A genome-wide association study of thyroid stimulating hormone and free thyroxine in Danish children and adolescents

Background
Hypothyroidism is associated with obesity, and thyroid hormones are involved in the regulation of body composition, including fat mass. Genome-wide association studies (GWAS) in adults have identified 19 and 6 loci associated with plasma concentrations of thyroid stimulating hormone (TSH) and free thyroxine (fT4), respectively.

Objective
This study aimed to identify and characterize genetic variants associated with circulating TSH and fT4 in Danish children and adolescents and to examine whether these variants associate with obesity.

Methods
Genome-wide association analyses of imputed genotype data with fasting plasma concentrations of TSH and fT4 from a population-based sample of Danish children, adolescents, and young adults, and a group of children, adolescents, and young adults with overweight and obesity were performed (N = 1,764, mean age = 12.0 years [range 2.5-24.7]). Replication was performed in additional comparable samples (N = 2,097, mean age = 11.8 years [1.2-22.8]). Meta-analyses, using linear additive fixed-effect models, were performed on the results of the discovery and replication analyses.

Results
No novel loci associated with TSH or fT4 were identified. Four loci previously associated with TSH in adults were confirmed in this study population (PDE10A (rs2983511: beta = 0.112SD, p = 4.8.10(-16)), FOXE1 (rs7847663: beta = 0.223SD, p = 1.5 . 10(-20)), NR3C2 (rs9968300: beta = 0.194SD), p = 2.4 . 10(-11)), VEGFA (rs2396083: beta = 0.088SD, p = 2.2 . 10(-10))). Effect sizes of variants known to associate with TSH or fT4 in adults showed a similar direction of effect in our cohort of children and adolescents, 11 of which were associated with TSH or fT4 in our study (p
Assisted reproductive technologies (ARTs) have a strong impact on breeding especially when coupled with genomic selection (GS). The routine implementation of in vitro production (IVP) and GS of embryos before embryo transfer (ET) in breeding companies is not yet possible. Improvement of oocyte donor and embryo recipient quality is needed to make realistic a commercialization of these procedures in the near future. A better understanding of both biological mechanisms and molecular markers associated to IVPET related traits is necessary to improve the prediction of donor and recipient cow quality for IVP procedures. The huge amount of data generated from high throughput technologies has a tremendous...
impact in the search for biomarkers of complex traits. This paper reviews integrative genomics and systems biology approaches as applied to both Bos indicus and Bos taurus cattle reproduction by both conventional and ARTs such as OPU-IVP. The integration of systems biology information across different biological layers generates a complete view of the different molecular networks that control complex traits and can provide a strong contribution to the understanding of traits related to ARTs.

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**Basic and practical aspects of pregnancy establishment in cattle**
Bovine embryos are increasingly produced using reproductive technologies, e.g. ovum pick-up (OPU), in vitro embryo production (IVP) and embryo transfer (ET). Such in vitro manipulated embryos are known to deviate in several aspects compared to in vivo derived embryos. Pregnancy establishment in cattle involves timed biological events including fine-tuned communication, initiated and carried out by both the embryo and the endometrium. This stimulates research to increase the understanding of events and interactions taking place in the uterus after embryo transfer, both from a biological and systems biology point of view. This review will focus on the biological events taking place during early embryonic development, implantation and beginning of placentation, with focus on transfer of in vitro produced embryos, including a systems biology approach for selection of superior embryo recipients.

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Differential expression and co-expression gene networks reveal candidate biomarkers of boar taint in non-castrated pigs

Boar taint (BT) is an offensive odour or taste observed in pork from a proportion of non-castrated male pigs. Surgical castration is effective in avoiding BT, but animal welfare issues have created an incentive for alternatives such as genomic selection. In order to find candidate biomarkers, gene expression profiles were analysed from tissues of non-castrated pigs grouped by their genetic merit of BT. Differential expression analysis revealed substantial changes with log-transformed fold changes of liver and testis from -3.39 to 2.96 and -7.51 to 3.53, respectively. Co-expression network analysis revealed one module with a correlation of -0.27 in liver and three modules with correlations of 0.31, -0.44 and -0.49 in testis. Differential expression and co-expression analysis revealed candidate biomarkers with varying biological functions: phase I (COQ3, COX6C, CYP2J2, CYP2B6, ACOX2) and phase II metabolism (GSTO1, GSR, FMO3) of skatole and androstenone in liver to steroidogenesis (HSD17B7, HSD17B8, CYP27A1), regulation of steroidogenesis (STARD10, CYB5R3) and GnRH signalling (MAPK3, MAP2K2, MAP3K2) in testis. Overrepressed pathways included "Ribosome", "Protein export" and "Oxidative phosphorylation" in liver and "Steroid hormone biosynthesis" and "Gap junction" in testis. Future work should evaluate the biomarkers in large populations to ensure their usefulness in genomic selection programs.
Genomic study and Medical Subject Headings enrichment analysis of early pregnancy rate and antral follicle numbers in Nelore heifers

Zebu animals (Bos indicus) are known to take longer to reach puberty compared with taurine animals (Bos taurus), limiting the supply of animals for harvest or breeding and impacting profitability. Genomic information can be a helpful tool to better understand complex traits and improve genetic gains. In this study, we performed a genomewide association study (GWAS) to identify genetic variants associated with reproductive traits in Nelore beef cattle. Heifer pregnancy (HP) was recorded for 1,267 genotyped animals distributed in 12 contemporary groups (CG) with an average pregnancy rate of 0.35 (+/- 0.01). Disregarding one of these CG, the number of antral follicles (NF) was also collected for 937 of these animals, with an average of 11.53 (+/- 4.43). The animals were organized in CG: 12 and 11 for HP and NF, respectively. Genes in linkage disequilibrium (LD) with the associated variants can be considered in a functional enrichment analysis to identify biological mechanisms involved in fertility. Medical Subject Headings (MeSH) were detected using the MESHR package, allowing the extraction of broad meanings from the gene lists provided by the GWAS. The estimated heritability for HP was 0.28 +/- 0.07 and for NF was 0.49 +/- 0.09, with the genomic correlation being -0.21 +/- 0.29. The average LD between adjacent markers was 0.23 +/- 0.01, and GWAS identified genomic windows that accounted for > 1% of total genetic variance on chromosomes 5, 14, and 18 for HP and on chromosomes 2, 8, 11, 14, 15, 16, and 22 for NF. The MeSH enrichment analyses revealed significant (P <0.05) terms associated with HP-"Munc18 Proteins," "Fucose," and "Hemoglobins"-and with NF-"Cathepsin B," "Receptors, Neuropeptide," and "Palmitic Acid. "This is the first study in Nelore cattle introducing the concept of MeSH analysis. The genomic analyses contributed to a better understanding of the genetic control of the reproductive traits HP and NF and provide new selection strategies to improve beef production.

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Identification of potential biomarkers in donor cows for in vitro embryo production by granulosa cell transcriptomics

The Ovum Pick Up-In vitro Production (OPU-IVP) of embryos is an advanced reproductive technology used in cattle production but the complex biological mechanisms behind IVP outcomes are not fully understood. In this study we sequenced RNA of granulosa cells collected from Holstein cows at oocyte aspiration prior to IVP, to identify candidate genes and biological mechanisms for favourable IVP-related traits in donor cows where IVP was performed separately for each animal. We identified 56 genes significantly associated with IVP scores (BL rate, kinetic and morphology). Among these, BEX2, HEY2, RGN, TNFAIP6 and TXNDC11 were negatively associated while Mx1 and STC1 were positively associated with all IVP scores. Functional analysis highlighted a wide range of biological mechanisms including apoptosis, cell development and proliferation and four key upstream regulators (COX2, IL1, PRL, TRIM24) involved in these mechanisms. We found a range of evidence that good IVP outcome is positively correlated with early follicular atresia. Furthermore we showed that high genetic index bulls can be used in breeding without reducing the IVP performances. These findings can contribute to the development of biomarkers from follicular fluid content and to improving Genomic Selection (GS) methods that utilize functional information in cattle breeding, allowing a widespread large scale application of GS-IVP.

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In vitro production of bovine embryos: cumulus/granulosa cell gene expression patterns point to early atresia as beneficial for oocyte competence

In vitro production (IW) of bovine embryos has become widespread technology implemented in cattle breeding and production. Here, we review novel data on cumulus/granulosa cell gene expression, as determined by RNAseq on cellular material from pooled follicular fluids at the single animal level, and relate these finding to previous data on oocyte developmental competence and ultrastructure. The cumulus/granulosa cell gene expression patterns indicate that early follicular atresia is associated with increased blastocyst yield and this hypothesis is supported by previous data on oocyte competence and ultrastructure.

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RNA-Seq transcriptomics and pathway analyses reveal potential regulatory genes and molecular mechanisms in high- and low-residual feed intake in Nordic dairy cattle

The selective breeding of cattle with high-feed efficiencies (FE) is an important goal of beef and dairy cattle producers. Global gene expression patterns in relevant tissues can be used to study the functions of genes that are potentially involved in regulating FE. In the present study, high-throughput RNA sequencing data of liver biopsies from 19 dairy cows were used to identify differentially expressed genes (DEGs) between high- and low-FE groups of cows (based on Residual Feed Intake or RFI). Subsequently, a profile of the pathways connecting the DEGs to FE was generated, and a list of candidate genes and biomarkers was derived for their potential inclusion in breeding programmes to improve FE. The bovine RNA-Seq gene expression data from the liver was analysed to identify DEGs and, subsequently, identify the molecular mechanisms, pathways and possible candidate biomarkers of feed efficiency. On average, 57 million reads (short reads or short mRNA sequences

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Single nucleotide polymorphism discovery in bovine liver using RNA-seq technology

Background
RNA-seq is a useful next-generation sequencing (NGS) technology that has been widely used to understand mammalian transcriptome architecture and function. In this study, a breed-specific RNA-seq experiment was utilized to detect putative single nucleotide polymorphisms (SNPs) in liver tissue of young bulls of the Polish Red, Polish Holstein-Friesian (HF) and Hereford breeds, and to understand the genomic variation in the three cattle breeds that may reflect differences in production traits.

Results
The RNA-seq experiment on bovine liver produced 107,114,4072 raw paired-end reads, with an average of approximately 60 million paired-end reads per library. Breed-wise, a total of 345.06, 290.04 and 436.03 million paired-end reads were obtained from the Polish Red, Polish HF, and Hereford breeds, respectively. Burrows-Wheeler Aligner (BWA) read alignments showed that 81.35%, 82.81% and 84.21% of the mapped sequencing reads were properly paired to the Polish Red, Polish HF, and Hereford breeds, respectively. This study identified 5,641,401 SNPs and insertion and deletion (indel) positions expressed in the bovine liver with an average of 313,411 SNPs and indel per young bull. Following the removal of the indel mutations, a total of 195,3804, 152,7120 and 205,3184 raw SNPs expressed in bovine liver were identified for the Polish Red, Polish HF, and Hereford breeds, respectively. Breed-wise, three highly reliable breed-specific SNP-databases (SNP-dbs) with 31,562, 24,945 and 28,194 SNP records were constructed for the Polish Red, Polish HF, and Hereford breeds, respectively. Using a combination of stringent parameters of a minimum depth of ≥10 mapping reads that support the polymorphic nucleotide base and 100% SNP ratio, 4,368, 3,780 and 3,800 SNP records were detected in the Polish Red, Polish HF, and Hereford breeds, respectively. The SNP detections using RNA-seq data were successfully validated by competitive allele-specific PCR (KASPTM) SNP genotyping assay. The comprehensive QTL/CG analysis of 110 QTL/CG with RNA-seq data identified 20 monomorphic SNP hit loci (CARTPT, GAD1, GDF5, GHRH, GHRL, GRB10, IGFBL1, IGF1, LEP, LHX4, MC4R, MSTN, NKAIN1, PLAG1, POU1F1, SDR16C5, SH2B2, TOX, UCP3 and WNT10B) in all three cattle breeds. However, six SNP loci (CCSER1, GHR, KCNIP4, MTSS1, EGFR and NSMCE2) were identified as highly polymorphic among the cattle breeds.

Conclusions
This study identified breed-specific SNPs with greater SNP ratio and excellent mapping coverage, as well as monomorphic and highly polymorphic putative SNP loci within QTL/CGs of bovine liver tissue. A breed-specific SNP-db constructed for bovine liver yielded nearly six million SNPs. In addition, a KASPTM SNP genotyping assay, as a reliable cost-effective method, successfully validated the breed-specific putative SNPs originating from the RNA-seq experiments.

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