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WHAT CAN RESEARCH ON THE GENETICS OF HUMAN WELL-BEING TELL US ABOUT IMPROVING LIVESTOCK WELL-BEING?

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SUMMARY

Genetics of common disease and subjective well-being in human populations has been given a major boost in the last 15 years through genome-wide association studies (GWAS). Tens of thousands of loci have been identified that are robustly associated with one or more of these traits, with strong evidence for pleiotropy. Limitations for cross-species comparisons of traits, genes and pathways are the arbitrariness of defining phenotypes and the current lack of resolution in gene and variant mapping. Developments in both livestock and human genetic studies imply that better comparisons will be feasible in the near future. Methods underlying genomic prediction are converging between livestock and humans.

INTRODUCTION

The title of this short paper was suggested by the Organisers of the AAABG 2021 conference. The initial response to the question is 'not a lot', because humans can be asked directly about their well-being where inference in livestock has to be made otherwise, for example by measuring proxy phenotypes. Also, 'Improving' well-being in humans is by changing the environment whereas in livestock it is by genetic selection. Nevertheless, there may be room for cross-fertilisation of the two disciplines on the topic of well-being, and we have tried to draw a few conclusions by reviewing what experimental designs and data have worked best in humans.

MATERIALS AND METHODS

Well-being can be defined in many ways. An operational measure in humans might be absence of disease or a long and healthy life. One definition that geneticists and economists are both interested in is called 'subjective well-being', which is asking individuals to rate themselves on well-being on a quantitative score. "Disease count" has been used as a quantitative trait in human genetic studies and is a sum of the presence/absence of a number of common diseases and disorders, measured in biobanks or obtained from electronic health records.

RESULTS AND DISCUSSION

Livestock and humans share biology and a number of studies have tested whether genes that explain variation for a particular trait in one species also explain variation is a similar trait in another. For the trait stature or size, this is clearly the case (Pryce *et al.* 2011; Kemper *et al.* 2012; Bouwman *et al.* 2018; Raymond *et al.* 2020). For other traits where the corresponding traits are less easy to define aligning "well-being" traits across species may not be straightforward.

To our knowledge, the only study that has directly tried to integrate genetic analyses of livestock and humans for a well-being trait was a recent study using the trait of temperament, measured as flight time after release from a weighing box in beef cattle (Costilla *et al.* 2020). In fact, the study was initiated with the misplaced hypothesis that studying traits in livestock (where temperament can be measured objectively) could inform genetic analyses of behavioural traits in humans. It came as a surprise to us that human studies (using self-report questionnaire data) are very much more powered than cattle data sets to detect trait-marker associations, because of the superior experimental sample sizes. In that study we tested for enrichment of genetic associations for flight time in orthologous gene sets associated with the human behavioural trait of neuroticism

(quantitative measure of an anxiety-related emotional state), and three disorders of the brain: schizophrenia, an adult onset disorder with lifetime risk ~1%; autism spectrum disorder, a childhood onset disorder lifetime risk ~1% of the population; developmental delay disorders, which are less common with more severe early childhood behavioural traits and *de novo* mutations. We found evidence supporting shared genetic signals between flight time and autism spectrum disorders, perhaps because the age when the cattle were measured (10 – 14 months) equates best on the onset of these disorders in humans. In this study, we also integrated the cattle temperament associated genes, with gene expression measured in human tissues from the GTEx consortium. In summary, the study was less illuminating than we had hoped, but large sample sizes for human behavioural traits continue to accumulate, and the study provides a template for the analyses that can be conducted.

GWAS have been conducted on disease account, subjective well-being and 'life satisfaction' on 100,000s of thousands of samples, all reporting multiple genome-wide significant loci (Okbay *et al.* 2016a; Zhu *et al.* 2018). Subjective well-being is genetically strongly negatively correlated with neuroticism and depression (Okbay *et al.* 2016a) and utilising that information improves polygenic prediction accuracy (Turley *et al.* 2018). From functional enrichment analyses, all subjective well-being and traits correlated with it all point to the brain. More generally, there is clear evidence in humans that genetic variation that is associated with behaviour is correlated with risk of many diseases and disorders, likely in a causal manner. For example, a polygenic predictor (= EBV in animal breeding, see Wray *et al.* (2019)) for 'educational attainment' (= the number of years of schooling), which is an imperfect proxy for intelligence, is negatively correlated with risk of dementia and neuroticism (Okbay *et al.* 2016b). Although more research is needed, it appears that there are both behavioural and physiological pathways to many diseases.

One known limitation of GWAS is that neither the causative mutations (polymorphisms) nor the target gene are identified, and that makes it hard to make meaningful species comparisons. However, sample size of exome and whole genome sequence studies are increasing, with the advantage that associated rare mutations that have predicted pathogenic effects (e.g., non-synonymous coding mutations) are likely to be causal and the target gene is known. This will allow a better comparison of genes and pathways related to traits across species. Similarly, the identification of additional dominant and recessive mutations in cattle for a number of syndromes (Reynolds *et al.* 2021) may lead to improved identification or prediction of pathogenic mutations in humans.

In addition to comparisons of genetic variation for well-being and disease traits in livestock and humans, there is increasing interest in humans in the application of polygenic (genomic) prediction. Although many researchers in human genetics don't realise that genomic prediction has its origin in animal breeding, as pointed out by Wray *et al.* (2019), there is increasing convergence in (Bayesian) methods to maximise accuracy. Even though the primary purpose of genomic prediction is in identifying people in the population who are at high risk of developing disease, so that preventative or therapeutic interventions can be better targeted, there is also a growing interest in using genomic predictors in the context of IVF and embryo selection. Within-family genomic selection in humans! Not surprisingly, the theory presented on the expected gains and (in)accuracy of prediction in the context of embryo selection using polygenic scores (Karavani *et al.* 2019; Turley *et al.* 2021) could come straight out of an animal breeding textbook. Finally, for some traits (such as human height) the discovery (training) datasets are becoming so large that using statistically significant (GWS) loci only in the prediction is approaching BLUP and other Bayesian approaches that use all genetic variants.

CONCLUSIONS

Well-being and disease studies in humans are characterised by ever-larger genome studies,

many of which are now reaching millions of individuals. GWAS is slowly moving from using SNP arrays and imputation to the use of whole-genome sequence data, thereby facilitating a better identification of causal variants and target genes and, ultimately, better prediction accuracy. This, combined with more discovery of specific causative mutations and target genes in livestock species, will allow better comparisons of genes and traits across species.

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