2	2	1	2	1	1	2	1
0AR3_155839999.1	2	1	2	1	2	1	1	1
0AR3_155880429.1	1	2	1	1	1	1	1	1
0AR3_155932611.1	2	2	2	1	1	1	2	1
0AR3_155973774.1	2	2	2	1	1	1	1	1
0AR3_156007768.1	1	2	1	1	1	1	1	1
0AR3_156022698.1	1	2	1	2	1	1	1	1
0AR3_156064229.1	2	2	2	2	2	2	1	1

What we are looking for across parents of affected animals

Yellow- two SNPs same
Blue - two SNPs different

Compare affected, parents and control animals

ID_Hap	889_S	890_S	891_S	892_S	893_S	894_S	895_S	896_S
0AR3_153042045.1	1	1	2	1	2	1	1	2
0AR3_153072398.1	2	1	1	1	1	2	1	1
0AR3_153199019.1	2	2	1	2	1	2	2	2
0AR3_153238355.1	1	2	1	2	1	2	2	1
0AR3_153278443.1	1	1	1	1	1	1	1	1
0AR3_153462015.1	1	1	1	1	1	1	1	1
0AR3_153501802.1	2	2	2	2	2	2	2	2
0AR3_153541443.1	2	2	2	2	2	2	2	2
0AR3_153570088.1	2	2	2	2	2	2	2	2
0AR3_153598690.1	1	1	1	1	1	1	1	1
s47510.1	2	2	2	2	1	1	1	2
0AR3_153687173.1	1	1	1	1	1	2	2	1
0AR3_153703374.1	2	1	2	1	2	2	1	1
0AR3_153758491.1	2	1	2	1	2	1	1	1
s22496.1	2	1	2	1	2	1	1	1
0AR3_154013741.1	1	1	2	2	1	1	1	1
0AR3_154110053.1	1	1	1	1	1	2	1	1
0AR3_154151089.1	1	1	2	2	1	2	1	1
0AR3_154209677.1	1	1	2	2	1	1	1	1
0AR3_154298018.1	1	1	2	2	2	2	1	1
0AR3_154426406.1	1	2	2	2	2	2	1	1
0AR3_154456922.1	2	1	1	1	1	1	1	1
s71507.1	1	2	1	2	2	2	1	1
s64952.1	1	2	1	2	2	2	2	1
0AR3_154597839.1	2	1	1	1	1	1	2	1
0AR3_154650682.1	2	2	1	1	1	1	2	1
0AR3_154661602.1	1	2	1	2	1	1	1	1
0AR3_154707289.1	1	1	1	1	1	2	1	1
0AR3_154771125.1	1	1	1	1	1	1	2	1
0AR3_154796395.1	1	1	1	1	1	2	1	1
s49048.1	1	1	1	1	1	2	1	1
0AR3_154879265.1	2	2	1	2	1	2	1	1
0AR3_154913369.1	1	1	2	2	1	1	1	1
0AR3_154922296.1	1	1	2	2	1	1	1	1
0AR3_154940822.1	1	2	2	2	2	1	2	1
0AR3_155015529.1	1	2	1	1	1	1	2	1
0AR3_155022791.1	1	2	1	1	1	1	2	1
0AR3_155081787.1	1	1	1	2	1	1	1	1
0AR3_155103999.1	1	2	2	1	1	1	2	1
0AR3_155236610.1	1	1	1	2	1	1	1	1
0AR3_155262167.1	1	1	2	1	2	2	1	1
0AR3_155288261.1	1	1	1	1	1	1	1	1
0AR3_155337562.1	1	2	1	2	1	1	2	1
0AR3_155355052.1	1	2	1	2	1	1	2	1
0AR3_155454982.1	2	2	1	2	2	2	1	1
0AR3_155486772.1	1	1	1	1	1	1	2	1
0AR3_155531793.1	1	1	1	2	2	1	2	1
0AR3_155555840.1	1	1	1	1	2	1	1	1
0AR3_155652351.1	1	1	1	2	2	1	2	1
s23658.1	1	1	2	1	1	1	1	1
0AR3_155737327_X.1	1	1	1	2	2	1	2	1
0AR3_155763724.1	1	2	2	2	2	1	1	1
s66272.1	2	2	1	2	1	1	2	1
0AR3_155839999.1	2	1	2	1	2	1	1	1
0AR3_155880429.1	1	2	1	1	1	1	1	1
0AR3_155932611.1	2	2	2	1	1	1	2	1
0AR3_155973774.1	2	2	2	1	1	1	1	1
0AR3_156007768.1	1	2	1	1	1	1	1	1
0AR3_156022698.1	1	2	1	2	1	1	1	1
0AR3_156064229.1	2	2	2	2	2	2	1	1

What we are looking for across affected animals

Yellow- two SNPs same
Blue - two SNPs different

Compare affected, parents and control animals

ID_Hap	889_S	890_S	891_S	892_S	893_S	894_S	895_S	896_S
0AR3_153042045.1	1	1	2	1	2	1	1	2
0AR3_153072398.1	2	1	1	1	1	2	1	1
0AR3_153199019.1	2	2	1	2	1	2	2	2
0AR3_153238355.1	1	2	1	2	1	2	2	1
0AR3_153278443.1	1	1	1	1	1	1	1	1
0AR3_153462015.1	1	1	1	1	1	1	1	1
0AR3_153501802.1	2	2	2	2	2	2	2	2
0AR3_153541443.1	2	2	2	2	2	2	2	2
0AR3_153570088.1	2	2	2	2	2	2	2	2
0AR3_153598690.1	1	1	1	1	1	1	1	1
s47510.1	2	2	2	2	1	1	1	2
0AR3_153687173.1	1	1	1	1	1	2	2	1
0AR3_153703374.1	2	1	2	1	2	2	1	1
0AR3_153758491.1	2	1	2	1	2	1	1	1
s22496.1	2	1	2	1	2	1	1	1
0AR3_154013741.1	1	1	2	2	1	1	1	1
0AR3_154110053.1	1	1	1	1	1	2	1	1
0AR3_154151089.1	1	1	2	2	1	2	1	1
0AR3_154209677.1	1	1	2	2	1	1	1	1
0AR3_154298018.1	1	1	2	2	2	2	1	1
0AR3_154426406.1	1	2	2	2	2	2	1	1
0AR3_154456922.1	2	1	1	1	1	1	1	1
s71507.1	1	2	1	2	2	2	1	1
s64952.1	1	2	1	2	2	2	2	1
0AR3_154597839.1	2	1	1	1	1	1	2	1
0AR3_154650682.1	2	2	1	1	1	1	2	1
0AR3_154661602.1	1	2	1	2	1	1	1	1
0AR3_154707289.1	1	1	1	1	1	2	1	1
0AR3_154771125.1	1	1	1	1	1	1	2	1
0AR3_154796395.1	1	1	1	1	1	2	1	1
s49048.1	1	1	1	1	1	2	1	1
0AR3_154879265.1	2	2	1	2	1	2	1	1
0AR3_154913369.1	1	1	2	2	1	1	1	1
0AR3_154922296.1	1	1	2	2	1	1	1	1
0AR3_154940822.1	1	2	2	2	2	1	2	1
0AR3_155015529.1	1	2	1	1	1	1	2	1
0AR3_155022791.1	1	2	1	1	1	1	2	1
0AR3_155081787.1	1	1	1	2	1	1	1	1
0AR3_155103999.1	1	2	2	1	1	1	2	1
0AR3_155236610.1	1	1	1	2	1	1	1	1
0AR3_155262167.1	1	1	2	1	2	2	1	1
0AR3_155288261.1	1	1	1	1	1	1	1	1
0AR3_155337562.1	1	2	1	2	1	1	2	1
0AR3_155355052.1	1	2	1	2	1	1	2	1
0AR3_155454982.1	2	2	1	2	2	2	2	1
0AR3_155486772.1	1	1	1	1	1	1	2	1
0AR3_155531793.1	1	1	1	2	2	1	2	1
0AR3_155555840.1	1	1	1	1	2	1	1	1
0AR3_155652351.1	1	1	1	2	2	1	2	1
s23658.1	1	1	2	1	1	1	1	1
0AR3_155737327_X.1	1	1	1	2	2	1	2	1
0AR3_155763724.1	1	2	2	2	2	1	1	1
s66272.1	2	2	1	2	1	1	2	1
0AR3_155839999.1	2	1	2	1	2	1	1	1
0AR3_155880429.1	1	2	1	1	1	1	1	1
0AR3_155932611.1	2	2	2	1	1	1	2	1
0AR3_155973774.1	2	2	2	1	1	1	1	1
0AR3_156007768.1	1	2	1	1	1	1	1	1
0AR3_156022698.1	1	2	1	2	1	1	1	1
0AR3_156064229.1	2	2	2	2	2	2	1	1

Region to explore further

Further refined by comparisons with non affected unrelated animals

Yellow- two SNPs same
Blue - two SNPs different

But its not without its challenges

- Sheep SNP chip has ~50,000 SNPs
~ 1% of all SNPs in genome
- Need high quality DNA and accurate records
- Works better if the affected phenotype is very clear
- Sequencing can help get better markers, but it does not guarantee the causative will be found

Even the most determined don't always succeed

Charlier et al., 2008

Disease	Cases	Controls	Marker/Variant Identified
Muscular Dystonia 1	12	14	Yes/Yes
Muscular Dystonia 2	7	24	Yes/Yes
Ichthyosis Fetalis	3	9	Yes/Yes
Crooked Tail	8	14	Yes/ No
Renal Lipofusconis	6	24	Yes/ No

Providing some help

- 2009 – Established Industry Club on Inherited Diseases

The idea

Bringing together interested Industry partners to discuss and develop tools and methods to help solve a common problem

- Supported by the RIDGENE research project
 - *Conducted by Uni. Edinburgh, AHT and SAC*
 - *Sponsored by BKTN, EBLEX and QMS*
 - *Started July 2009*



What the RIDGENE project will deliver

- Best practice guidelines and tools that will allow a breeder or breed society of **any species** to:
 - *Collect useful and enough samples*
 - *Assess if their problem is a recessive inherited disease*
 - *Estimate of the likely cost of developing a genetic test*
 - *Determine how best to validate the new markers*
 - *Develop the most appropriate strategy for using the test in their own breeding programme*
- Demonstration of the processes in practice for examples in sheep, cattle and pigs



What the RIDGENE project will deliver

- Best practice guidelines and tools that will allow a breeder or breed society of **any species** to:
 - *Collect useful and enough samples*
 - *Assess if their problem is a recessive inherited disease*
 - *Estimate of the likely cost of developing a genetic test*
 - *Determine how best to validate the new markers*
 - *Develop the most appropriate strategy for using the test in their own breeding programme*
- Demonstration of the processes in practice for examples in sheep, cattle and pigs



What the RIDGENE project will deliver

- Best practice guidelines and tools that will allow a breeder or breed society of **any species** to:
 - *Collect useful and enough samples*
 - *Assess if their problem is a recessive inherited disease*
 - *Estimate of the likely cost of developing a genetic test*
 - Understanding and confidence to address any problems that may arise *eir*
- Demonstration of the processes in practice for examples in sheep, cattle and pigs



Progress so far

- Publication of the RIDGENE manual and associated notes planned for later this year
- Will include information on more than three case studies – and many useful lessons

If you would like a copy please let us know

info@biosciencektn.com



Who should use the manual

- Individual Breeders?
- Breeder Groups?
- Breed Societies?

Conclusions

- Inherited diseases are common and can result in substantial health and welfare problems
- With a genetic test they can be managed or eliminated
- New technologies are making development of useful tests easier and more affordable
- The RIDGENE manual should provide breeders the knowledge and confidence to tackle any problems that may arise
- **The first step to success is recording and collecting useful samples**



Acknowledgements

- John Woolliams, Steve Bishop (Roslin Institute)
- Sarah Blott (AHT)
- The RIDGENE team for their excellent work
- All that have taken part in the Industry Club



Knowledge
Transfer
Network

Biosciences

Biosciences KTN is Sponsored by:

Technology Strategy Board

Driving Innovation



The Scottish
Government



EUROPE & SCOTLAND

European Regional Development Fund
Investing in your Future



Thank you for your attention