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Elucidation of the genetic nature of the Inverdale gene (FecX): Segregation with a twist

K.G. DODDS, G.H. DAVIS, J.C. McEWAN AND P.F. FENNESSY

AgResearch, Invermay Agricultural Centre, Private Bag, Mosgiel, New Zealand.

ABSTRACT

A major gene, affecting a quantitative trait in farmed livestock, is usually detected by observing segregation of the gene within families such as half-sib sire families. In the case of the Inverdale, a maternal family was observed to contain some highly prolific ewes. Progeny testing of four rams from this family revealed two rams with prolific progeny, but segregation amongst these progeny was not apparent. The data appeared to be consistent with the hypothesis of an X-linked major gene, but were not conclusive. A further progeny test involving six sons and five maternal grandsons of a putative Inverdale ram was undertaken. Three of the maternal grandsons but no sons had prolific daughters, confirming the X-linked hypothesis. Further major gene searches should consider X-linked as well as other modes of inheritance. The mode of inheritance, and effect of one and two copies of the Inverdale gene, have important consequences for its use in research and production.

Keywords: sheep; prolificacy; Inverdale gene; major gene.

INTRODUCTION

In recent years, several quantitatively measured traits of importance in livestock production have been found to be strongly influenced by a single gene (Hanset, 1982; Piper *et al.*, 1985). Such genes are referred to as 'major genes'. The discovery and elucidation of the Inverdale gene provides an interesting non-standard case study.

The genetic code for an individual is contained in a set of molecules known as deoxyribonucleic acid (DNA) which are copied into every cell. The DNA is arranged in structures called chromosomes which occur in pairs (27 pairs for sheep). One such pair matches only for one sex (females, in the case of mammals) with the other sex having a non-matching pair. In mammals these pairs are denoted as XX and XY respectively, and are known as the sex chromosomes, while other chromosomes are known as autosomes.

The process of meiosis which leads to the production of gametes (sperm for males, eggs for females) results in them containing only one of each pair of chromosomes. At fertilisation these are combined and the resulting individual has one of each pair of chromosomes from each parent, with its sex determined by which of the sex chromosomes (X or Y) the sperm carried.

A gene is a piece of DNA on a particular position on a chromosome (and its pair) having a particular biological function. An allele refers to the possible forms of a gene; but sometimes these are also referred to as a gene (such as the Inverdale gene). A genotype is the combination of the two alleles of an individual for a gene; when the alleles are the same the individual is referred to as being homozygous, otherwise heterozygous. The phenotype refers to the visible appearance for the trait.

If one allele, A, masks the presence or absence of another allele, B, (i.e. the phenotypes of AA and AB individuals are the same), then A is said to be dominant (to B) and B is recessive (to A).

Segregation

The discovery of major genes has been through the study of segregation patterns in families. These arise from the presence of heterozygous individuals who pass a copy of the gene on to some of their progeny, but not to others (i.e. the gene *segregates* in their progeny).

The study of segregation patterns is aided by a variety of methods ranging from the simple inspection of data to sophisticated statistical techniques (Elsen *et al.*, 1988; Le Roy *et al.*, 1989; Le Roy and Elsen, 1992; Kinghorn *et al.*, 1993). If a major gene is present in a population or family, then their distribution of phenotypes will be different from populations or families where the gene is absent. In particular, the spread of phenotypes will be greater, possibly resulting in multimodal distributions. Simple inspection of the data may reveal extreme phenotypes within family lines, and larger than expected variation within a family group. More complicated methods incorporate Mendel's laws of genetic inheritance along with traditional quantitative genetic models (such as those used for genetic selection) in an effort to uncover more subtle effects.

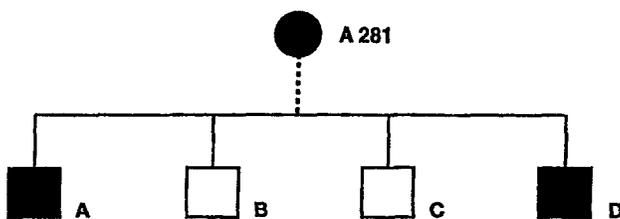
In general, major genes influencing livestock production are autosomal (since the autosomes comprise the majority of the genetic material), and not fully dominant. This appears to be the case for all of the major genes postulated to influence prolificacy (Piper *et al.*, 1985; Bradford *et al.*, 1986; Elsen *et al.*, 1991) before the discovery of the Inverdale gene. For example, heterozygous and homozygous Booroola ewes (denoted B+ and BB respectively) have increased ovulation rates (OR) by 1.65 and 3.30 respectively compared with non-Booroola (++) ewes (Piper *et al.*, 1985). Because the gene is autosomal, a BB Booroola ram will pass a copy of the Booroola gene (Fec^B) to all his progeny (both male and female). Similarly a B+ Booroola ram will, on average, pass a copy of the Booroola gene to half his progeny (both male and female).

Because one ram is mated with many ewes, large half-sib sire families are common in sheep breeding. If the sire is heterozygous for a major gene, and has a large group of progeny, these present a convenient set of data for detecting segregation (Le Roy *et al.*, 1989; Goddard *et al.*, 1994). In some cases it may be useful to generate a set of progeny specifically to test for segregation, using ewes known not to have the putative gene.

The Inverdale gene

In order to elucidate the genetics involved in the high ovulation rates of a family of Romneys that were part of a high prolificacy trial at Woodlands Research Station (Kelly *et al.*, 1983), progeny tests were carried out for four rams, all descendants of the family's founder ("A281"; Davis *et al.*, 1988). The daughters were laparoscoped at 1.5 years of age (between 1987 and 1989) to measure their OR. The mean OR for the progeny of two of the rams (B and C) were similar to those of control rams, whereas for the other two rams (A and D) the OR were significantly higher (Fig 1). As the only close relationship among the four rams was through ewe A281, and there was considerable variation in their OR breeding values, it was postulated that a major gene (subsequently named Inverdale and denoted *FecX¹*) for OR was present in A281.

FIGURE 1: Progeny testing of descendants of A281. Filled symbols denote individuals hypothesized to carry the Inverdale gene; determined by the progeny test results for rams A to D.



The next question to ask was "what is the effect of this gene, and what are the genotypes of rams A and D?". It appeared that A and D had the same genotype, since both increased OR by about the same amount (0.8 to 1.0; Davis *et al.*, 1991b). Furthermore it seemed unlikely that these two rams could be homozygous for the gene, as this would require the gene to be present in the general New Zealand sheep population at a reasonable frequency. We therefore expected A and D to be heterozygous, and thus pass a copy of the gene to half of their daughters. However, the distribution of OR in the daughters of these two sires appeared to be more compact than those of B+ Romneys (Davis *et al.*, 1991b), suggesting that all daughters were receiving a copy of the gene. This appeared to contradict the expectation that the rams were heterozygous. In addition, the rams did not appear to be of BB genotype, as their daughter OR were too low (Davis *et al.*, 1991b).

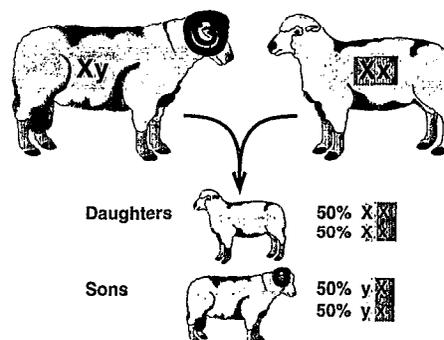
Several types of inheritance were considered, but discounted. A type of dominance, other than codominance, was discounted as the animals involved at that stage were expected to have only one copy of a major gene coming from A281. Mitochondrial DNA is inherited only from the dam,

while imprinting effects (where the expression of a gene depends upon its parental origin) was discounted because daughters of both male and female carriers appeared to express the gene.

Inverdale is X-linked

A possible biological explanation for these phenomena was that the Inverdale gene was X-linked, i.e. located on the X-chromosome. Males, having only one X-chromosome, would have either zero or one copy of the gene (denoted + and I respectively). Sires A and D were hypothesized to have the gene, whereas B and C (along with the controls) did not have the gene. Males pass their X-chromosome to all their daughters, and their Y-chromosome to all their sons, so all daughters of an Inverdale ram would receive a copy of the Inverdale gene from their sire, but no sons would (Fig 2). Thus we have segregation of the gene in the progeny, but can measure the trait of interest only in those progeny that received the Inverdale gene, i.e. the daughters. Females, having two X-chromosomes, could have either zero, one or two copies of the gene (denoted ++, I+ and II respectively). On average, I+ ewes would pass a copy of the gene to half of their progeny (both male and female). An II ewe would be expected to pass a copy of the gene to all her progeny. The family of A281 appeared to be consistent with this hypothesis, although the small numbers of female progeny of any one ewe gave too little information for a formal test.

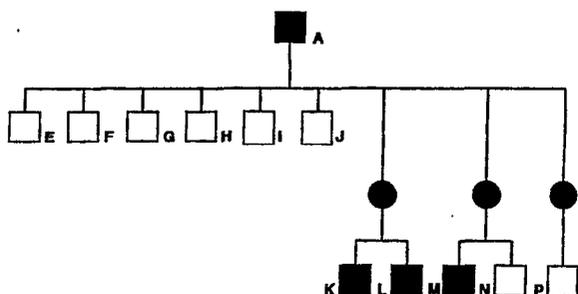
FIGURE 2: Inheritance of the Inverdale gene. X-chromosomes carrying the Inverdale gene are denoted by X; those that are not, by x.



To verify the hypothesis, we needed to demonstrate segregation in the progeny of the putative I+ ewes. Daughters of these ewes would have too few OR records to be able to definitively distinguish them as ++ or I+. However, sons could be accurately classified via a progeny test that generated a sufficiently large group of daughters. Therefore five sons of three daughters of sire A were progeny tested in 1988. Six sons of sire A were also included. If the X-linked hypothesis was correct, then none of these six would be an I genotype. If the gene was autosomal and an unlikely series of events had led to sire A being homozygous, then all six sons would have the Inverdale gene.

The results of this progeny test confirmed the X-linked hypothesis (Fig 3). Three of the maternal grandsons of sire A had daughters with a high mean OR (2.9 - 3.3) while daughters of the other two had mean OR of 1.8 and 2.0, similar to those of the control rams (1.9; Davis *et al.*, 1991a). The daughters of the six sons of A had mean OR between 1.8 and 2.0, again similar to that of the controls.

FIGURE 3: Progeny testing of six sons and five maternal grandsons of ram A. Filled symbols denote individuals hypothesized to carry the Inverdale gene; determined by the progeny test results for rams E to P.



Further consequences

The X-linked nature of the Inverdale gene raises issues other than those related to its discovery. These are heightened by the discovery that II ewes are infertile (Davis *et al.*, 1992).

- **Introgression.** If an autosomal gene is being introgressed into another breed or strain, a ram carrying the gene is mated with the new strain. Sons may then be progeny tested to find those that carry the gene, for use in the next cycle of introgression; daughters will be of unknown status, and difficult to classify. With the Inverdale gene the sons are of no use, since they will all be + genotypes; however, the daughters are all I+, and no phenotypic measurements are needed to classify them. These ewes are then mated with rams from the new strain. At this stage the gene is segregating (in both

sexes) and the sons need to be tested (via progeny testing or genetic or physiological markers) to see which have the Inverdale gene.

- **Progeny testing rams.** If an Inverdale ram is mated with I+ ewes, then half of their female progeny are expected to be II. These can be identified at a young age, allowing the rams to be classified a year earlier than would otherwise be possible (Davis *et al.*, 1994).
- **Sheep production.** Management systems and industry structures need to be implemented to take advantage of the increased reproduction rate of I+ ewes, while avoiding the generation of the infertile II ewes (McEwan *et al.*, 1995). Fixing the Inverdale gene in a flock is not viable because II ewes are infertile.
- **Physiology.** Because the sex chromosomes determine sex, it is interesting to speculate on the possible mode of action of an X-linked gene influencing OR. We know of no X-linked genes in any other livestock species that have been shown to influence prolificacy or fertility. The role that X-inactivation might play in the expression of this gene is also of interest.
- **Genetic markers.** The search for a linked marker, and for the gene itself, is immediately narrowed to a single chromosome (Galloway *et al.*, 1995).
- **Animal selection.** Designers of selection strategies for animal improvement need to consider the possibility that the traits of interest may be partly controlled by genes on the sex chromosomes. This would involve checking that genetic parameters estimates, derived from different types or relationships, are consistent. If a component of sex-linked inheritance is implicated, standard software for breeding value estimation will need modification to take account of this.
- **Major gene searches.** Searches for major genes should consider X-linked as well as other modes of inheritance.