Introduction

There are many known congenital disorders of Australian livestock and new disease entities continue to emerge with alarming regularity. To ensure that our livestock health surveillance system grows towards the highest of standards, we need to continue to search for and describe new and emerging disease entities, particular those present at birth as these often cause considerable anxiety to producers and on occasions, severe economic losses (Jago et al, 1993). Efficient disease surveillance is needed to identify and estimate the impact of those where we may need to develop evidence-based interventions in a timely manner, in order to manage the risks they may pose to livestock production. This brief review discusses the pathogenesis and methods for investigating congenital disorders and introduces a range of inherited disorders that appear to be emerging here, or are recognised overseas and may well be here but are largely or completely unrecognised.

Why are congenital disorders important?

Knowledge of congenital diseases of livestock is important for a number of reasons. Firstly it is necessary to facilitate the diagnostic exclusion of traumatic, toxic and infectious disorders that can compromise production or be confused with transboundary diseases, such as the transmissible spongiform encephalopathies (Windsor et al, 2011a,b). Secondly, to assist our understanding of the management of the continuously emerging inherited diseases, we need to promptly recognise them and for those where the prevalence of heterozygotes or the welfare impacts are of sufficient concern, develop methods of heterozygote detection to minimise their negative impacts on animal production and welfare. Finally, there exist opportunities from studies of congenital disease in animal populations that offers insights into basic mechanisms of pathogenesis and these are useful models for human disorders.

Surveillance for congenital disorders is challenging

Although surveillance to enable the early recognition of new and emerging inherited diseases is important, it is often challenging as the clinical signs of congenital diseases do not necessarily provide signposts to the aetiology of the disorder. When examining a ruminant animal with congenital disease, the clinician commonly asks the question, what are the non-genetic disorders that can produce these signs, plus, what are the genetic disorders that occur in this age of animal and in this species, breed and body system? For this reason, known inherited
disorders are usually tabulated according to species, breed and age to aid the diagnostic process. When a genetic disease or malformation is diagnosed, it is worth remembering that this case probably represents only the ‘tip of the iceberg’ of those actually occurring (Jolly and Windsor, 2010). Further, there is often an expectation that inherited disorders will only occur in pure-bred animals. However in-breeding in the cattle industries with sire-daughter mating or similar close-breeding is still commonly practised, with some mutations first found in mixed-breed animals.

The diagnosis of a suspected inherited disorder usually requires the exclusion of other aetiologies and infections in particular, adding to the cost of disease investigation. This is particularly important in Australia where toxic plants are widespread, bovine pestivirus (BPV) is broadly endemic, and the Simbu group of viruses and Akabane virus (AKV) in particular have regional endemicity that can change at the whim of climatic events that influence the distribution of midges. A number of toxic plants cause dysfunction of enzymic cellular mechanisms that have also been described as compromised by mutations, as in Darling Pea poisoning and alpha-Mannosidosis (Windsor et al, 2011a). Both BPV and AKV cause a range of congenital disorders in ruminants that are readily confused with inherited disorders, as has recently been described in Arthrogryposis Multiplex of Angus that was initially confused with AKV disease (Windsor et al, 2011a,b).

Currently the cost of investigating congenital disorders is largely imposed on producers. This is a major impediment to the comprehensive studies that are required for detailed investigation of new inherited defects. What is required is systematic clinical and pathological and epidemiological investigation and documentation, elimination of ‘phenocopies’ from the differential diagnosis, parentage verification, pedigree analysis and collection of samples from homozygous affected, heterozygous and homozygous normal populations for molecular studies that can lead to development of heterozygote detection tests.

Although the recognition of a new recessively inherited disorders can be difficult during the emergence of early cases, the cost of controlling the disease when it is well established is considerably greater and more complex when anxiety levels and financial damage through loss of reputation of breeders is heightened. Pro-active surveillance to identify and limit the dissemination of genetic defects at an early stage in the course of the emerging disease, through industry funded surveillance programs has been suggested as being more cost effective than efforts to eliminate a new genetic defect several generations after becoming established (Windsor and Agerholm, 2009).

**International perspectives on inherited disorders**

Modern breeding of ruminants increasingly involves the use of artificial reproduction techniques, enabling the international trade in the germplasm of elite sires and dams. Thousands of offspring from selected individuals can be rapidly introduced into many countries to improve production through genetic gain. However as all individuals also carry defective genes, the rapid spread of ‘desirable’ and ‘undesirable’ alleles often results in the simultaneous occurrence of unwanted genetic defects in a number of countries. In the last few decades of cattle breeding, we have seen the emergence of dominant breed, particularly the Holstein-Friesian for milk, Angus for temperate beef and Brahman for tropical beef production. However we have also seen the almost simultaneous recognition in several countries of undesirable traits linked to elite individuals standing at artificial breeding centres, where within a few generations they and their offspring are being mated to their descendents. Fortunately the tools to manage these undesirable traits have improved significantly in recent years.
Another interesting development with the emerging internationalism of inherited disorders, has been the recognition by veterinarians interested in inherited disorders on different continents that they need to share as much as is possible, their new observations of potential genetic diseases. Australia has been a leader in the detection and reporting of new inherited congenital diseases of ruminants. This may be due to the presence of the ‘founder effect’ as occurs when a new breed is introduced into a country and ‘bred-up’ from relatively few pure-bred founder animals, usually through initial crossbreeding (Jolly and Windsor, 2010). Australia has also made a significant contribution in the development of OMIA (Online Mendelian Inheritance in Animals; http://omia.angis.org.au/). OMIA enables the rapid examination of the literature and cross referencing of disorders between species and it is important that an OMIA identity for every new disorder should be established and included in their publication as soon as is convenient. To facilitate wider understanding of new inherited disorders, this presentation will illuminate these issues with examples of ‘international’ genetic disorders, highlighting those that are yet to be described here. Of interest is we suspect, presume as very likely, or occasionally even know that certain deleterious mutations are already present in our bovine populations and cases are likely to have occurred, as in Complex Vertebral Malformation (CVM) of Holstein-Friesian cattle (Windsor and Agerholm 2009).

**Modes of Inheritance**

Although other modes of inheritance have been described in inherited congenital cattle disorders in Australia, such as Angus Proportionate Dwarfism (Latter et al, 2006), the majority of ruminant hereditary disorders are monogenic and inherited in a Mendelian manner. These defects involve a single mutant gene linked to the disease phenotype through an absent or dysfunctional gene product. This includes developmental genes involved in organogenesis of embryos, often presenting as reproductive failure eg Neuropathic Hydrocephalus in Angus (Windsor et al, 2011a). An inherited disease phenotype may have more than one genotype due to mutations of other genes in the same area of metabolism or structural integrity (Jolly and Windsor, 2010).

The majority of genetic disorders are inherited in an autosomal recessive manner, with the mating of two clinically normal heterozygous animals carrying the mutant gene. The progeny will be in the proportions of ¼ diseased or homozygous affected, ½ clinically normal or heterozygous animals, and ¼ genetically normal or homozygous normal individuals (ratio 1:2:1). Autosomal recessive defects usually involve functional proteins such as enzymes, with the enzyme produced as a product of the remaining one normal gene being sufficient to maintain metabolism (Jolly and Windsor, 2010). As heterozygous individuals have a mutant gene producing a defective enzyme, they have enzyme activity levels midway between normal and diseased, a feature used in the biochemical heterozygous detection methods.

Diseases inherited in a dominant manner are often associated with structural proteins, including receptor proteins, and tend to be severe and/or easily recognised in 50% of offspring. As the heterozygotes are often not viable, or are undesirable to the breeder, they are usually excluded from the breeding herd and are thus relatively less common than recessive disorders. In contrast, incomplete dominant disorders occur where there are 3 potential phenotypes, i.e. normal, affected and more severely affected, as in Dexter cattle. The short-legged phenotype of Dexter was desired by many breeders, not aware that these animals are heterozygous of one of 2 mutations identified in the gene coding for aggrecan protein (Cavanagh et al, 2007). Aggrecan is involved in the integrity of cartilage that develops in endochondral ossification. The mating of two heterozygous Dexter cattle results in ¼ normal, ½ short legged Dexter phenotype and ¼
non-viable bulldog dwarf (Harper et al, 1997). Identification of the mutations in Australia enabled development of heterozygote detection by PCR and management of the disorder.

So what are we missing?

There are a number of disorders that appear to have been emerging and deserving of more attention, including polymelia, dwarfism, hydrocephalus and aplasia of the paramesonephric ducts in Angus, and chondrodysplasia in a number of breeds. The following lists some cattle breeds present in Australia, where disorders are recorded overseas (Gentile et al, 2012) that may well be here but are yet to be recognised or yet to be described in Australian cattle. Go find them!

**Holstein-Friesian**

*Brachyspina.* Autosomal recessive involving the gene FANC I gene (BTA 21) encoding Fanconi anemia, complementation group I, although mutation is unpublished. Main clinical findings include extensive malformation of almost all vertebrae causing significant shortening of the spine, reduced body size and disproportion between legs and vertebral column, inferior brachygnatism, hypoplasia of abdominal organs, e.g. kidneys, gonads and intestine (atresia), a high rate of embryonic and foetal mortality with full term cases rare (Agerholm et al. 2006; Windsor and Agerholm, 2009).

*Complex Vertebral Malformation (CVM) in Holstein-Friesian.* Autosomal recessive involving the gene SLC 35A3 gene (BTA 3) encoding the Golgi-resident transporter of UD P-N-acetylglucosamine. Main clinical findings include reduced body size, symmetrical arthrogryposis, malformations in the cervical and/or thoracic vertebral column with misshapen and fused vertebrae and high rate of prenatal death (Agerholm et al. 2004; Windsor and Agerholm, 2009).

*Hereditary Myopathy of Diaphragmatic Muscle.* Autosomal recessive involving Hsp70 gene (BTA 23) encoding the heat shock 70kDa protein 1A. Main clinical finding is late onset of rumenal tympany and respiratory insufficiency (Sugimoto et al., 2003).

*Dilated Cardiomyopathy in Red Holstein and Simmental.* Autosomal recessive involving OPA3 gene variant 2 (BTA 18) encoding the optic atrophy 3 protein, located in the outer membrane of the mitochondria. Main clinical findings include right side heart failure due to systolic dysfunction of the heart muscle, with cardiomegaly due to ventricular and atrial dilation and hypertrophy. Onset is usually between 2-4 years of age (Owczarek-Lipska et al., 2011).

**Belgian Blue**

*Crooked Tail Syndrome.* Autosomal recessive involving the MRC 2 gene, encoding the Endo180 protein. Affected animals are homozygotes for the c.2904-2905delAG , or compound c.2904-2905delAG – c.1906T>C heterozygotes. Main clinical findings include growth retardation, increased muscular development, tail deviation, stocky head, short straight limbs, scoliosis, spastic paresis (Fasquelle et al., 2009).

*Stunted Growth with compromission of the inflammatory response.* Autosomal recessive involving the RN F11 gene (BTA 3) encoding the Ring finger protein 11, a key regulator in inflammatory response. The main clinical findings include growth retardation, decreased resistance to diseases (pneumonia, polyarthritis). Note that heterozygous animals benefit from an unspecified selection advantage (Sartelet et al., 2012a,b).

*Congenital Muscular Dystonia I – Pseudomyotonia.* Autosomal recessive involving AT P2A1 gene (BTA 25), encoding the sarco(endo)plasmic reticulum of muscle fibers. Main clinical findings include generalized muscle contractures, impaired swallowing, fatigue upon stimulation or exercise, inability to flex limbs and injurious falling, with death within a few weeks of age as a result of respiratory complications (Charlier et al., 2008).
**Congenital Muscular Dystonia II.** Autosomal recessive involving SLC 6A5 gene (BTA 29), encoding the Na+/Cl- dependent glycine transporter (GlyT2) which is responsible for maintaining an abundant presynaptic pool of neurotransmitters at glycinerigic synapses. Main clinical findings include severe episodes of myoclonus upon acoustic or tactile stimulation and death within a few hours of birth (Charlier et al., 2008).

**Limousin**
*Martan syndrome-like disease.* Autosomal dominant involving FBN1 gene (BTA 10), encoding fibrillin-1, a component of the extracellular microfibrils. Main clinical findings include disproportionately long limbs and digits, joint laxity, cardiovascular defect (aortic and mitral valves), ocular disease (myopia and ectopia lentis). Animals usually die in the first few years of life from ruptured aortas (Singleton et al., 1995).

**Red Angus**
*Osteopetrosis – Marble bone disease.* Autosomal recessive involving the SLC 4A2 gene (BTA 4), a protein involved in the bone development. Main clinical findings include premature calves (10-30 days before expected date), with affected calves typically aborted late in gestation, displaying skull deformities and exhibiting a marked reduction of osteoclasts. If the calf is born alive, death occurs within 24 hours after birth, with shorter lower jaw and impacted molars, plus long and fragile bones (O’Toole et al., 2011).

**Romagnola**
*Paunch Calf Syndrome.* Autosomal recessive involving gene KDM2B, with main clinical findings including malformation of the splanchnocranium (shortened and flattened face and, in some cases, enlarged head with a ‘bulldog’ aspect, lack of the medial dewclaws, ascites and hepatic fibrosis (Testoni et al., 2009).

**References**


