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Strategy and statistical methods in fine mapping QTL affecting clinical mastitis and somatic cell count.

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The extensive recording of health traits in the Nordic countries provides a unique resource to map QTL for resistance to mastitis. Genome scans have been conducted in Finland, Sweden, and Denmark and the results suggest that QTL for mastitis resistance segregate in Nordic cattle populations. The EC funded project (QLK5-CT-2002-01186, MASTITIS RESISTANCE) uses these resources to confirm, fine map and identify genetic loci underlying variation in mastitis resistance (clinical mastitis and somatic cell count).

Initially results from the three national projects were used to identify six chromosomal regions with consistent results across countries and traits. New families were identified, which resulted in a combined granddaughter design with DNA samples and comparable phenotypes from 78 half-sib families, including 4000 bulls representing Nordic Red and Holstein-Friesian breeds.

In the project statistical methods are developed that aim at optimal use of the genetic structure of the population and the distributions of phenotypic measurements. In fine mapping we define a QTL-correlations structure based on IBD probabilities conditional on similarities of observed marker haplotypes. However, in the Nordic mapping population, the conditional probabilities are different when haplotypes within and across breeds are compared. Therefore, methods will be implemented that calculates the IBD probabilities while taking into account the breeds and family structure within the breeds.

Clinical mastitis is a trait with low heritability. This indicates the potential importance of performing multi trait analyses with genetically correlated traits (GSE 163:605-622, 2003), which is why we extended the fine-mapping methods to multi-trait technology (Genetics 163:405-410). The most obvious correlated trait to use is somatic cell count (SCC). SCC is a longitudinal trait, but it is usually modeled as an average of a number of repeated measurements over the course of a lactation. However, using the average of measurements is only appropriate if the QTL effect is constant over the course of lactation. Since SCC is increased for a period after infection the average QTL effect might be small and much information is expressed as the pattern of QTL effects over time. The

pattern might also depend on the infective pathogen for which the QTL gives resistance. In such cases it has been shown in simulation studies that the use of longitudinal models can increase statistical power dramatically and can provide biological information on the identified QTL (7WCGALP. CD-ROM Communication N° 21-28). The aim is to use multi-trait models with SCC expressed as a longitudinal trait and clinical mastitis as a single measurement trait.

Preliminary analysis of the Erasmus Rucphen Family Study

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In 2001, we have started a unique large family-based cohort, the Erasmus Rucphen Family (ERF) study. This is a 10 year study which was started in 2001. The Erasmus Rucphen Family study includes 2500 relatives from a genetically isolated population. The participants are phenotyped for hundreds of quantitative traits, which could be classified in five blocks:

biochemical traits, body composition, as assessed by dual energy x-ray absorptiometry, cardio-vascular traits, cognition and ophthalmologic traits.

In the ERF study, the 2500 subjects form a single large pedigree. The presence of multiple loops in the pedigree opens the opportunity for homozygosity mapping. Also, some times the distance between relatives is large, which could be exploited for the purposes of fine-mapping.

By the end of 2003, we phenotyped first 1000 of the participants. Currently, we are estimating heritabilities for selected traits. Our next step will be genome-wide scan and genotyping of the candidate genes. Here, we describe the ERF design and report results of our preliminary analysis of the ERF data.