Have we forgotten about inherited disease?

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Introduction

At its simplest, the performance and conformation of the pig (the phenotype) depends on the combined effects of its genetic make-up (the genotype), which is mostly fixed at conception, and the environment, which includes health, nutrition, management, housing and climate.

There are also interactions between the genotype and the environment including between genetics and health. Potentially, this could be exploited by having pigs that are genetic resistance to disease - this has long been promised as a 'holy grail' for the global pig industry.

Differences in breed susceptibility have been reported for several diseases, including Sarcocystis infection, Foot and Mouth Disease (FMD), PRRS (Porcine Reproductive and Respiratory Syndrome), PCVAD (Porcine Circovirus Associated Disease) and African Swine Fever (ASF). In outbreaks of the latter it has been reported that wild African native pigs (warthog and bushpig) show no clinical effect. There is also some evidence that locally adapted breeds show resistance (a good reason for supporting the conservation of traditional breeds!).

There is also evidence of within-breed variation for several diseases including ASF, Atrophic rhinitis, Aujeszky's, PRRS, PCVAD, respiratory disease and Salmonellosis.

Although PRRS is a relatively new disease having first 'emerged' in Canada in 1979 it is the most important pig disease globally as it is now endemic in nearly all countries causing devastating production and economic loses due to reduced piglet production, rebreeding problems and respiratory disorders. Various estimates suggest that between a quarter and a third of the global cost attributed to infectious disease is due to PRRS. Often the disease is persistent so that infected pigs tend to recover but still shed virus so that they infect naïve pigs.

A recent collaborative study based at the Roslin Institute, Edinburgh (Lewis, Torremorell, and Bishop, 2009) was the first genome-wide SNP study to ask the question 'can some of the genetic variation be captured by genetic markers?' The researchers did this by analysing data collected on more than 8000 litters in a single herd over a ten-year period during which two PRRS outbreaks were reported. A 7K SNP chip was used and identified several significant SNP's acting independently suggesting that many genetic regions affect PRRS tolerance. The genotypes included Landrace, Large White, Pietrain, Meishan, Duroc composite, and various crosses. Interestingly, the impact of the PRRS virus was greater in the Meishan breed compared with their European counterparts. Validation is now underway in other herds using the latest and larger SNP chip to see if the identified SNP's are again significant across herds and also to check whether there are any adverse correlated effects in production traits.

Meanwhile, in Italy (Botti *et al*., 2010), a resource database combining DNA samples plus pedigree and performance data for health and production traits has been collected from more than 5000 animals from four genotypes (Duroc, Landrace, Large White and Pietrain) in 18 genetically connected commercial farms. Several highly significant SNP's were identified, and the work is continuing to look at multiple markers and to investigate whether markers are consistent across trials.

All the above suggests that we have definitely not forgotten about inherited disease! However, if we ignore the complex diseases (and chromosomal defects) and turn our attention to the typical 'genetic' defects seen on-farm then the industry appears to have made little progress over the last few decades. So what is the definition of a 'genetic' defect? In this paper it includes the range of gross disorders from those under the control of one gene (single-locus) to those due to the combined action of many genes (polygenic) and/or involving non-genetic or discrete environmental factors. In addition there are disorders that appear to run in families but where there is insufficient evidence to conclude what genes might be involved.

Incidence

So what about the incidence of these 'genetic' defects? There are many reports in the literature but most are out of date and/or involve limited numbers and/or do not define genotypes or environments. In addition many papers report on 'congenital' defects (seen at birth) without considering the defects that are observed mostly in later life. Below is a summary from three reports which have some veracity:

a) Steane (1985) reported the results from the UK Commercial Product Evaluation from all the major UK Breeding Companies over a three year period where every pig was evaluated at birth by trained technicians.

b) Partlow *et al.* (1993) pooled the data from 28 farms in a coordinated survey.

c) Bampton (1994) reported on data from 74,039 liveborn pigs from nucleus herds where, again, every pig was evaluated at birth by trained technicians.

The incidence of 'genetic' defects from these reports were:

	Steane	Partlow	Bampton
Atresia ani	0.30	0.15	0.12
Splay Leg	0.15	0.87	0.21
Inquinal/scrotal hernia			0.13
Umbilical hernia	0.30	0.39	0.28
Cryptorchid	0.24	0.39	0.02
Intersex	0.09	0.08	0.04
Kinky tail	1.70		0.03
Ear defects	0.76		0.08
Cleft palate			0.01
Major leg deformity			0.22
Other	0.42	1.21	1.76
Total	**4.96**	**3.09**	**2.87**

As the above data reflected the genetics and management of some twenty years ago a recent confidential survey was undertaken in a large anonymous European Breeding Company dam-line (Large White and Landrace) nucleus/multiplier over a four year period ending March 2010. In total, 175,843 purebred and first-cross pigs born were evaluated by trained technicians who recorded every born pig within twelve hours of birth in the farrowing house:

	Defects as % of Total Pigs Born
Atresia ani	0
Splay Leg	0
Inquinal/scrotal hernia	0.383
Umbilical hernia	0.001
Cryptorchid	0.410
Intersex	0.080
Female genitalia	0.020
Kinky tail	0.001
Ear defects	0.005
Cleft palate	0
Major leg deformity	0.002
Epitheliogenesis imperfecta	0.001
Other	0.001
Total	**0.904**

There were significant genotype effects identified in the data. GGP litters had significantly less inquinal/scrotal hernias, cryptorchids and total defects than GP litters. Within the GP litters, the breed of the sire of the litter had a significant effect on the incidence of inquinal/scrotal hernias, cryptorchids and total defects with LR sired litters having more defects than Large White sired litters.

As the above data only include 'congenital' defects, further evaluations were made at the time of selection for performance testing (at 45 ± 3 kg.) and at the end of test (mean of 95 kg.) for purebred nucleus boars and gilts (GGP) and first-cross females (GP) for the same four year period ending March 2010:

Start of test:

	Purebred	Crossbred
Inguinal/scrotal hernia	0.17	0.18
Umbilical hernia	0.19	0.15
Other*	0.02	0.15
Total	0.38	0.48

* Mostly female genitalia and forelimbs.

End of test:

	GGP	GP
Umbilical Hernia	0.02	0.37
Other*	0.10	0.13
Total	0.12	0.50

* Mostly female genitalia and forelimbs.

It was interesting to observe the higher levels of defects in the GP herd compared with the GGP herd at the end of test – further data are being collected in more detail to investigate these differences.

Economic importance

Very few studies have investigated the economic loss from 'genetic' defects. The major exception was undertaken nearly forty years ago in 1972 in an unpublished report by Done, Reed and Deeble to the UK Ministry of Agriculture (MAFF). They reported on the incidence of 'genetic' defects recorded by trained technicians in the progeny of the first twenty 'viable' litters of all national Large White and Landrace A.I. boars. In most cases the dam was a first cross between Large White and Landrace. There was a significant difference between the two sire breeds:

	Large White Sire	Landrace Sire	% Death or culled
Pitryisis rosea	0.08	0.33	5
Tremors	0.02	0.09	100
Splayleg	0.14	1.25	50
Atresia ani	0.14	0.31	100♂/50♀
Inguinal/scrotal hernia	0.44	0.67	5
Cryptorchid/hypoplasia	0.13	0.31	0
Intersex	0.06	0.05	0
Female genital defect	0.05	0.10	0
Umbilical hernia	0.16	0.05	10
Bent legs	0.03	0.05	5
Thickened forelimbs	0	0.03	5
Mandible	0.02	0	50
Microtia (stunted ear)	0.02	0.03	0
Kyphosis	0	0.02	5
Kinky tail	0.70	0.09	0
Cranioshisis	0	0.02	100
Hydrocephalus	0	0.02	100
Eye defects	0	0.02	5
Total	**1.98**	**3.43**	

Note that records were maintained to indicate the approximate percentage of 'genetic' defects that resulted in death or culling. This allowed an assessment of the economic importance per commercial litter for parthogenicity traits with an incidence higher than 0.10%. An economic model was developed by a young researcher (W. Hill, FRS!) that assessed economic loss through the pyramid from nucleus to multiplier to weaner commercial herd on a per litter basis. This gene-flow model assumed ten pigs born per litter and concluded that the cost (converted to US$ at the prevailing exchange rate in 1972) of 'genetic' defects was dependent on the sire of the litter, as was expected from the higher incidence in Landrace-sired litters:

	Large White Sire	Landrace Sire
Pitryisis rosea	0	0.03
Tremors	0.15	0.35
Splayleg	0.05	0.48
Atresia ani	0.08	0.18
Inguinal/scrotal hernia	0.05	0.10
Umbilical hernia	0.03	0
Total	**0.36**	**1.13**

Using the same basic assumptions in the original gene-flow model these results have been updated on a per pig basis using modern litter sizes and the current marginal value of a weaner pig (which has increased 11 fold since 1972):

	Large White Sire	Landrace Sire
Pitryisis rosea	0	0.02
Tremors	0.07	0.25
Splayleg	0.04	0.34
Atresia ani	0.05	0.12
Inguinal/scrotal hernia	0.04	0.07
Umbilical hernia	0.02	0
Total	**0.25**	**0.80**

Extrapolating these data in a rather unscientific manner gives a global value of 'genetic' defects recorded at birth of US$ 807 million in 2009 (See Appendix One). Of course, using data from nearly forty years ago with an out-dated genetic/economic model might be misleading! In order to get a current snapshot of the actual, rather than estimated, mortality from 'genetic' disorders, the recent Breeding Company data (see above) was analysed for the actual number of deaths and culls.

	Number of defects	Number of deaths/culls	% of deaths/culls
Inquinal/scrotal hernia	674	36	5.3
Umbilical hernia	1	1	100.0
Cryptorchid	721	0	0
Intersex	142	0	0
Female genitalia	36	0	0
Kinky tail	2	0	0
Ear defects	9	0	0
Major leg deformity	2	2	100.0
Epitheliogenesis imperfecta	1	1	100.0
Other	1	1	100.0
Total defects	**1589**	**41**	**2.58**
Total pigs born	**175,843**		
% deaths and culls of Total pigs born	**0.0233**		

Using the above data and the same FAO data as in Appendix One, the global value of deaths and culls due to 'genetic' defects at birth in 2009 was US$17.9 million when the marginal value of a weaner was valued at US$50 per head. This figure is significantly lower than the result from the 'old' data but still indicates a high value on the economic losses from defects, particularly as it only includes birth defects and ignores defects occurring in later life.

The message from the above is that if we have forgotten about inherited disease then we need to start taking the economic losses seriously! It would also appear that there is an important requirement to use new models to obtain accurate estimates of economic loss taking account of the current incidence of 'genetic' defects and their known/possible cause(s). In particular, for single-locus recessive traits, the models must balance the economic loss through the use of known 'carriers' with the economic benefits in a pyramid of having high EBV sires (and dams).

What about recessives?

John Woolliams at Roslin has long talked about the 'curse' of the recessive (see Woolliams, 2010) where defects do not appear for two or more generations while carriers multiply unnoticed, particularly in populations with high rates of inbreeding. He also notes that suppression of information by breeders is not unknown! However, relatively few true Mendelian recessives are known in the pig.

The 'Bible' and vade mecum for recessives in animal species is the Online Mendelian Inheritance in Animals (**OMIA**) database of genes, inherited disorders and traits (see http://omia.angis.org.au/) that is authored by Frank Nicolas at the University of Sydney. The Table overleaf lists the 29 single-locus 'defects' in the OMIA database, together with most recent literature reference and whether it has been characterized at the molecular level:

Defect	Date of last reference	Characterised at molecular level
Arthrogryposis	2004	No
Progressive ataxia	2007	Yes
Dwarfism	2000	Yes
Gangliosidosis	1978	No
Haemophilia A	2002	No
Hairless, with age-dependent emphysema	2008	No
Hind limb paralysis	1963	No
Hypercholesterolaemia	2009	Yes
Hypotrichosis, dominant	1968	No
Hypotrichosis, recessive	1931	No
Legless	1939	No
Lymphosarcoma	1979	No
Malignant hyperthermia	2009	Yes
Rendement Napole (RN)	2007	Yes
Membranoproliferative glomerulonephritis type II (Dense deposit disease)	2002	Yes
Neonatal diarrhoea, F4	2009	No
Nucleoside transport defect	1992	No
Porphyria, congenital erythropoietic	1995	No
Porphyria, unclassified	1959	No
Progressive myopathy (Creeper)	1978	No
Protamine-2 deficiency	1990	No
Renal cysts	1980	No
Escherichia coli F18 receptor - resistance to oedema disease	2008	Yes
Sex reversal: XX male	1997	No
Immotile short-tail sperm defect	2008	Yes
Tremor Campus syndrome	1999	No
Tremor, X-linked	1996	No
Vitamin D-deficiency rickets, type I (PDDR)	2003	Yes
Von Willebrand disease	2005	No

It should be noted that many of these 'defects' are very rare – in some cases only one confirmed case has been reportrd. On the other hand, note that there are three major genes of significant importance to the industry – malignant hyperthermia and the two *E.coli* genes (F4 and F18) – where DNA tests are available to aid breeding programmes. With regard to F4 resistance the saga has moved from field observation that the progeny from certain boars appeared more susceptible to

molecular characterisation and genetic testing in 40 years. It has been an exciting and fascinating journey! In simple terms, to cause scouring and disease the bacteria have to adhere to the gut wall by means of surface antigens which attach to a receptor on the intestinal wall of the pig. Some pigs do not possess the receptor so that the bacteria cannot attach and there is no disease. This non-adherent factor is inherited as a simple recessive gene. Passive maternal protection is also important so that genetically susceptible litters born to resistant dams are not protected. At the same time, the exclusive use of genetically resistant sires within a herd would give complete protection as the only susceptible piglets would be born to susceptible dams which give maternal protection.

Resistance to post-weaning *E. coli* scour/oedema is also associated with the presence or absence of an intestinal receptor (F18). Molecular research has shown that this receptor is associated with alleles (genes) of the FUT1 gene on chromosome 6 while the pre-weaning receptor genes are located on chromosome 13. Now several international breeding programmes are involved in the complete eradication of one or both of these diseases.

The role of R and D

It is interesting to note that the OMIA list of defects shows that minimal research is taking place in many of the defects – outside the three cases cited above and the meat quality RN gene, only 5 defects have been cited in the scientific literature in the last five years.

Broadening the issue to R and D in all 'genetic' defects, it appears that this has become a very low priority. In the UK and Australia, recent research reviews have ignored research in this area. At this year's European Association of Animal Production (EAAP) Meeting there were 749 livestock papers with zero reference to defects and at the recent World Congress on Genetics Applied to Livestock Production (WCGALP) there was just one paper dedicated to 'genetic' defects (Matika *et al*., 2010). Interestingly, this concerned a 'new' defect resulting in leg weakness early in life where the evidence suggests that it might be a new Mendelian recessive.

In this paper no mention has been made of neoplastic diseases. Although the overall incidence in pigs is very low from most slaughter house surveys, it is known that Malignant melanoma is common in some breeds (Duroc, MeLiM, Sinclair, etc) and is increasingly used as the main model for experimental work in human skin cancer research. In this case the recent literature is full of references!

How seriously do the global Breeding Companies view 'genetic' defects?

Information was enlisted from five medium/large Breeding Companies to see how they viewed 'genetic defects' – the responses were, as follows:

We take 'genetic' defects very seriously. In many cases the 'threshold' nature causes us strife – if only it was more simple! For example, we had a nucleus that supplied three multipliers - two were clear, the other had a significant problem. Same genes and similar environments. We just could not find the 'trigger' that was causing the problem. Then, after five years, it 'went away'!

We monitor the situation carefully through the pyramid. 'Storms' do occur but they appear impossible to control effectively. It is very emotive when a customer has a problem. Perhaps DNA technologies will answer the 'maiden's prayer'!

We are aware of the dilemma! We can reject high EBV animals because they may be implicated in a problem but then our delta G (genetic progress) decreases and there are competitiveness issues that we face.

We do keep records but perhaps we need to upgrade our observation capabilities. Farrowing house staff are very busy looking after high output sows so good recording can be a problem.

'We have virtually eliminated the problem through our advanced genetic programme. Our producers can source our genetic material in total confidence'.

In conclusion, it appears that the suppliers of genes to the industry are mostly aware of the problems with 'genetic' defects and would welcome more 'help' with the problem. However, the ghastly arrogant marketing speak of one of the companies indicates a 'head in the sand' policy that may come back to haunt them!

Postscript

The publication of the draft genome less that a year ago and the cheaper and more sophisticated gene chips may greatly aid our industry in conquering 'genetic' defects. However, at the moment, it appears that we are in limbo – we have not ignored or forgotten about inherited disease but we are waiting for new developments to aid us in our quest for answers and practical success.

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Appendix One: Global annual value of 'genetic defects

1. Assume that the 'genetic' defect incidence and 'gene-flow' model reported by Done, Reed and Deeble (1972) is valid in 2009.
2. FAO statistics for 2009 (see http://faostat.fao.org/site/569/default.aspx#ancor) report slaughterings of 1,337,205,493 pigs.
3. Assume that total births are 115% of slaughterings so 2009 births was approximately 1,537,800,000.
4. Average US$ loss per pig due to 'genetic' defects was 0.525.
5. Total global loss = UD$807,345.