Greatly improved allele-specific tumor copy numbers with DNA microarrays when a matched normal is available

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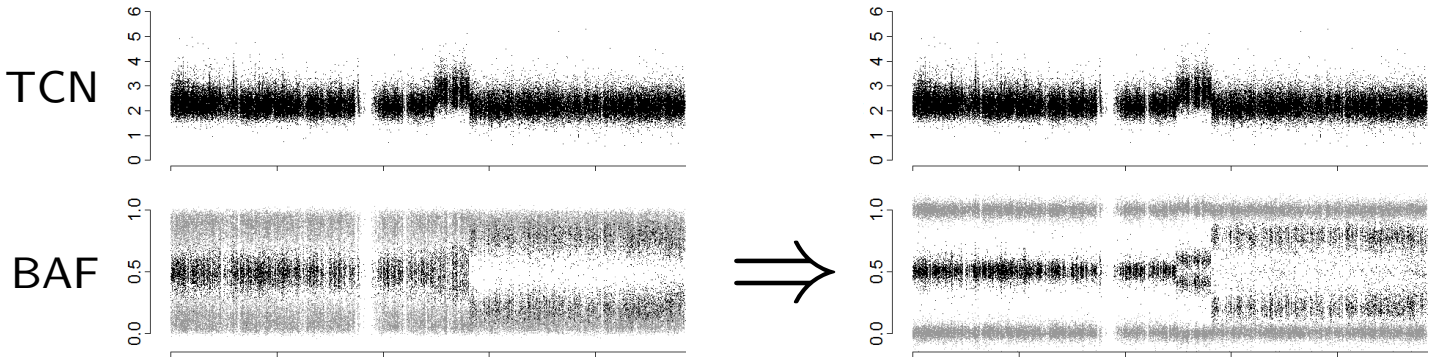
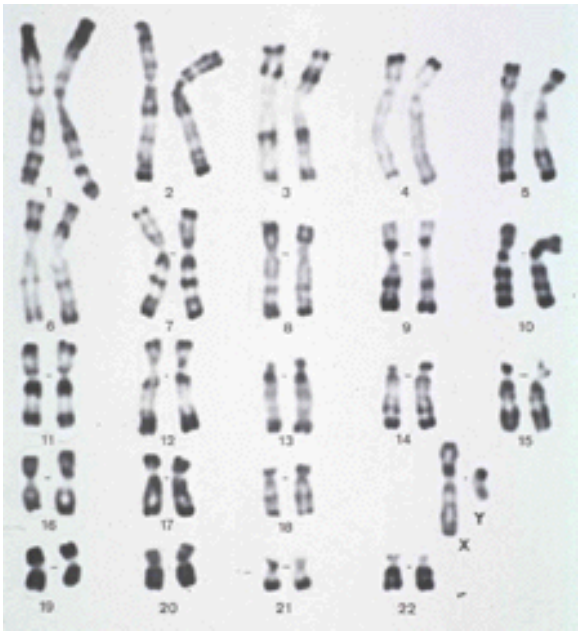
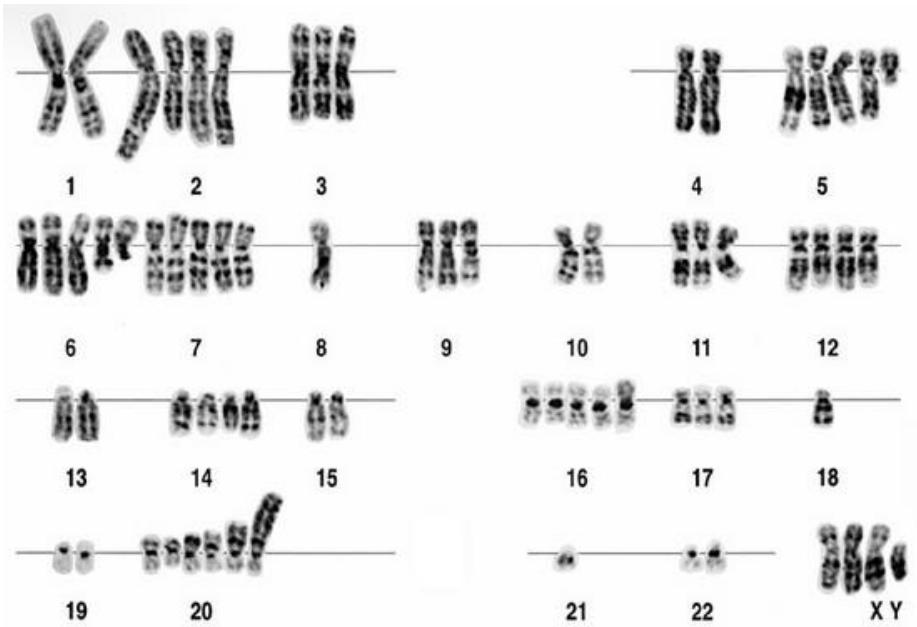


Genomic changes at the DNA level are hallmarks of cancer

We inherited 23 paternal and 23 maternal chromosomes, mostly identical.



Normal karyotype



Tumor karyotype

Goal: identify CN changes in cancer to improve their characterization, classification, and treatment

Tool: genotyping microarrays (aka SNP arrays)

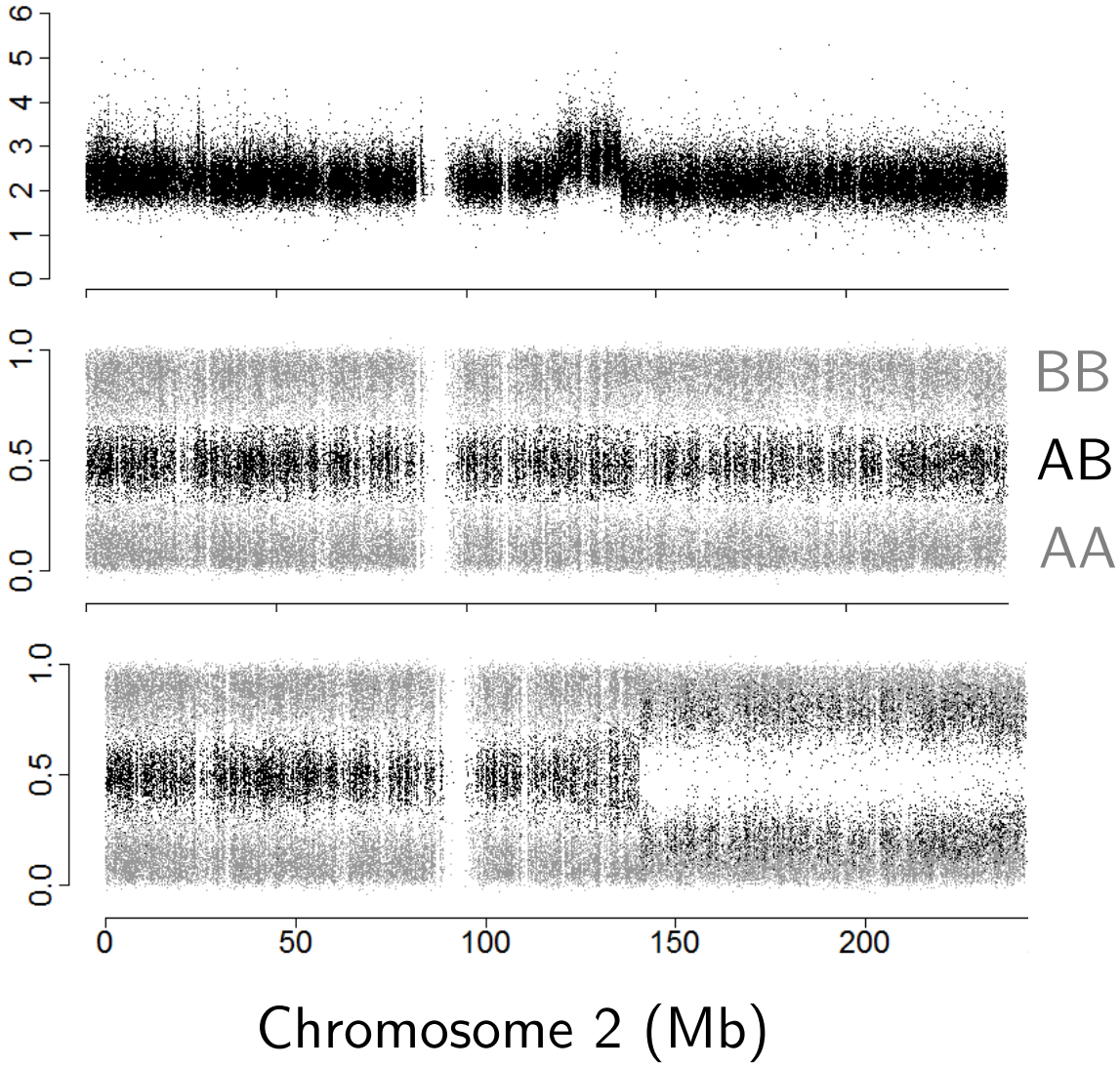
Allelic copy number measurements are noisy

Genomic signals from a tumor-normal pair of SNP arrays after preprocessing (CRMAv2)

Total copy number (TCN)

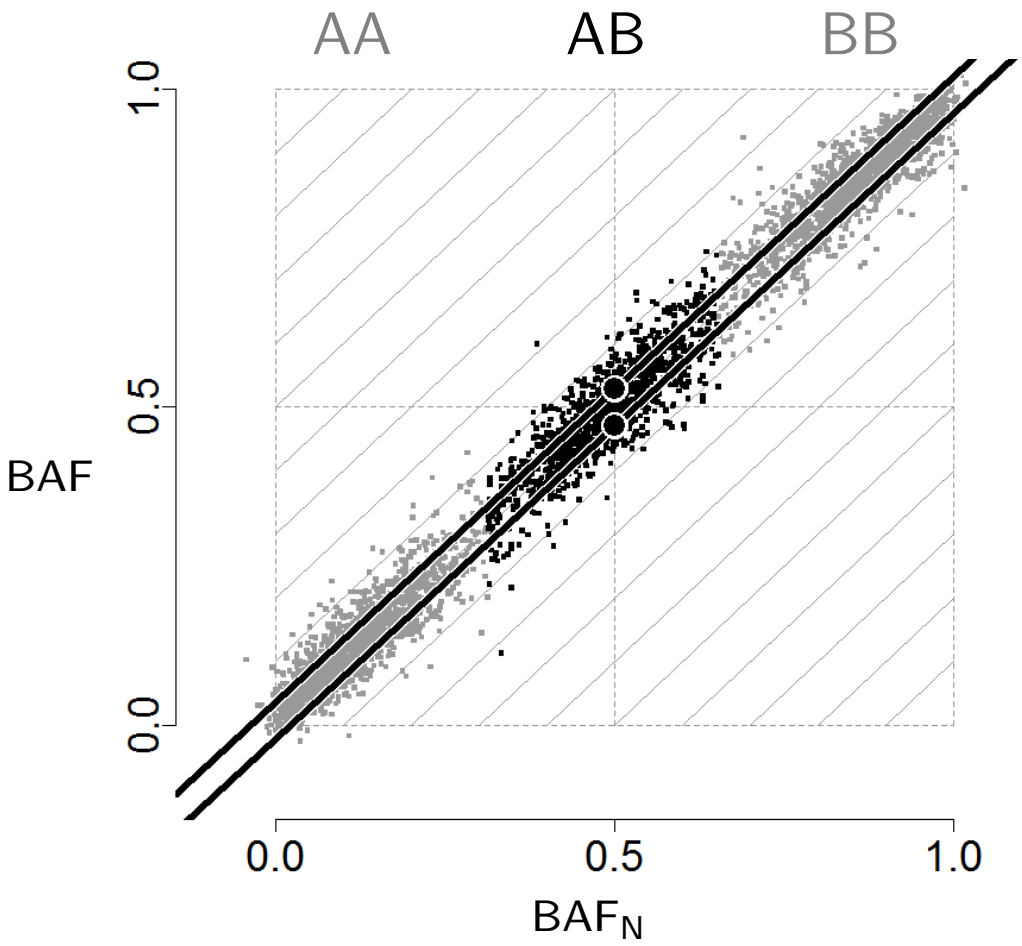
Allele B fraction, normal (BAF_N)

Allele B fraction, tumor (BAF)



"Noise" comes from a reproducible SNP effect

BAF: tumor vs normal in a region of no CN change in the tumor



BB

AB

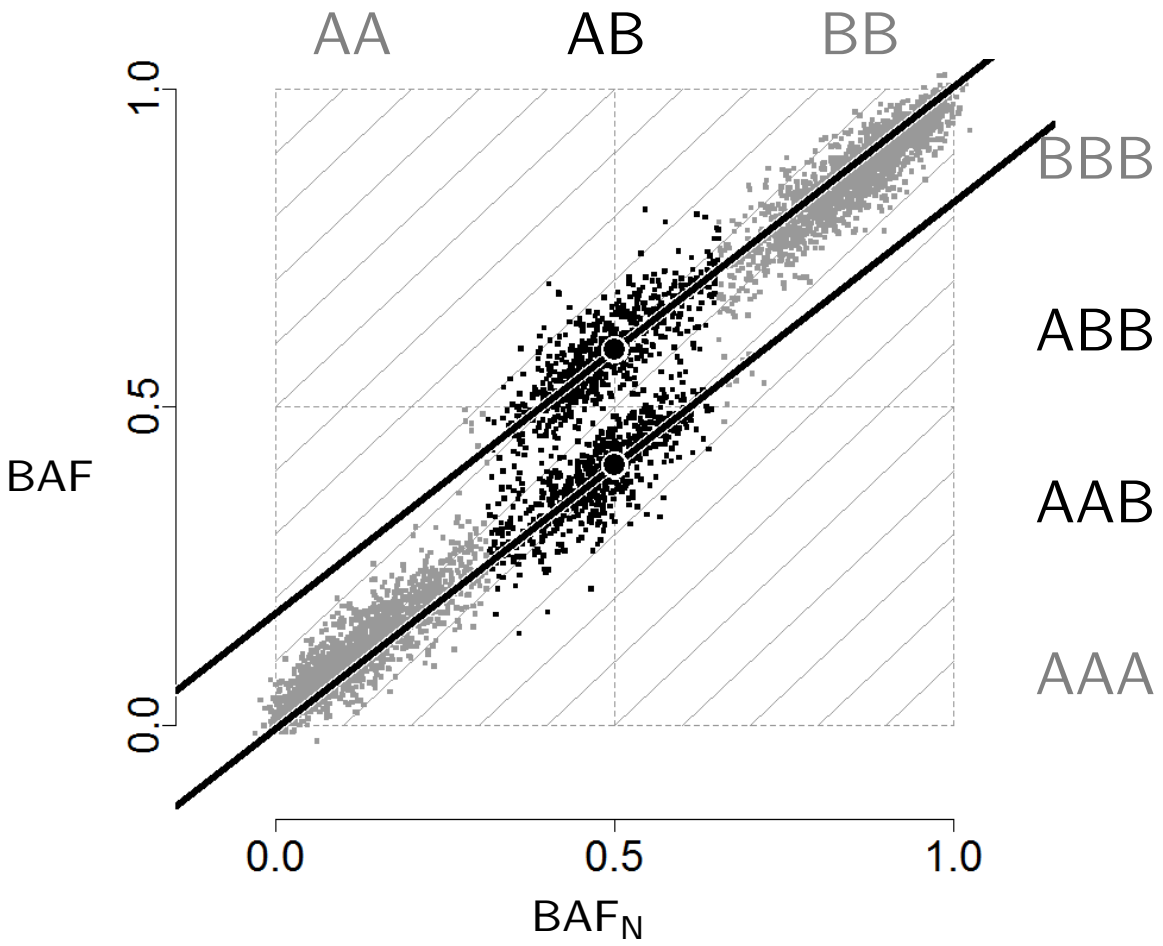
AA

- Expected: (0,0), $(\frac{1}{2}, \frac{1}{2})$, (1,1)
- Observed: elongated clusters

Deviation : a **SNP effect**, quite reproducible between the normal and the tumor

“Noise” comes from a reproducible SNP effect

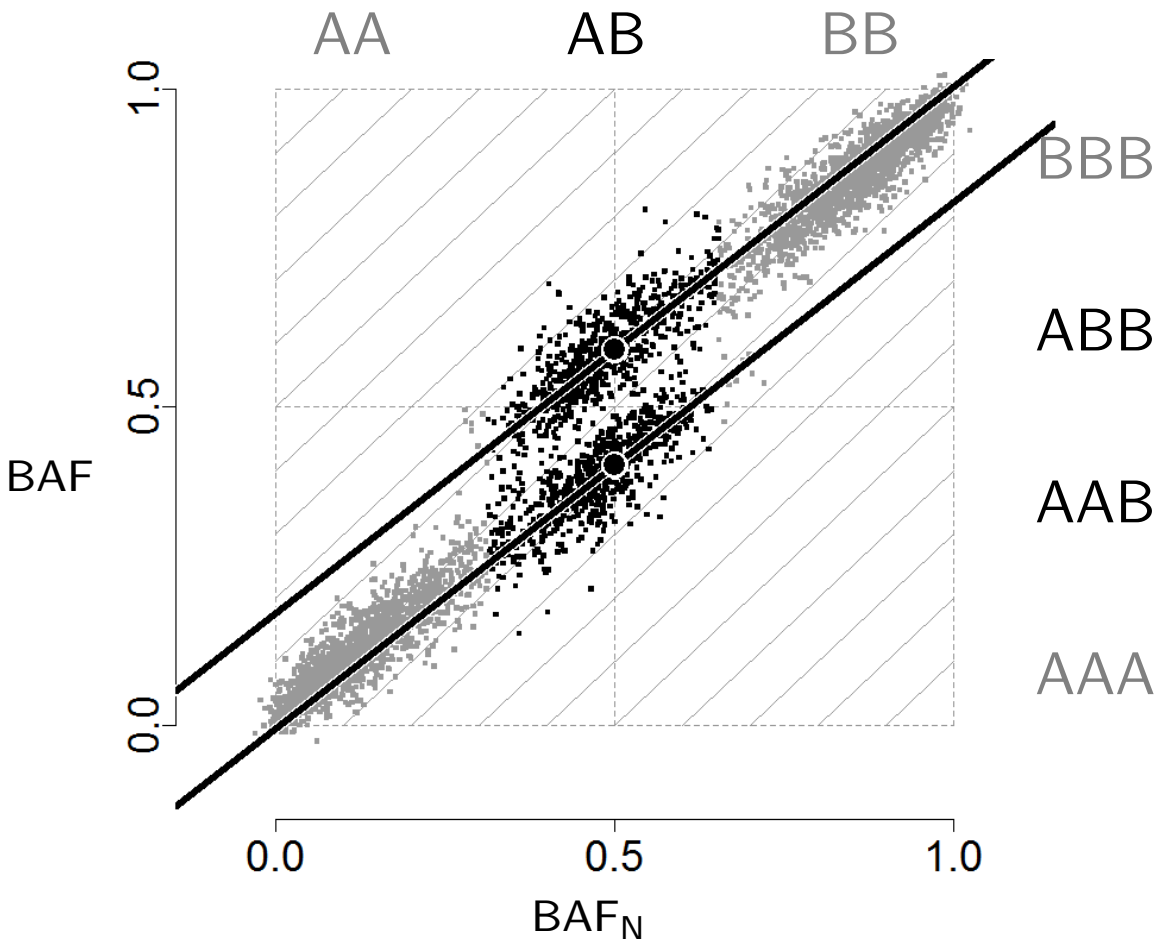
BAF: tumor vs normal in a region where the tumor has a gain



- Homozygous clusters are similar as before
- Heterozygous cluster is split in two, and tilted

"Noise" comes from a reproducible SNP effect

BAF: tumor vs normal in a region where the tumor has a gain



- Homozygous clusters are similar as before
- Heterozygous cluster is split in two, and tilted

In practice, copy number regions are not known in advance !

TumorBoost estimates and subtracts this "noise"

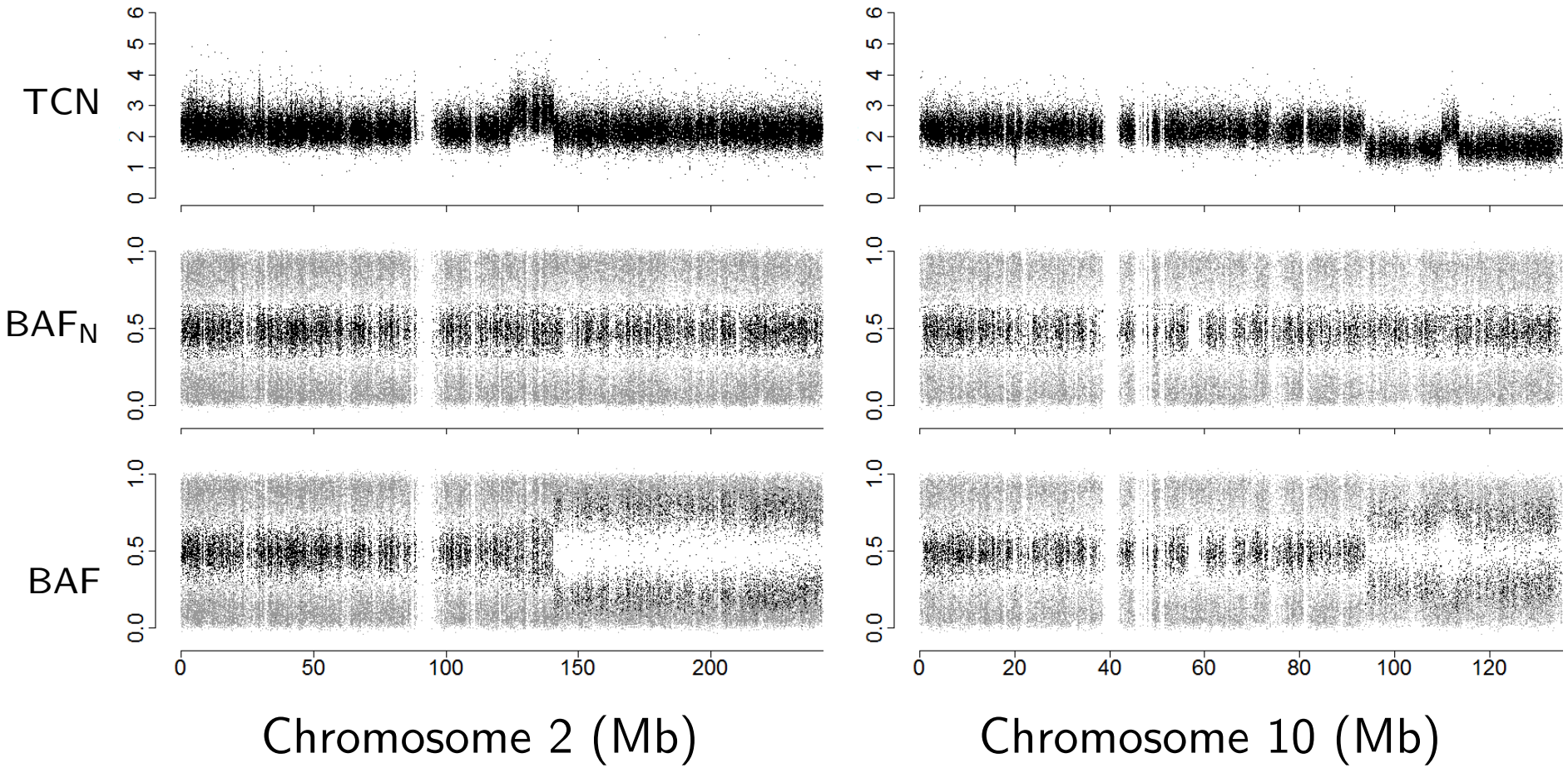
Idea

1. SNP effect is **reproducible** between tumor and normal
2. **truth** is easy to infer in the **normal**: three genotypes AA, AB, BB.

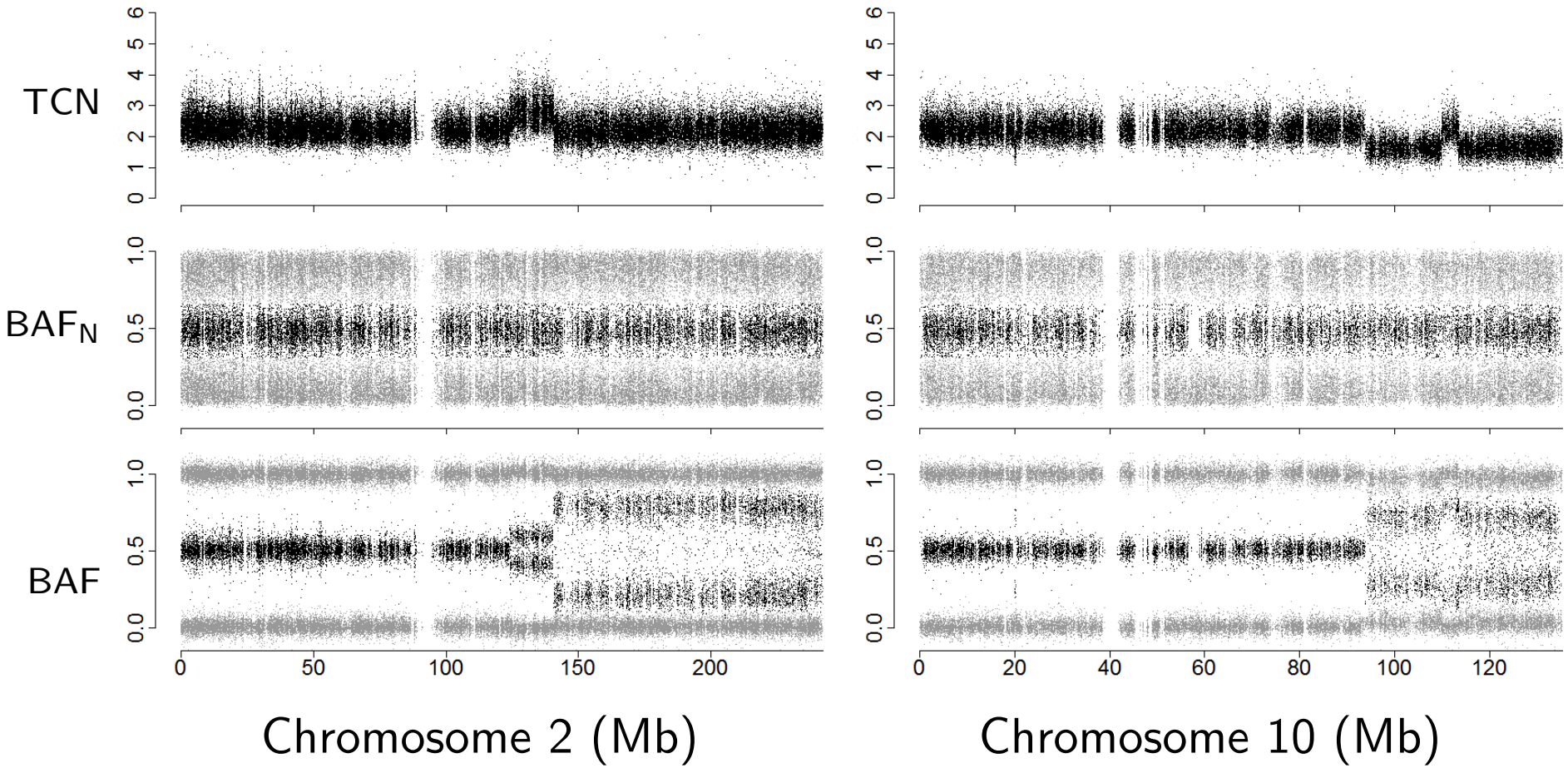
$\Rightarrow$ For each SNP, we estimate the SNP effect in the normal hybridization, and "subtract" it from the tumor.

H. Bengtsson, P. Neuvial, T. P. Speed, *BMC Bioinformatics*, 2010, **11**:245

Genomic signals before normalization



Genomic signals after normalization

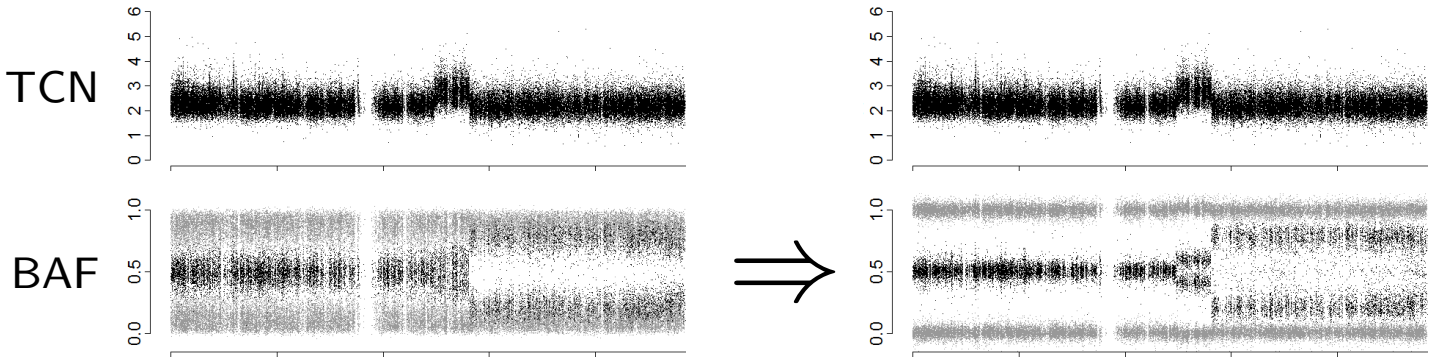


Conclusion

Features:

- no need to know copy number regions in advance
- normalization is performed for each SNP separately
- only requires one tumor/normal pair
- applicable to any SNP array technology (Affymetrix, Illumina)
- applicable after any preprocessing method

Results:

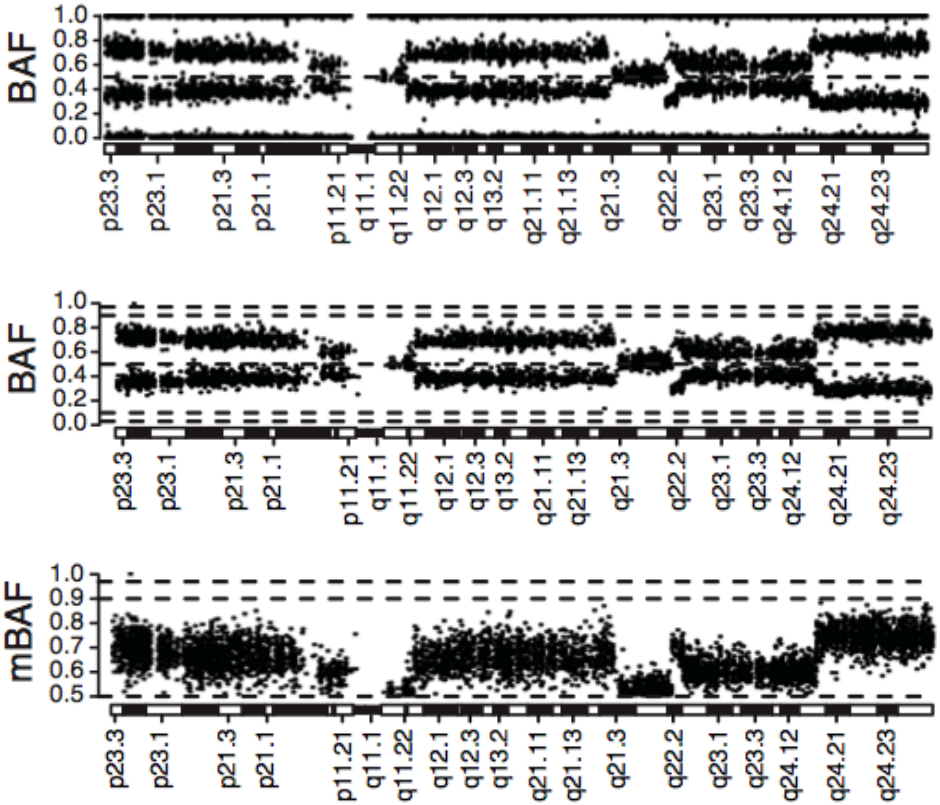


Open source R package: http://aroma-project.org/

Appendix

Detecting changes in allele B fractions

(Figure from Staaf *et al* (2006))



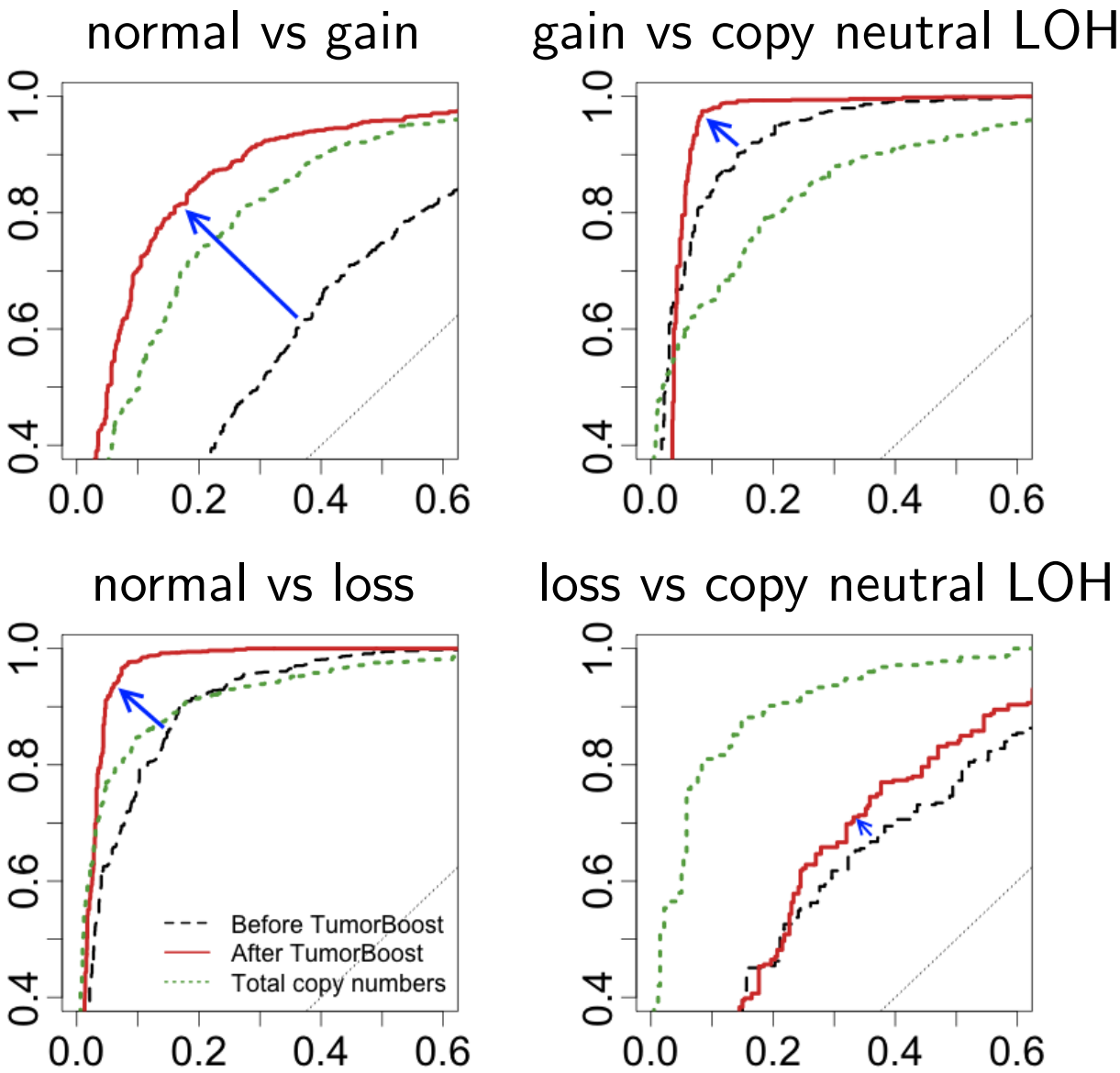
allele B fractions

allele B fractions for heterozygous SNPs

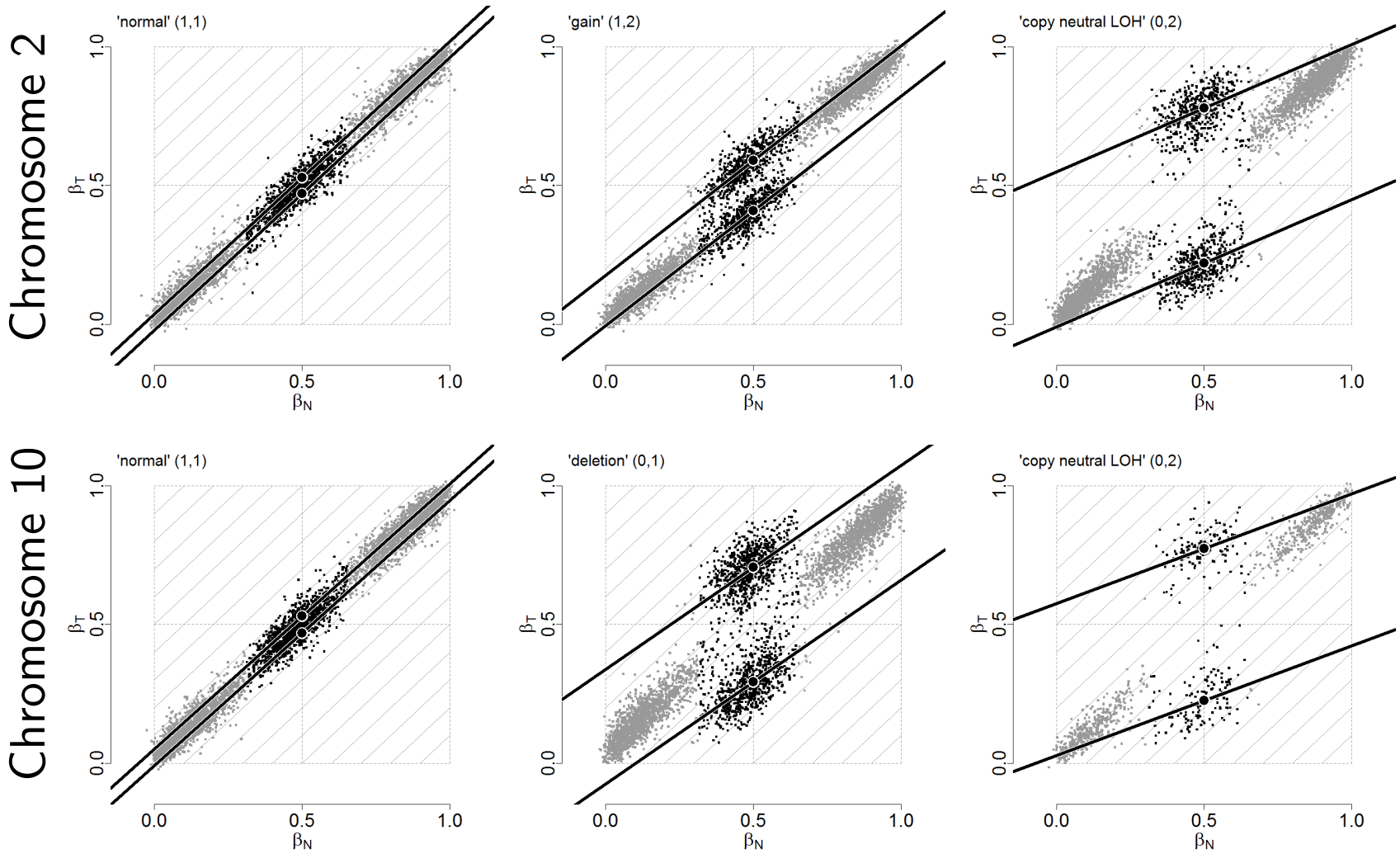
"mirrored" allele B fractions for heterozygous SNPs:
$mBAF = |BAF - 1/2|$

We use ROC analysis to assess how well separated two regions on each side of a known change point in *mBAF* are.

ROC analysis: TP rate vs FP rate



Allele B fractions before normalization: (BAF_T, BAF_N)



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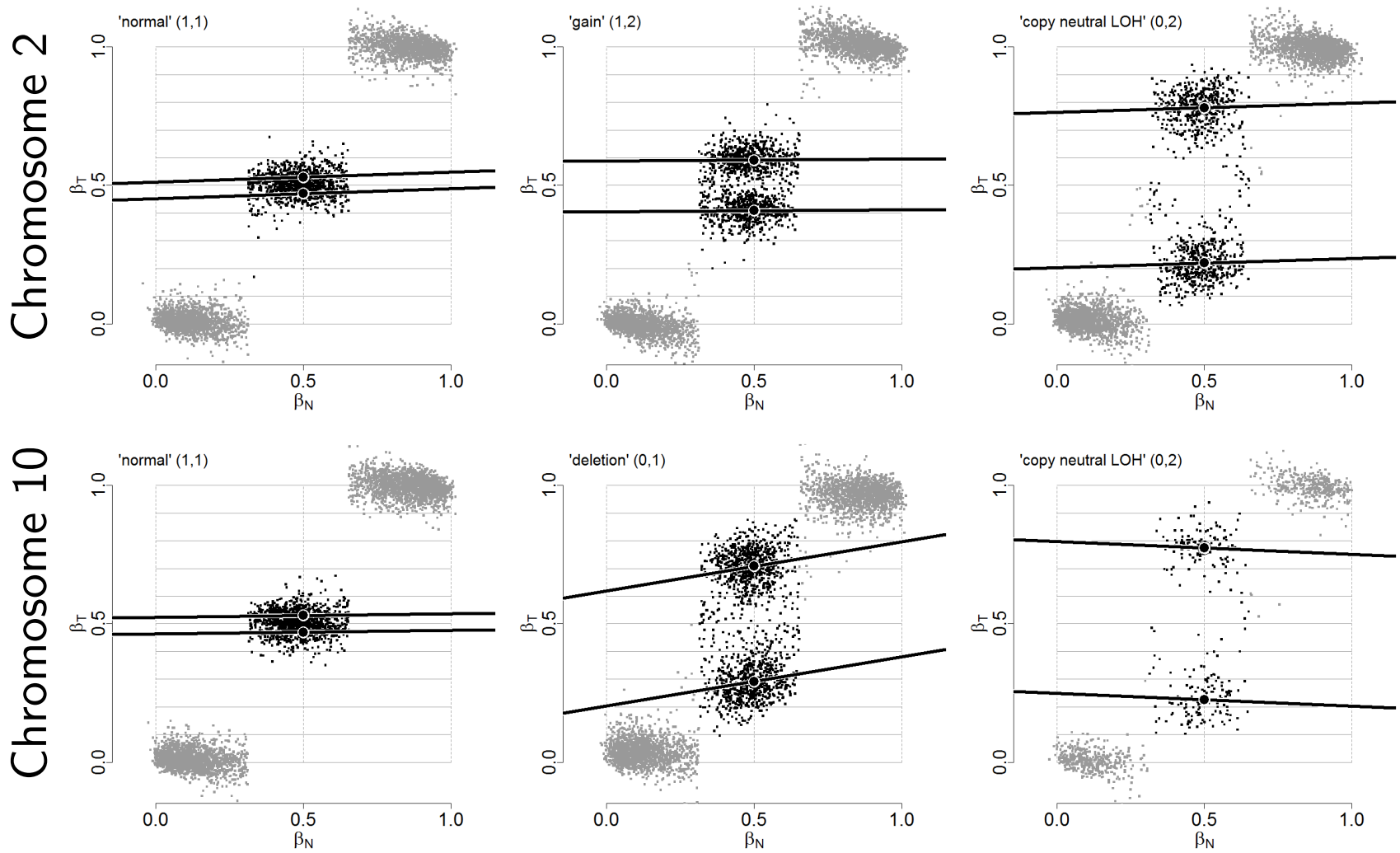
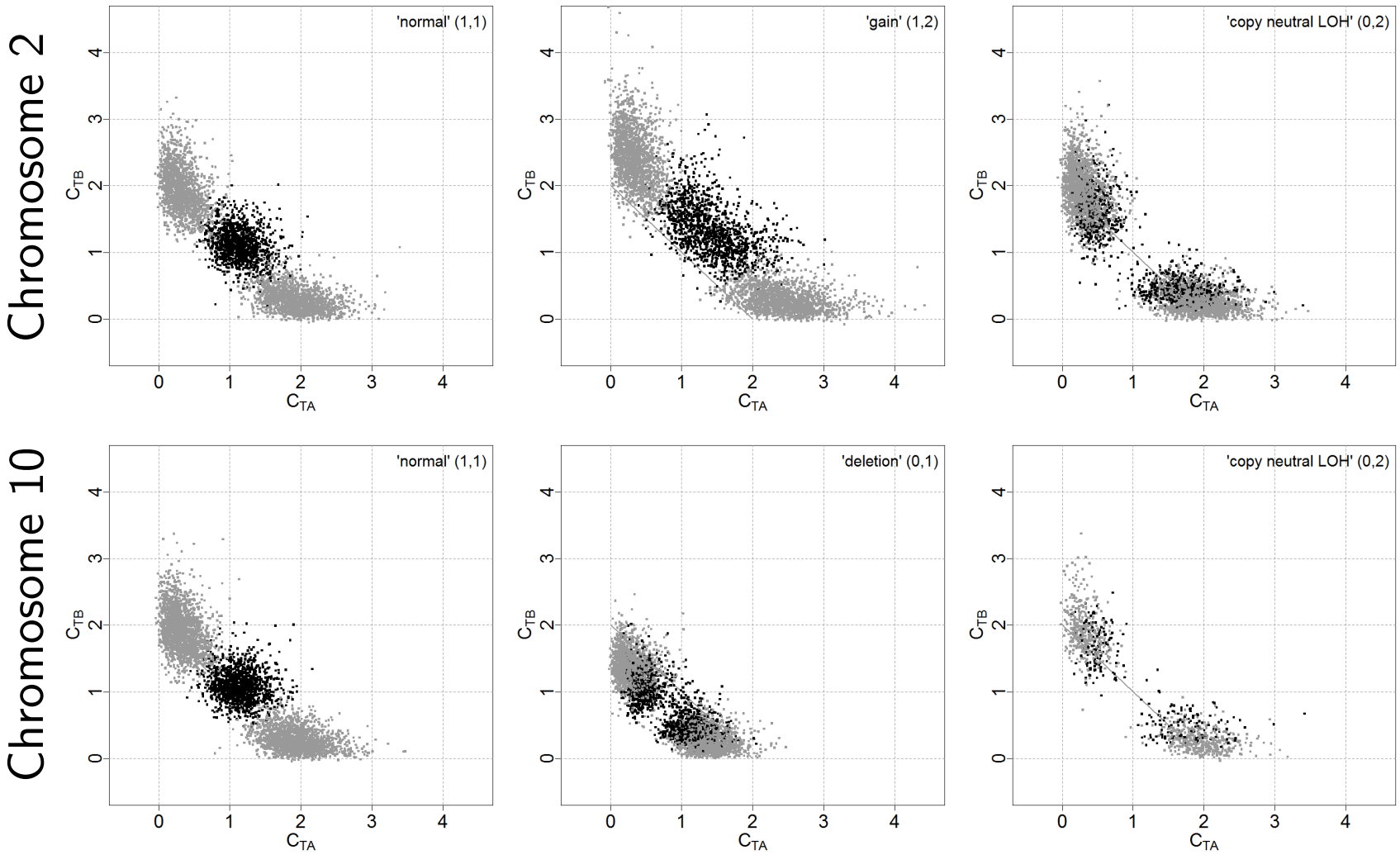
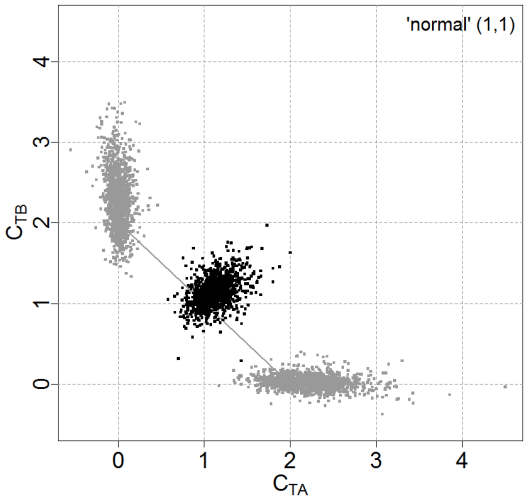


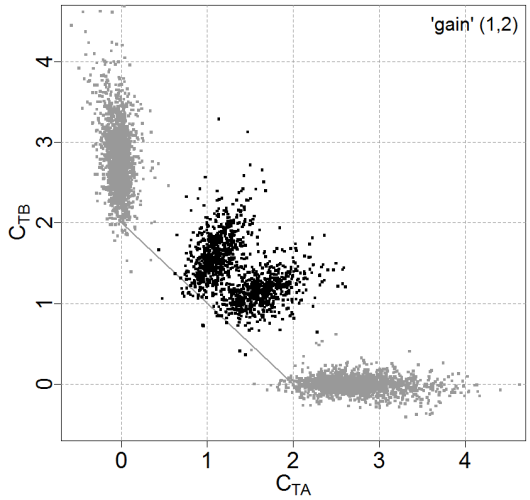
ASCNs before normalization: (C_{TB}, C_{TA})

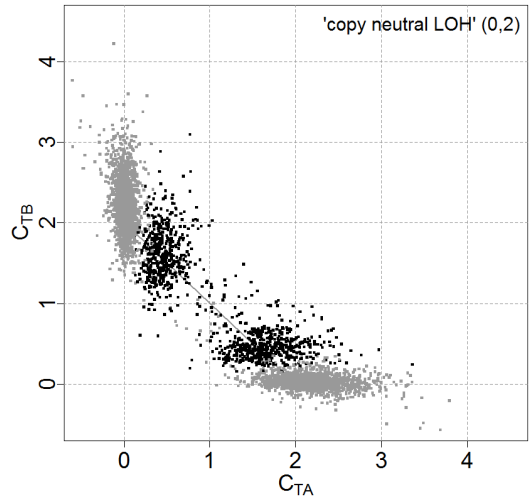


ASCNs after normalization: (C_{TB}, C_{TA})

Chromosome 2







Chromosome 10