Reducing ovine progressive pneumonia by selecting \textit{TMEM154} haplotypes in sheep

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Topics

- Ovine progressive pneumonia (OPP)
- A major sheep gene affecting OPP
- Implications for disease control
The disease has been known for a long time

First reported in 1862 in Texel sheep

Imported with Spanish rams

Called zwegerziekte – “labored breathing sickness”.

In 1915 Graaff-Reinet disease was recognized in South African sheep

Graaff-Reinet was founded by Dutch East India Company
In 1923 Montana Sheep Disease was reported the United States

Thin ewe syndrome

In 1939 Visna-Maedi disease was recognized in Iceland

Visna – wasting
Maedi – heavy breathing

Imported with Karakul rams from Germany.

In 1942 “la bouhite” was reported in France.

These diseases are widespread and all caused by ovine lentivirus infections.
Ovine lentivirus

- The prototype “slow virus”
  - long incubation period
  - gradual onset of symptoms
  - irreversible and terminates in death

- “Trojan horse” model of infection
  - The virus infects circulating white blood cells
  - The viral DNA integrates into the host DNA
  - When the cell arrives at the site of infection, the virus breaks out of Trojan horse.

- Now classified as small ruminant lentivirus
  - primarily sheep and goats

Clinical OPP in adult sheep at MARC

- The virus replicates in macrophages at sites of inflammation
- Affects the lungs, mammary glands, lymph nodes, joints and central nervous system.

Normal

Diseased

interstitial pneumonia
Transmission of the OPP virus

- Primarily respiratory
- Among adults after age one
- Aerosolized respiratory secretions
- Also from infected colostrum
- From dam to offspring

Infections are life-long with no treatments or vaccines.

Cost of OPP in the USA

- 36% of sheep operations are infected
  - APHIS Veterinary Services, Centers for Epidemiology and Animal Health December, 2003
- Infected ewes:
  - are significantly less likely to lamb
  - wean 8% fewer lambs
  - Wean litters that are 24% lighter
- Infected flocks require frequent replacement of ewes.
- Our goal is to reduce and then eliminate OPP.
Breeds differ in their susceptibility to OPP virus

At USMARC, when purebred Finnsheep and Suffolk sheep were raised together, the Suffolk consistently had a lower incidence of OPP.

*This suggested there were genetic differences in susceptibility to the OPP virus.*
Discovery of *TMEM154* as a major gene affecting susceptibility to OPP virus

The *TMEM154* gene encodes a membrane protein

**Membranes** are the envelopes that surround animal cells.

**Proteins** are the body’s workhorse and required for the structure, function, and regulation of cells.

**Amino acids** are the building blocks of proteins.

**Genes** encode DNA sequences corresponding to amino acids in proteins.

**Viruses** bind to the “outside” part of membrane proteins.
Sheep have three common variants of the TMEM154 protein

Highly susceptible

Less susceptible

Evidence suggests that:
The K35 variant may reduce the virus’s grip on the door handle.

TMEM154 is the handle on a cellular doorway for the virus to gain entry.

The doorway model for TMEM154 function

Cells have many doors for entry.
Viruses have to get inside the cell to replicate.

Evidence suggests that:
TMEM154 is the handle on a cellular doorway for the virus to gain entry.
The K35 variant may reduce the virus’s grip on the door handle.
Effect of *TMEM154* variant K35 (haplotype 1)

In all kinds of sheep, the infection rate for those with two copies of *TMEM154* haplotype 1 was one third that of other sheep.

- Having two copies of haplotype 1 is good!

*Producing sheep with two copies of haplotype 1 reduces the risk of OPP.*

Haplotypes 1 distribution in 76 breeds around the world
Geographic origin of populations with *TMEM154* haplotype 1

Is full genetic resistance possible?
**TMEM154 has many variants**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Variant</th>
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<tbody>
<tr>
<td>1</td>
<td>K35</td>
</tr>
<tr>
<td>2</td>
<td>I70</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>A4, M44 (deletion)</td>
</tr>
<tr>
<td>5</td>
<td>I25, YB2 (deletion)</td>
</tr>
<tr>
<td>6</td>
<td>N33</td>
</tr>
<tr>
<td>7</td>
<td>H14, K35</td>
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<tr>
<td>8</td>
<td>I25</td>
</tr>
<tr>
<td>9</td>
<td>F74</td>
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<tr>
<td>10</td>
<td>V13, N33</td>
</tr>
<tr>
<td>11</td>
<td>T102</td>
</tr>
<tr>
<td>12</td>
<td>Q31, F74</td>
</tr>
</tbody>
</table>

*In a doorway model, these doors would have no handle.*

Sheep lacking **TMEM154** appear to be fully resistant.

**Origin of breeds with TMEM154 deletions**

- **Haplotype 4**: Suffolk (180), England; Hampshire (150), England; Rambouillet (541), France.
- **Haplotype 6**: Ojalada (2), Spain; Afshari (2), Iran; Karya (1), Turkey; Norduz (2), Turkey.
What can producers do with these results?

First determine if your flock is infected.

**Increase haplotype 1.**

**Decrease haplotypes 2 and 3.**

Options for hedging:

- Retain sheep with haplotype 4 (deletion)
- In Suffolk, retain sheep with haplotype 6 (deletion)
- In Rambouillet, retain sheep with haplotypes 1 and 10.

Summary

- OPP is a significant disease affecting the world’s sheep.

- A major gene affecting OPP susceptibility has been discovered.

- Full genetic resistance may be possible.

- Genetic testing and selection may help producers increase production while raising healthier sheep.
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![Image of researchers and lab equipment](image1.jpg)

![Image of animals and landscape](image2.jpg)

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![Image of researchers and lab equipment](image3.jpg)

![Image of animals and landscape](image4.jpg)