ECCB2010

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Università di Torino

Candidate gene prioritization based on spatially mapped gene expression: an application to XLMR

***Rosario M. Piro**, Ivan Molineris, Ugo Ala, Paolo Provero, and Ferdinando Di Cunto*

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and Dep. Genetics, Biology and Biochemistry
University of Torino, Italy

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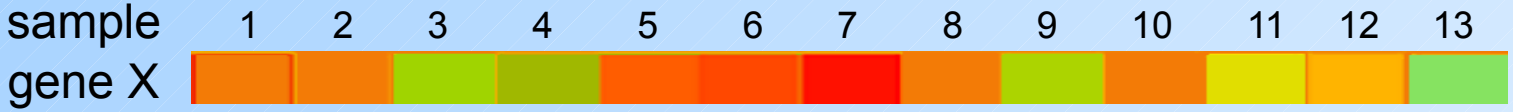
=> Computational ***disease gene prioritization***

3D expression data

- “Traditional” high-throughput expression data



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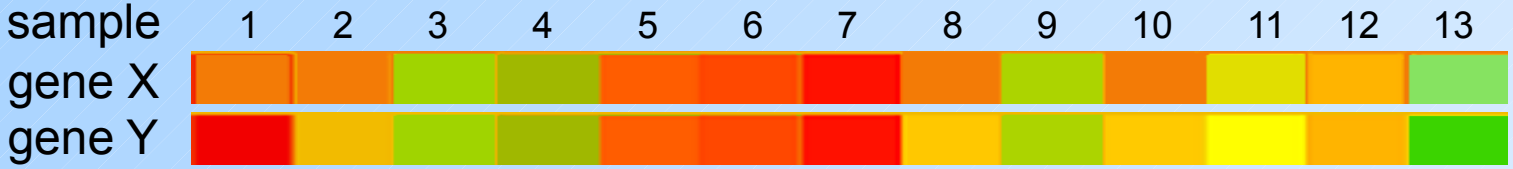

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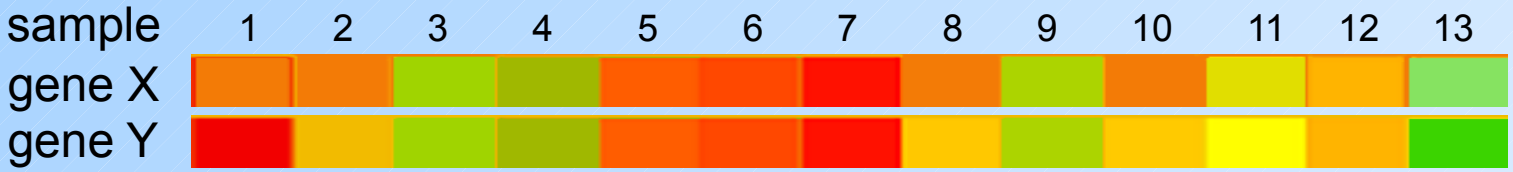

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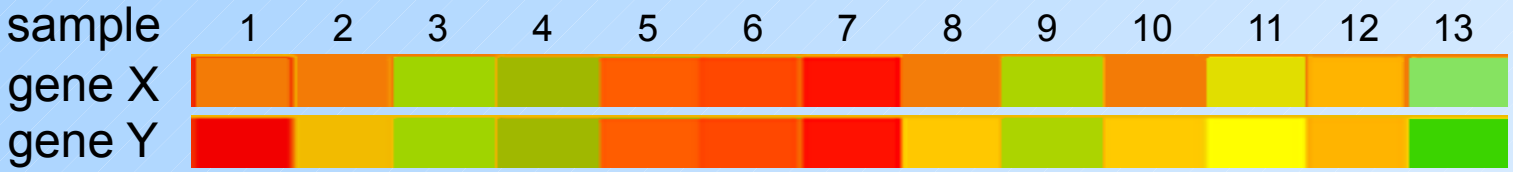

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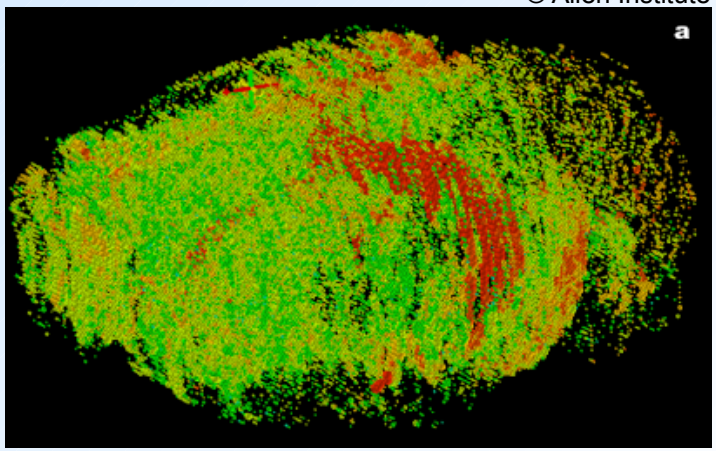

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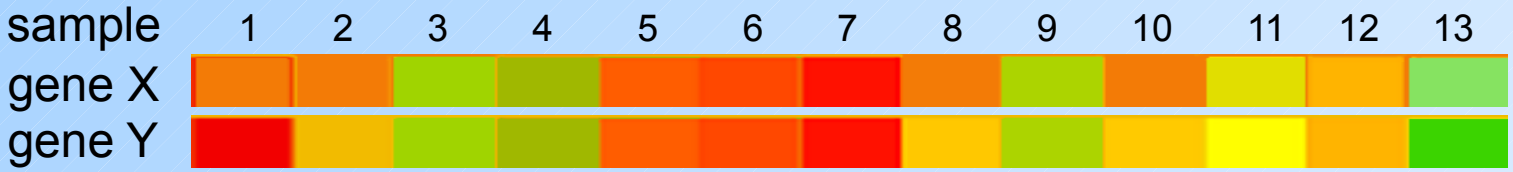

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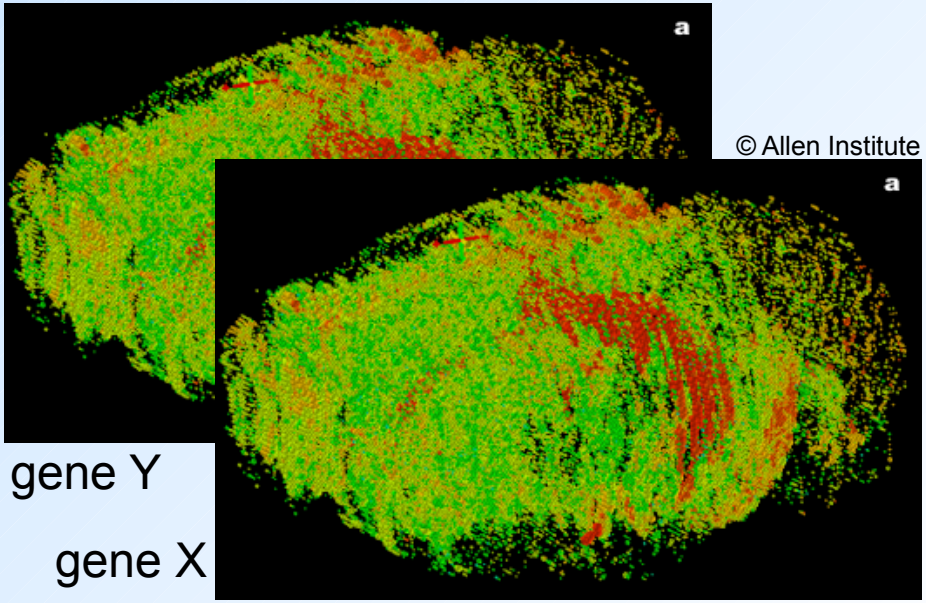

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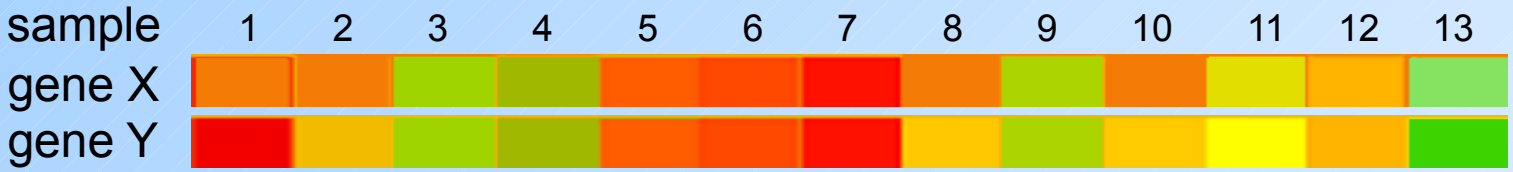

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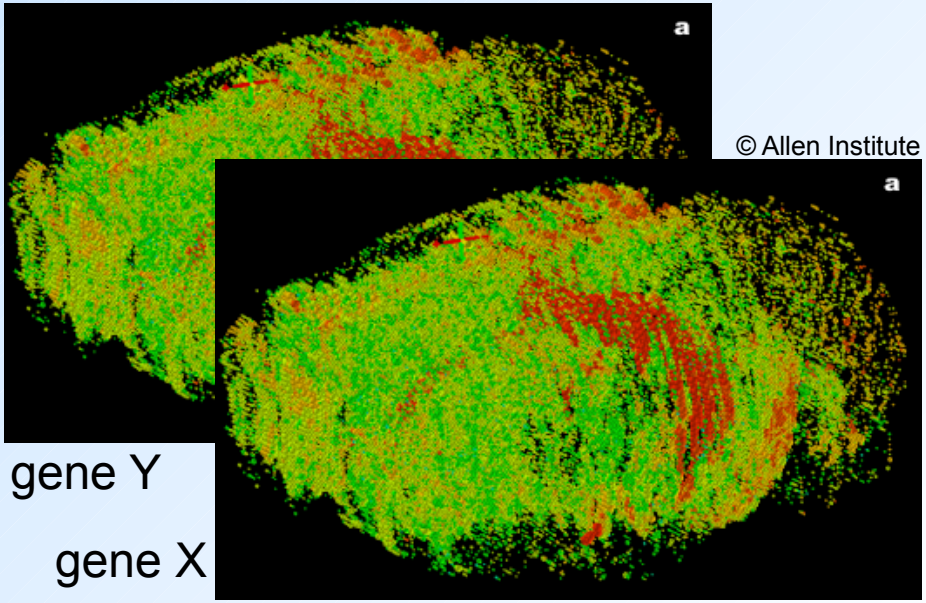
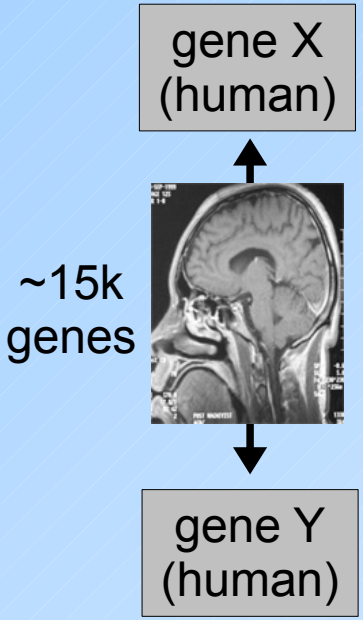
- Allen (Mouse) Brain Atlas
  (*Lein et al., Nature, 2007*)
  - http://www.brain-map.org/
  - ~20k genes (~18k with Entrez ID)
  - *in situ* hybridization (ISH)
  - covers the entire mouse brain
  - expression levels for "voxels" (cubes) of 200 µm side length



Mapping to human genes

- We use mouse expression data also for **human Mendelian disorders**



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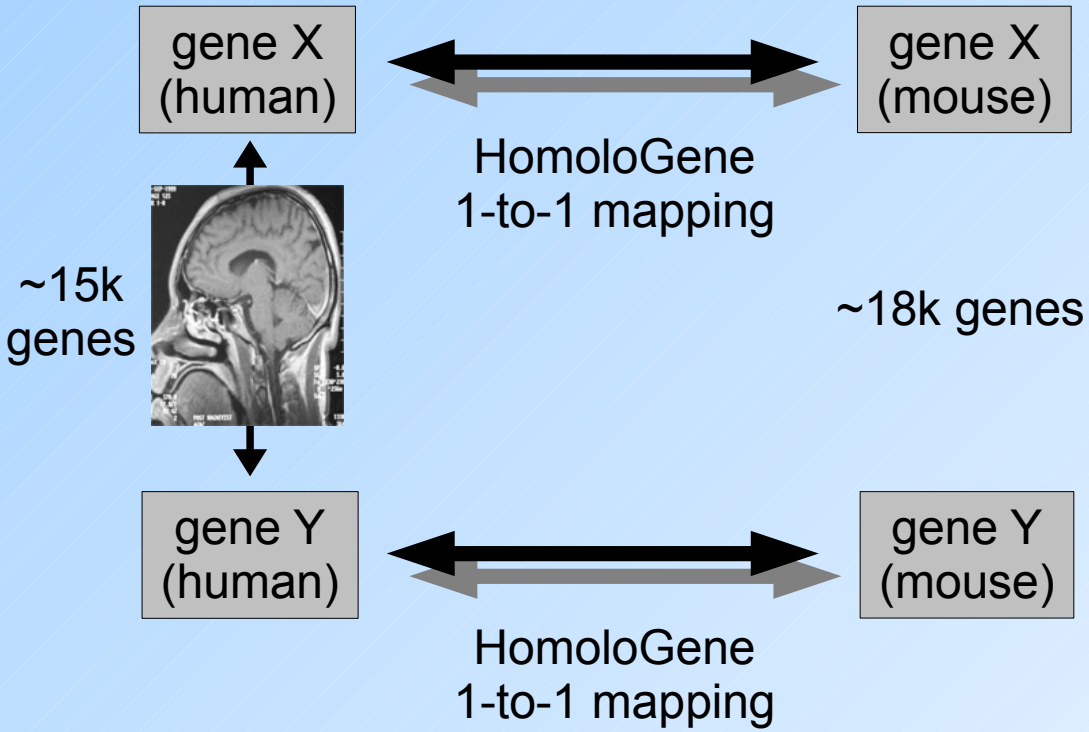

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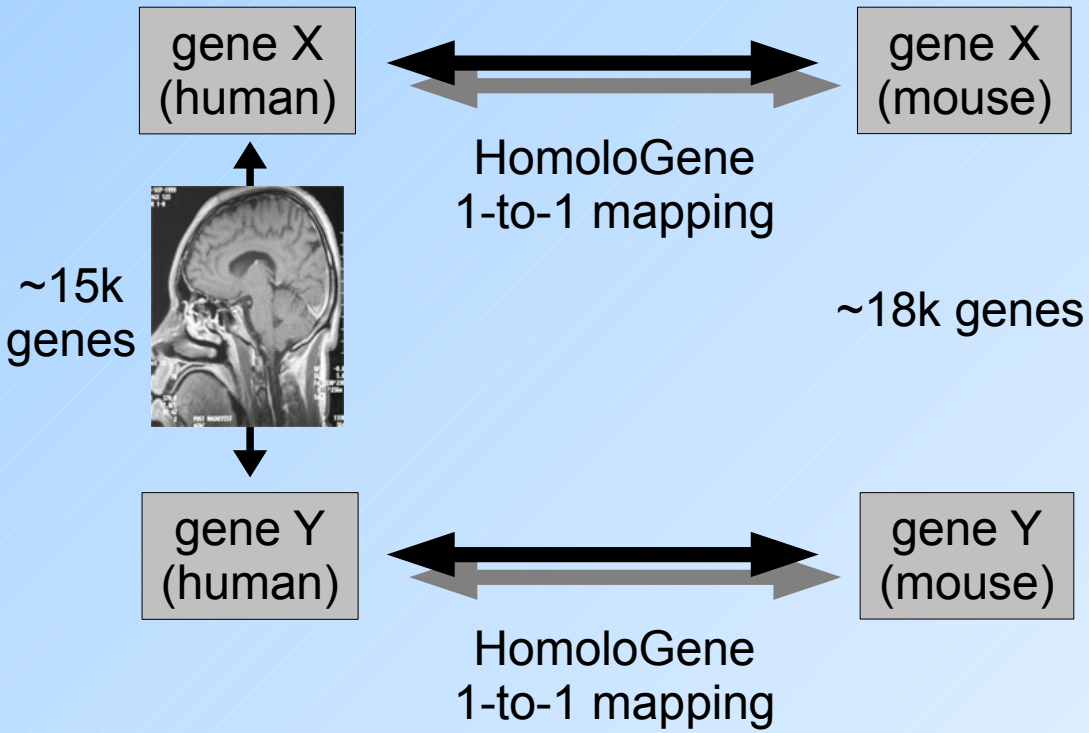

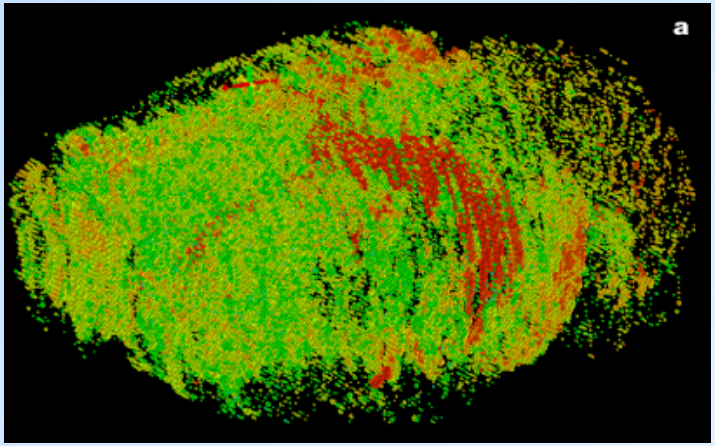

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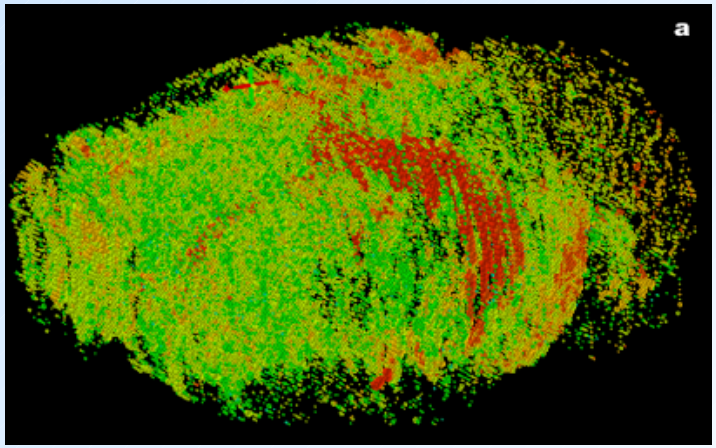

Prioritization approach (1)

- *Step 1 – select "reference genes"*
  - **genes already known** to be involved in the given phenotype or in similar phenotypes (MimMiner; *van Driel et al., Eur. J. Hum. Genet., 2006*)

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- *Step 4 – **score the candidates** (rank product)*

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Prioritization approach (2)

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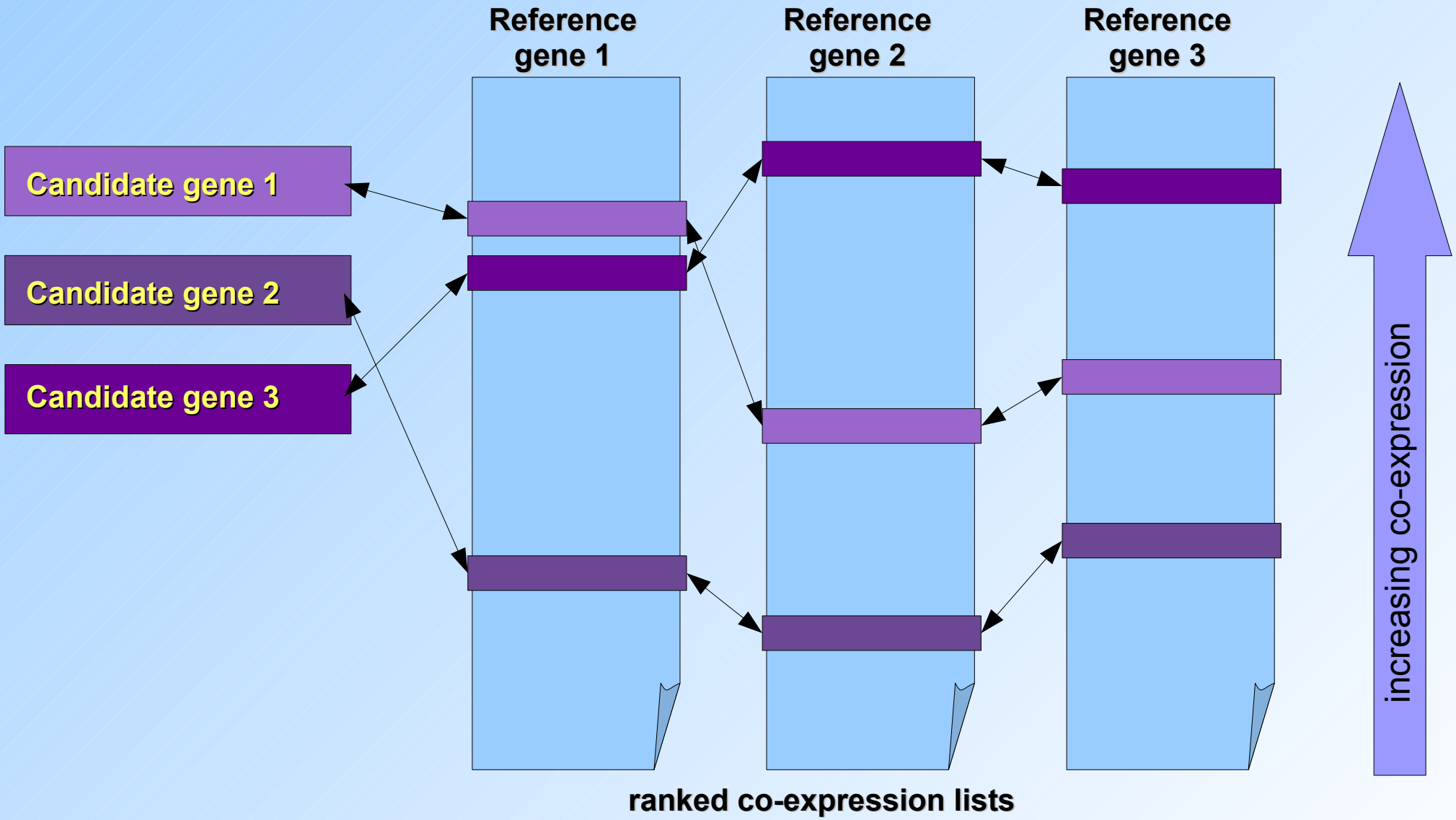

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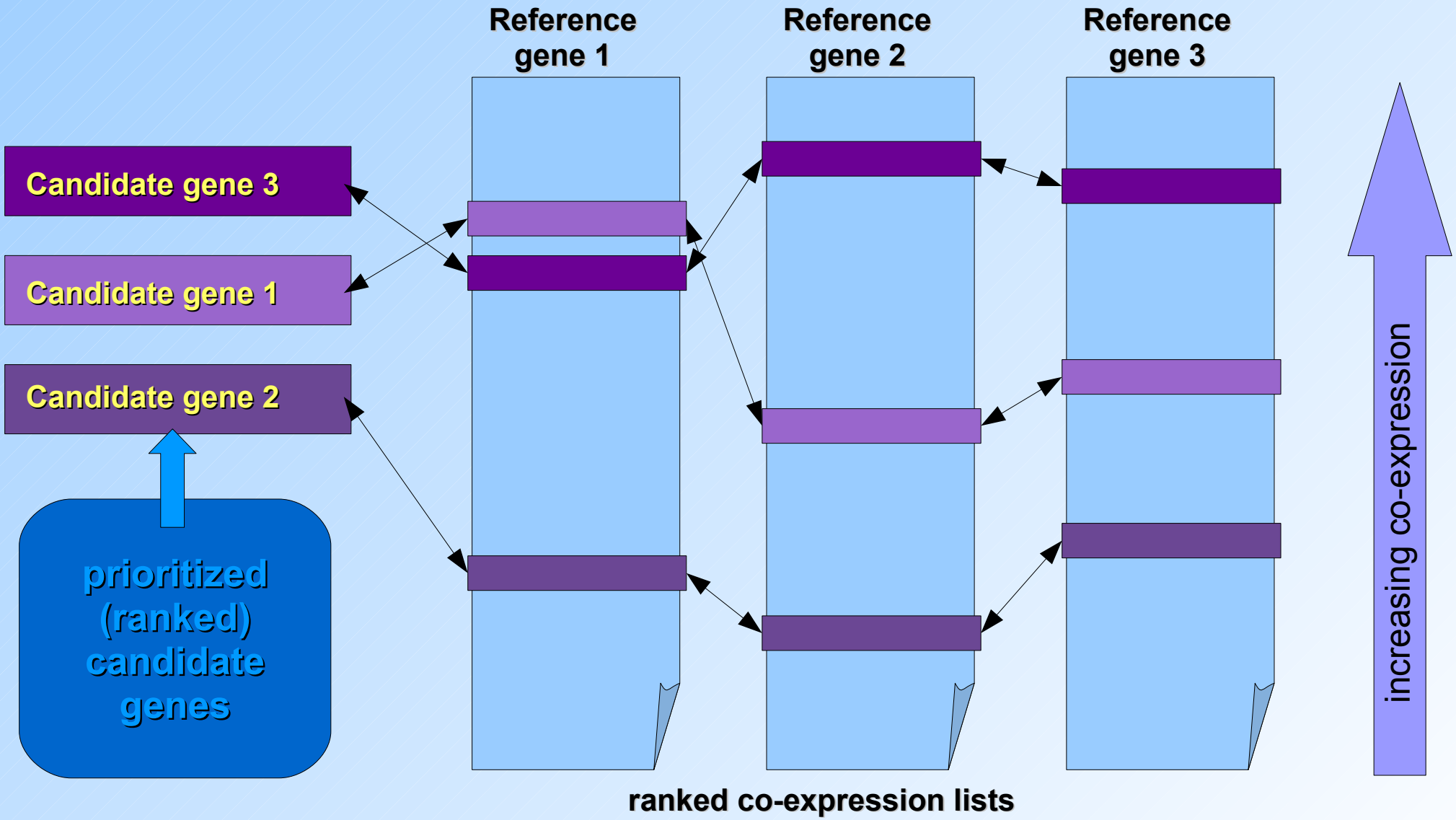

Leave-one-out validation

- Large-scale leave-one-out validations for ...
  - **… known CNS-related gene-phenotype associations** from different databases
    - Mouse Genome Database (MGD)
    - Online Mendelian Inheritance in Man (OMIM)
  - **… different sizes of loci**

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- Results suggest that the method can be applied for both mouse and human phenotypes
  - Example: for large loci with up to 401 genes the phenotype-causing genes rank 1st-10th significantly more often than expected by chance
    - mouse phenotypes: $P = 4.79e\text{-}09$
    - human disorders: $P = 4.84e\text{-}06$

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Case study: XLMR (1)

- Challenging, complex disorder:
  ~90 genes on Chr. X are known to be involved in some form of intellectual disability
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- Recent re-sequencing study of the exome of Chr. X
  (*Tarpey et al., Nat. Genet., 2009*)
  - 208 affected families
  - mutations in 3 novel (and several known) XLMR genes
  - many other mutations (also truncating), but in for most of the cases the genetic cause could not be reliably determined

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Case study: XLMR (2)

- Evaluation:
  - candidate genes: all re-sequenced genes
  - reference genes: only genes known to be involved in similar phenotypes (none of the candidates from Chr. X)
  - can we “predict” known disease genes **pretending XLMR to be a phenotype of unknown molecular basis**?

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- Important: evaluation and prediction have completely distinct sets of reference genes!

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Case study: XLMR - Results

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- Tarpey et al. have found **mutations** of highly conserved residues

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- Spatial 3D expression data remain an exception
  - Human Brain Atlas (Allen Institute) to be completed in 2013
    - our work can be considered a pioneer study towards a direct application of human 3D expression data
  - so far only “normal” brain tissue; some potentially interesting applications would require disease conditions
    - “differential spatial expression”?

Summary

- We have shown that spatially mapped (3D) gene expression data can be successfully exploited for candidate gene prioritization
  - mouse CNS-related phenotypes
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- Application to XMLR:
  - we successfully “re-discovered” known XLMR genes
  - the robustness of our prediction results led us to suggest some promising novel candidates

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Acknowledgments

- Team at CBU@MBC:
  - **Ugo Ala**
  - **Ivan Molineris**
  - **Paolo Provero**
  - **Ferdinando Di Cunto**
  - Christian Damasco
  - Antonio Lembo
  - Eva Pinatel
  - Elena Grassi
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Poster

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Questions?

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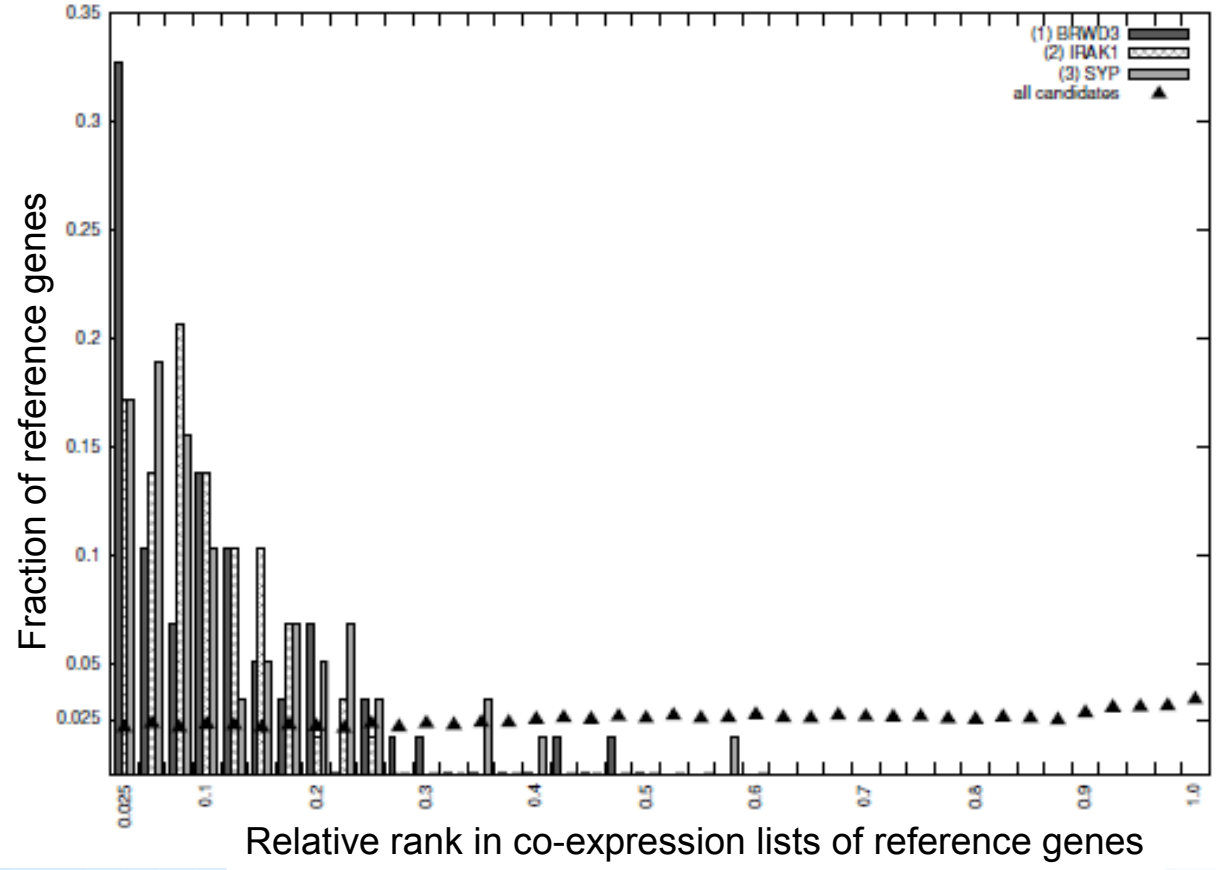

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