

## **Abstract**

Diseases that individuals develop late in life have no direct influence on their proliferation. Genes contributing to the susceptibility, onset or severity of these diseases are therefore likely to be kept in the population. Together with environmental factors, combinations of such defects lead to polygenic diseases. Some common autoimmune diseases (e.g. Multiple Sclerosis, Rheumatoid Arthritis) but also heart diseases and obesity are examples. Since genes need to be investigated in combination for their phenotypic effect, genetic studies in humans are difficult. Animal models came to rescue with shorter generation times, common environments and directed breeding.

Strains are searched that differ in the susceptibility to a disease. Genetic markers determine differences in the genotype. Statistical association of markers with differences in the trait of the disease among the individuals of the F2 and later generations led to the concept of quantitative trait loci (QTLs).

This presentation explains how to combine the genotyping and disease phenotypes with of RNA expression levels. Hereto, the RNA expression level of genes is interpreted as a trait of the disease. Equivalent analyses yield expression QTLs (e-QTLs) representing candidates for cis- and trans-controlling regions for gene expression. With genes interacting, the effect in the expression of genes may be changed by more than the sum of the individual loci (epistatic effects). The cross-comparison with information from Medline abstracts (presented is the iHOP system) yields explicit candidates for further evaluation.

The approach is discussed on the example of a murine model of Multiple Sclerosis (EAE).

## ***A brief description of the instructor(s) indicating the relevant qualifications and teaching experience***

Steffen Möller

1996	Diploma in Computer Science from the University of Hildesheim, Germany
1997-2001	EMBL fellowship for the European Bioinformatics Institute Cambridge, UK PhD from the University of Cambridge
since 2001	Postdoctoral position at the Institute of Immunology, University of Rostock, Germany

Robert Hoffmann

1999	Diploma in Biology from the University of Vienna, Austria
since 2001	PhD Student at the National Center of Biotechnology, Madrid, Spain
currently	Visitor at the EMBL-EBI European Bioinformatics Institute, Cambridge, UK

## ***Title and expected goals, objectives and motivation of the tutorial***

Title: Gene expression levels as traits in genetic linkage analysis: determining cis- and trans controlling loci as expression QTL, epistatic effects as candidates for gene interactions

Objectives: The audience understands the genotyping of individuals, how this information compares with knowledge collected from expression data. The focus of the presentation is the combination of both sources of information. The attendee will

learn how to yield insights on cis- and trans-controlling loci for the expression of genes and equivalently characterize candidates for gene-interactions.

Motivation: Expression data is accepted as a means to determine loci that are statistically associated with a disease. However, the cause for the monitored change in expression is not elucidated. The presentation suggests to keep DNA, RNA and protein from individuals genotyped in order to utilise the symbiotic effects of a combined analysis of expression data with genotyping. As novel technology like DNA chips becomes available, the presented principle becomes practical also for higher eukaryotes with longer generation times and humans.

Tutorial level: Introductory

### ***Intended audience***

Basic understanding of the biology of gene regulation is required. Novel concepts are introduced on a conceptual level to address the presentation both to the biologically and computationally primed researcher.

### ***Detailed outline of the presentation***

- Introduction and Motivation (45 min)
  - Bioinformatics and Diseases
  - Animal models of human diseases
  - QTL analyses
  - Expression data
- Expression-QTL: Combined Analysis of QTL and Expression data (2h)
  - Experimental setup
    - Mouse model of Multiple Sclerosis
    - Illumina BeadArray from Lymph Nodes
  - Description of available data
    - Phenotypes monitored
    - Reformatting of data
    - Submission to compute cluster for analysis
  - Analysis with R/qtl
    - Expression QTLs
    - Epistatic effects
  - Preparation of database for results and analyses
    - #influenced traits / regions
    - #interactions / region
    - Dependency on phenotype investigated
  - Literature mining with iHOP
    - Enumeration and Distinction of Loci and Interacting Loci
    - Mapping QTLs to the genome with EnsEMBL

- Formalization of queries
- Constraints for the analysis
- Summary (5 min)
- Discussions (10 min)