Family-based analysis of genome-wide gene × gene interactions

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Outline

Epistasis

- Epistasis: interaction between two or more genes
- known to be fundamental for the function of regulatory pathways in mammals
- implies its importance for the development of complex diseases such as cancer, Alzheimer‘s disease, diabetes

Traditional Approaches

- for yeast and worms large scale double knock-outs and knock-downs exist
- linkage and association studies in mammals concentrate on either single locus associations or interactions between few preselected loci
- major reasons: non-availability of large and suitable data for analysis of interaction effects, low power of the studies

Genome-Wide Screen in Mammals

- recent advances in biotechnology allow genome-wide genotyping of thousands of individuals
  $\longrightarrow$ can be used to **study epistatic effects over whole genome**
- genotyped individuals possibly related
  $\longrightarrow$ take population structure into account; even **make use of known relationships**

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Method

- idea: two markers whose genotypes are correlated are likely to interact
- measure association via χ^2-test for contingency table

	BB	Bb	bb	
AA	n_{AABB}	n_{AABb}	n_{AAbb}	
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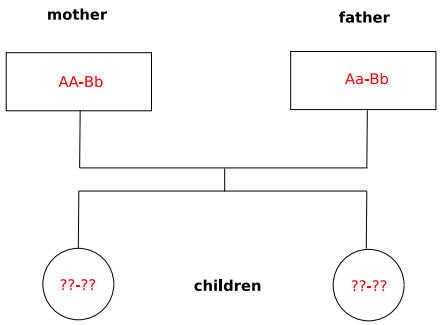
- make use of family information to avoid spurious findings:
  compare observed allele combination with what could have been inherited from parents
- additional correction for allelic drift



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- need to complement with additional, **external information**

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Databases

- use public knowledge about gene × gene interactions to confirm results;
  e.g. STRING: database of known and predicted physical and functional interactions
- include information from regulatory pathways

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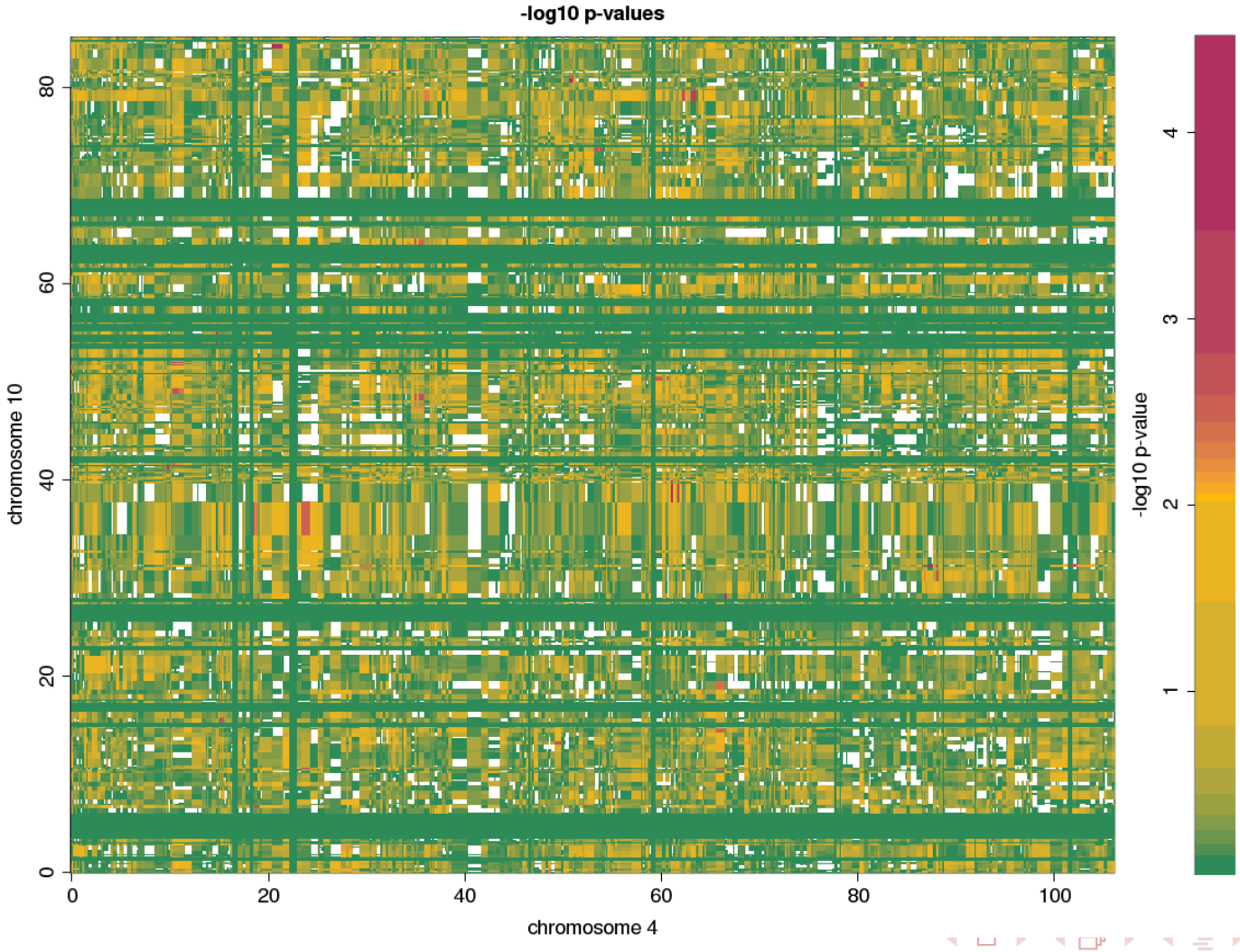
Data

- Solberg, L.C. et al. (2006). A protocol for high-throughput phenotyping, suitable for quantitative trait analysis in mice. *Mammalian Genome*, **17**, 129-146.

- genotype data from more than 2000 outbred mice consisting of $\sim 12,000$ markers
- only consider interactions on two different chromosomes

Modified χ^2-Test



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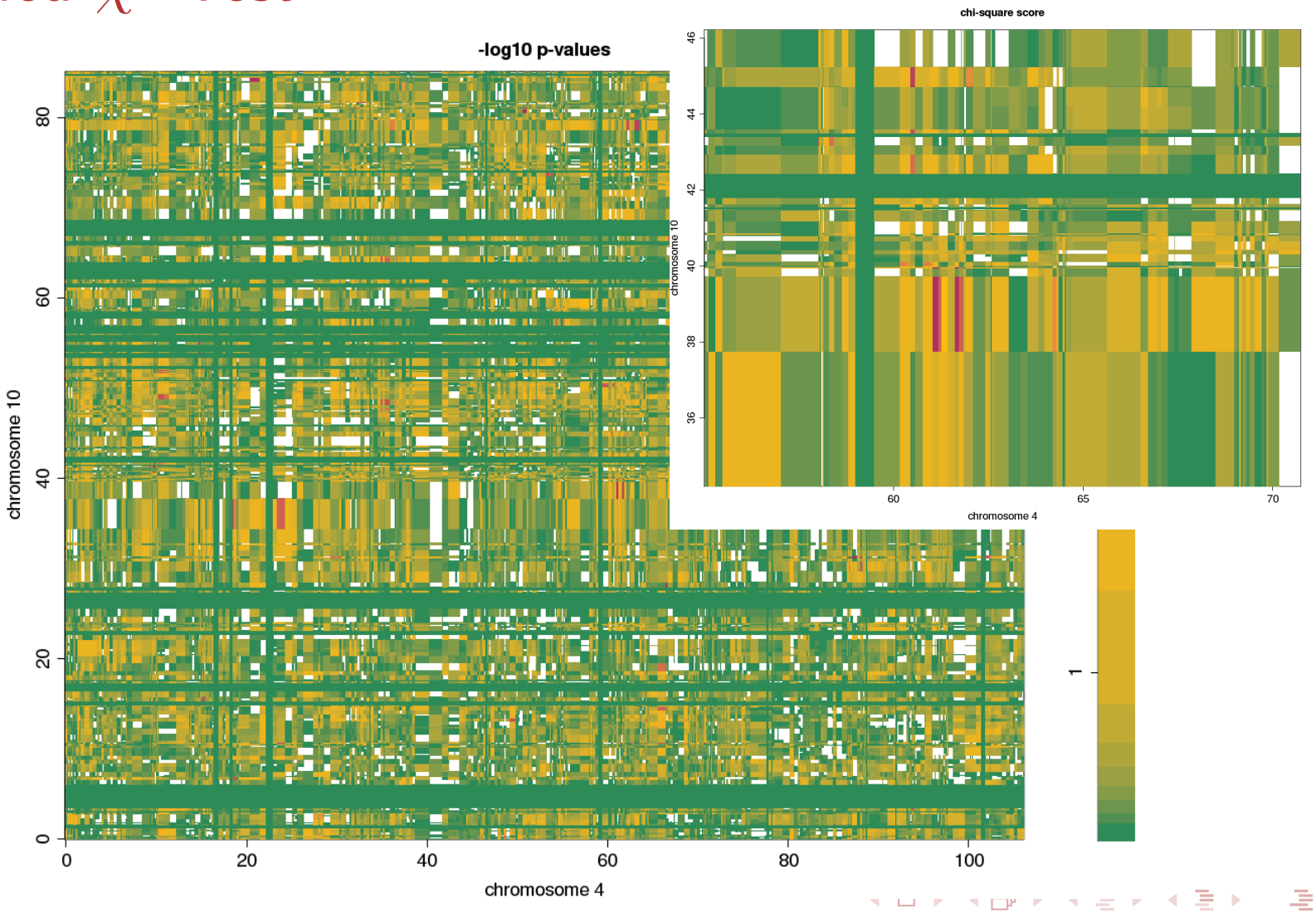
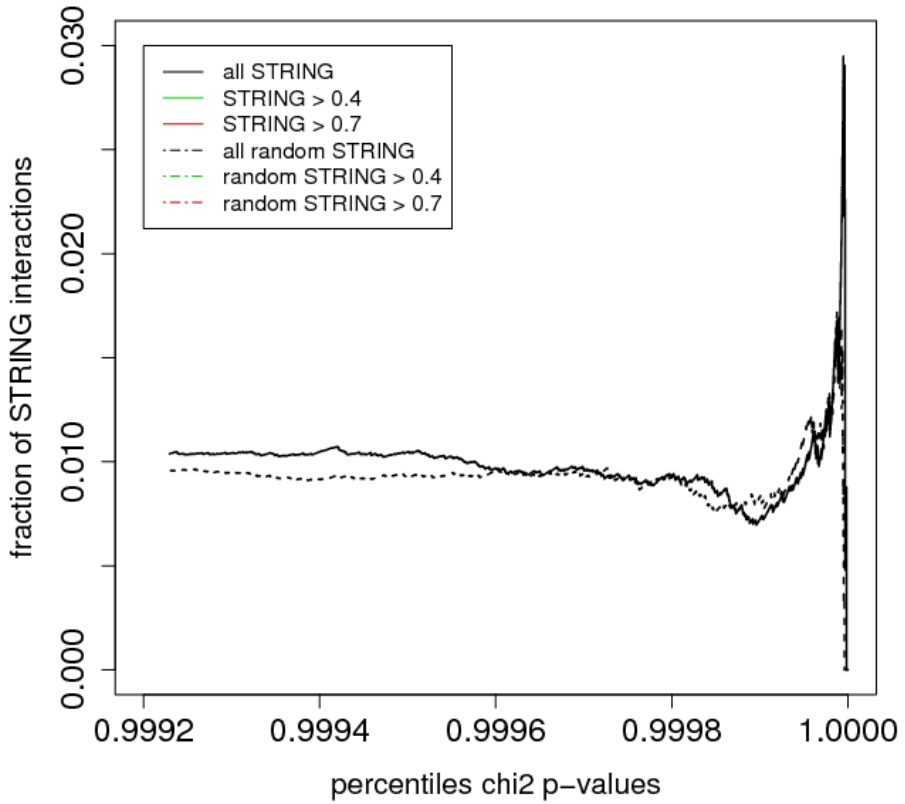


Confirmation with STRING

- fraction of SNP pairs with a low χ^2 p-value that lie close to interacting genes
- proportion of confirmed interactions should increase with increasing χ^2 score



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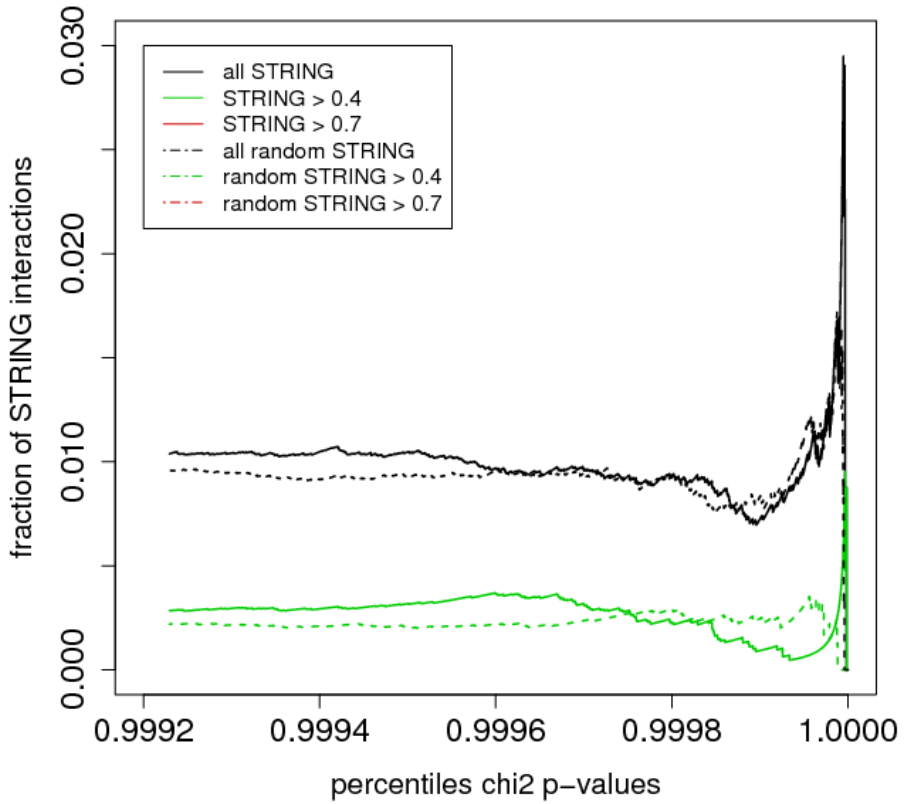

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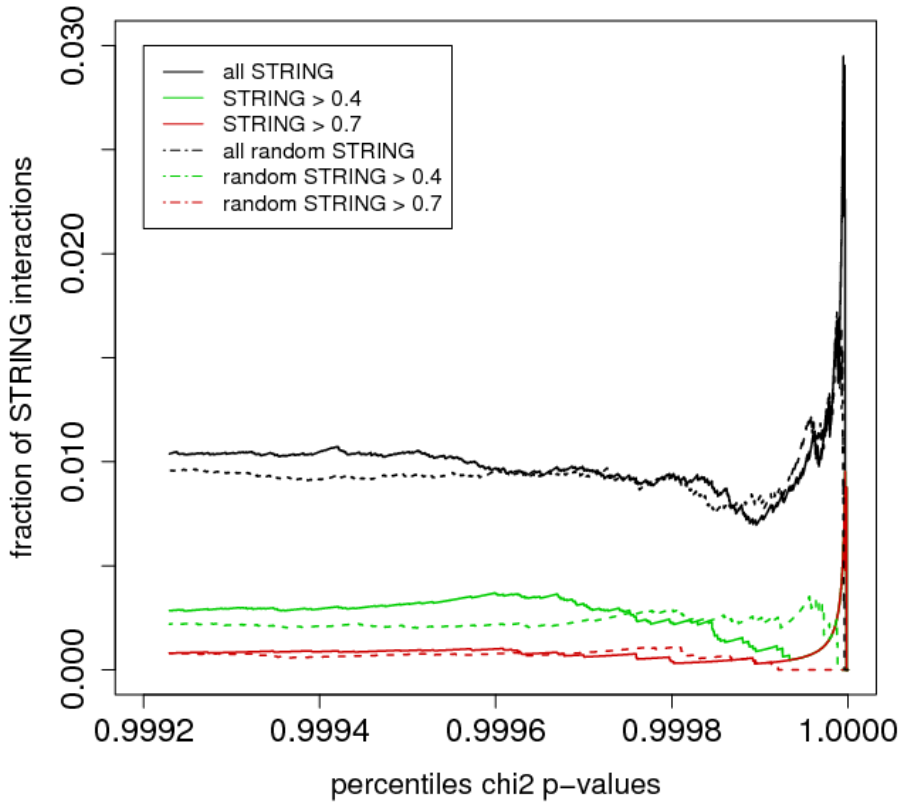
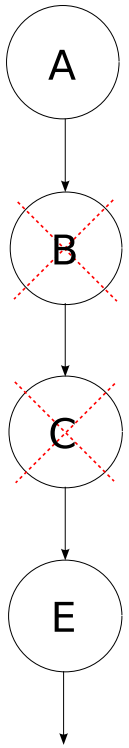


Incorporating Pathway Information

- interactions in one pathway can be crucial, e.g. when signal weakened by two consecutive dysfunctional pathway members



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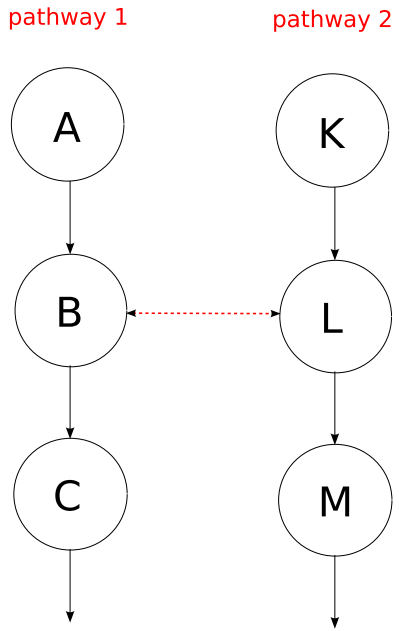
- interactions between pathways indicate common endpoint



Example: KEGG Pathway

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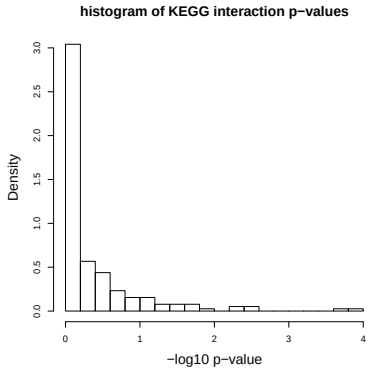

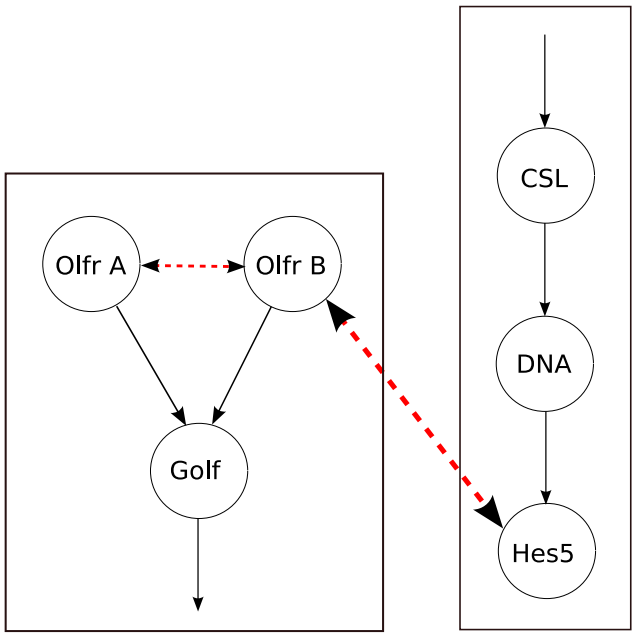

indicates importance of olfactory receptors in embryonic development and interplay with notch

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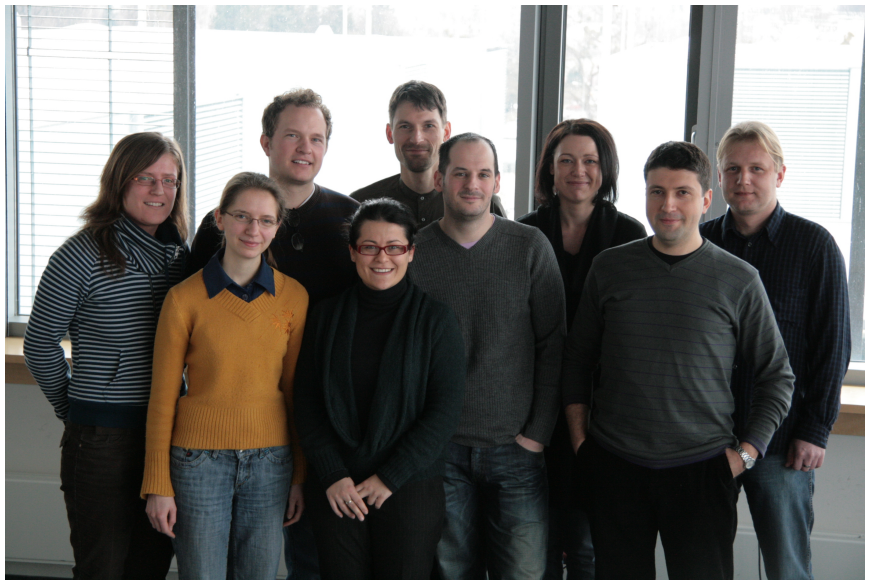
- data integration from different sources increases power and facilitates biological interpretation of results

Acknowledgements



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