An Integrated Approach for the Assessment of Chromosomal Abnormalities

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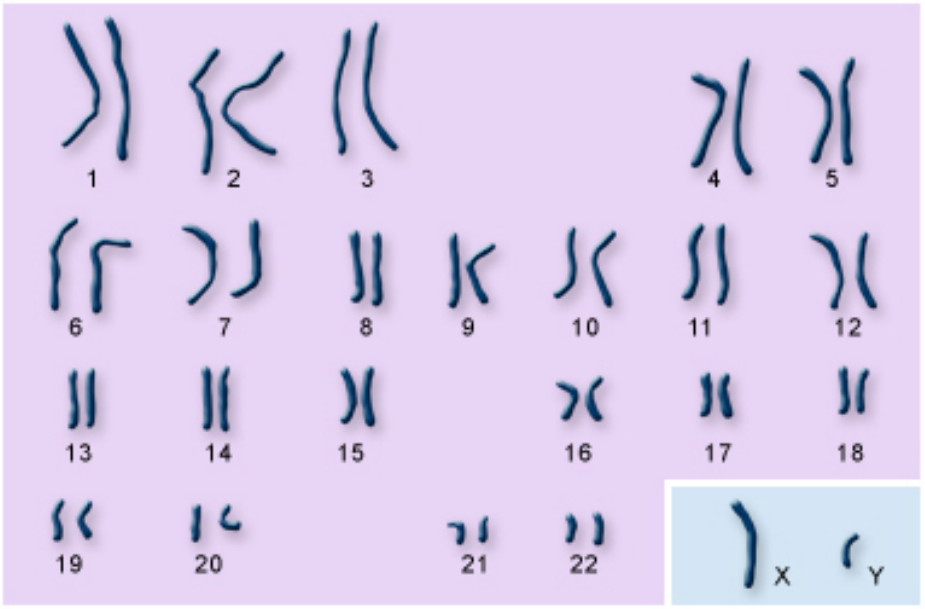
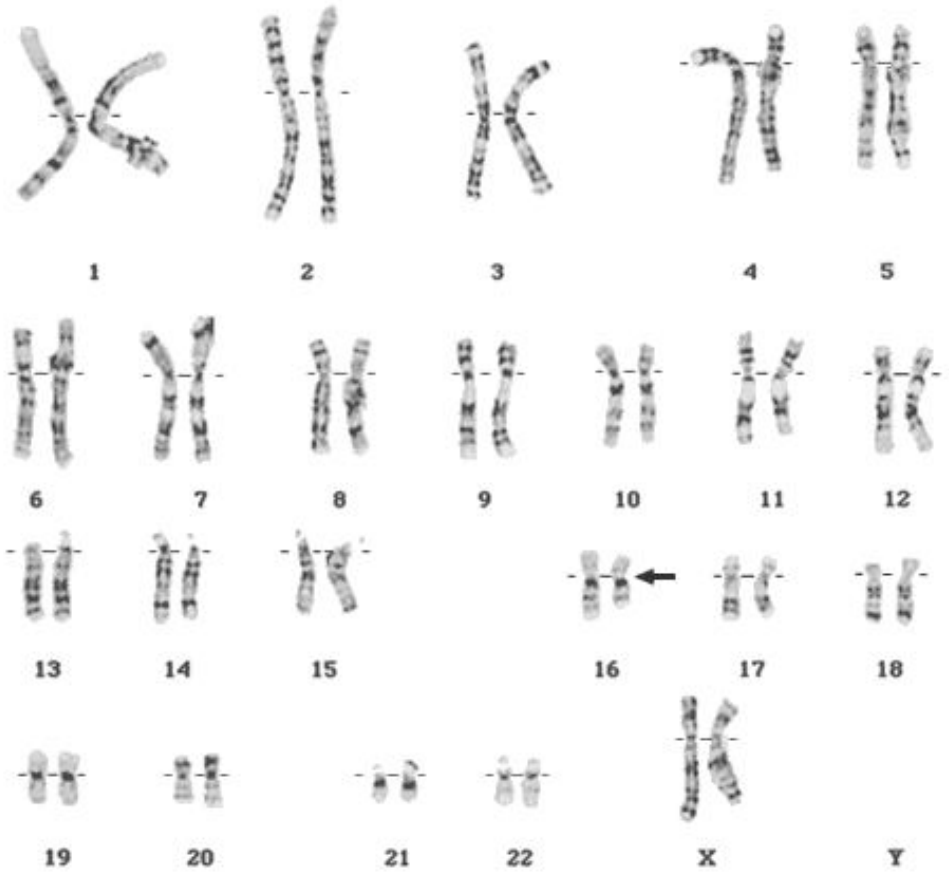
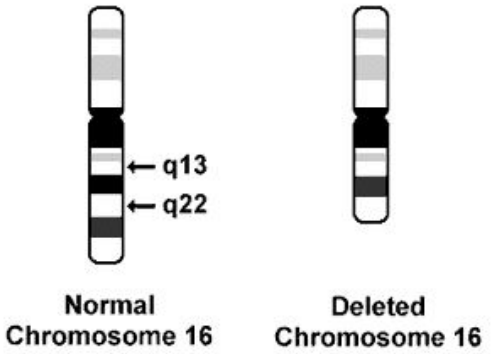
Karyotypes



U.S. National Library of Medicine

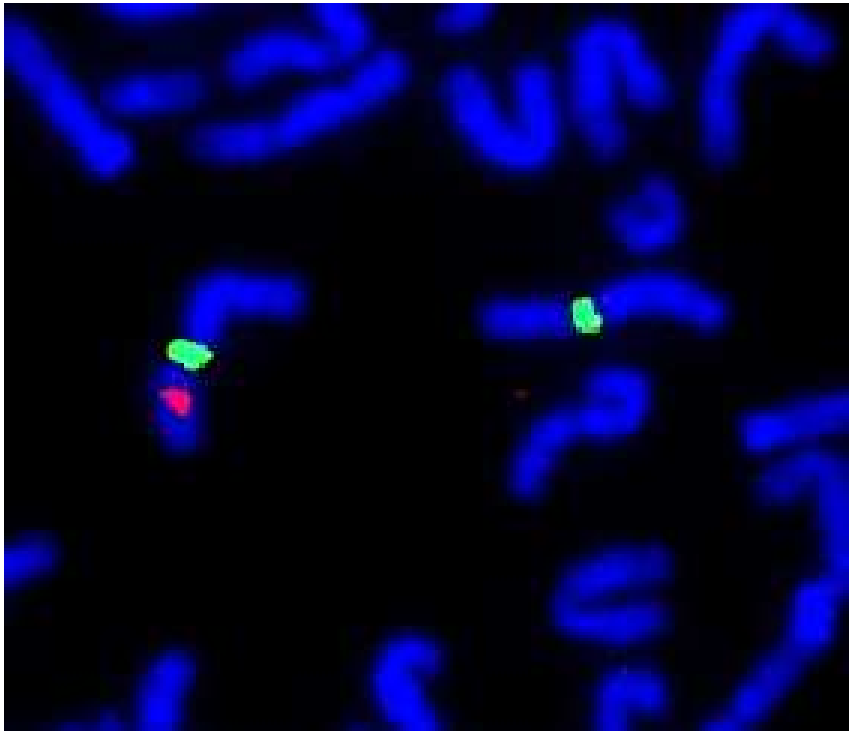
Karyotypes





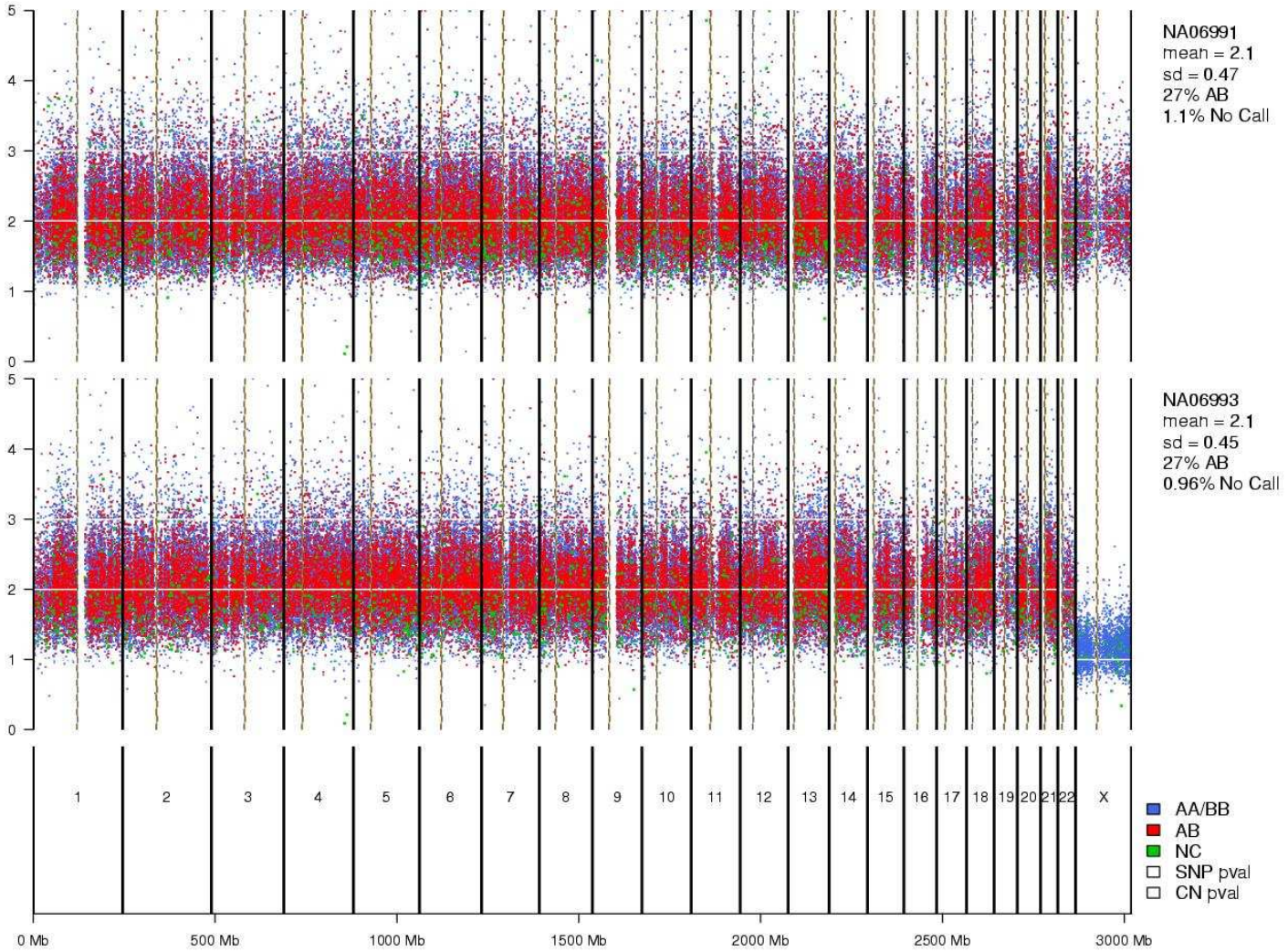
General Cytogenetics Information http://members.aol.com/chrominfo/

FISH



Courtesy of the Pevsner Laboratory

SNP chip data



Estimation

1. By SNP:

   Estimate genotype and copy number for each SNP.

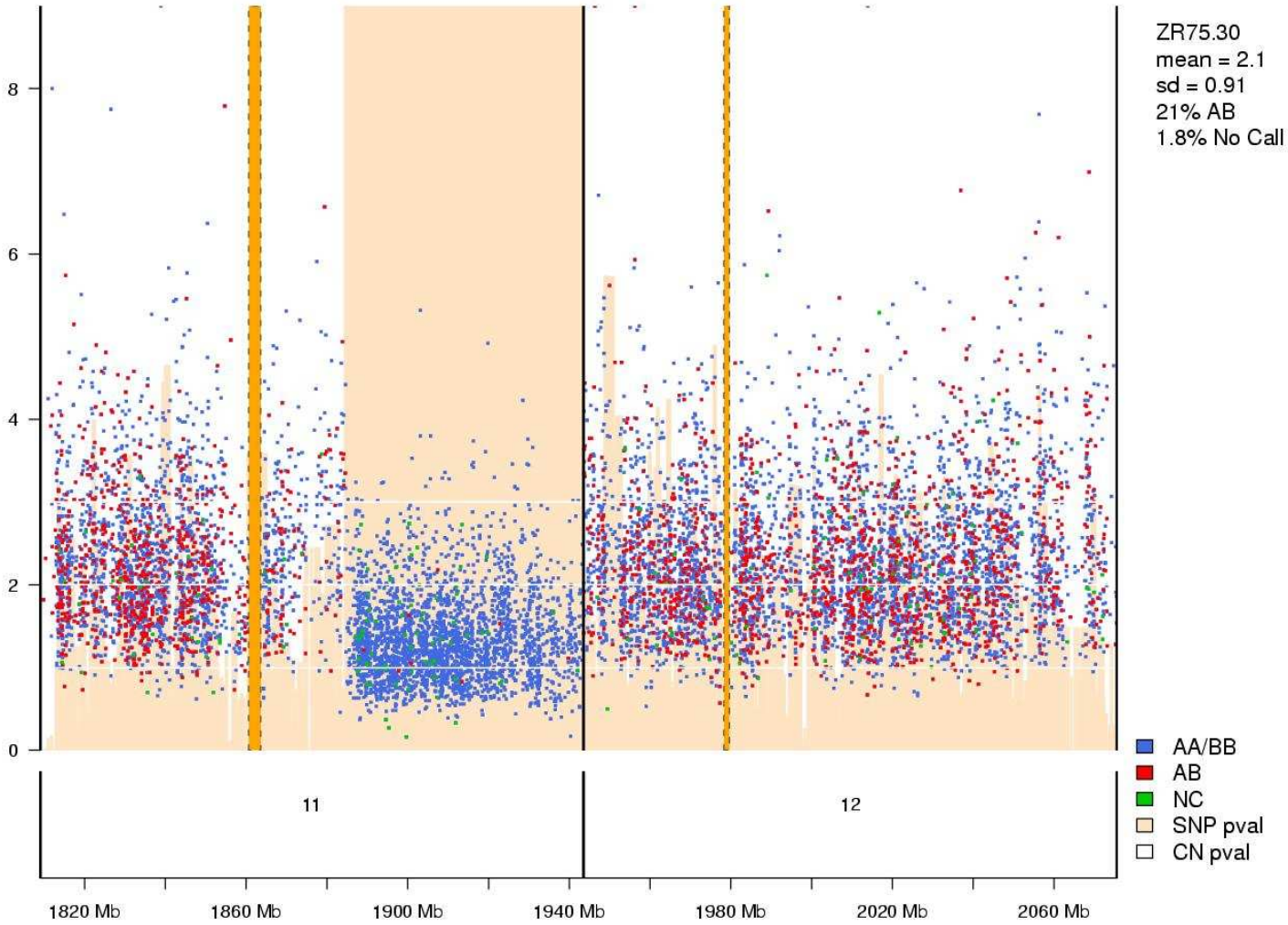
2. Within a sample:

   Borrow strength between SNPs to infer regions of LOH and copy number changes.

3. Between samples:

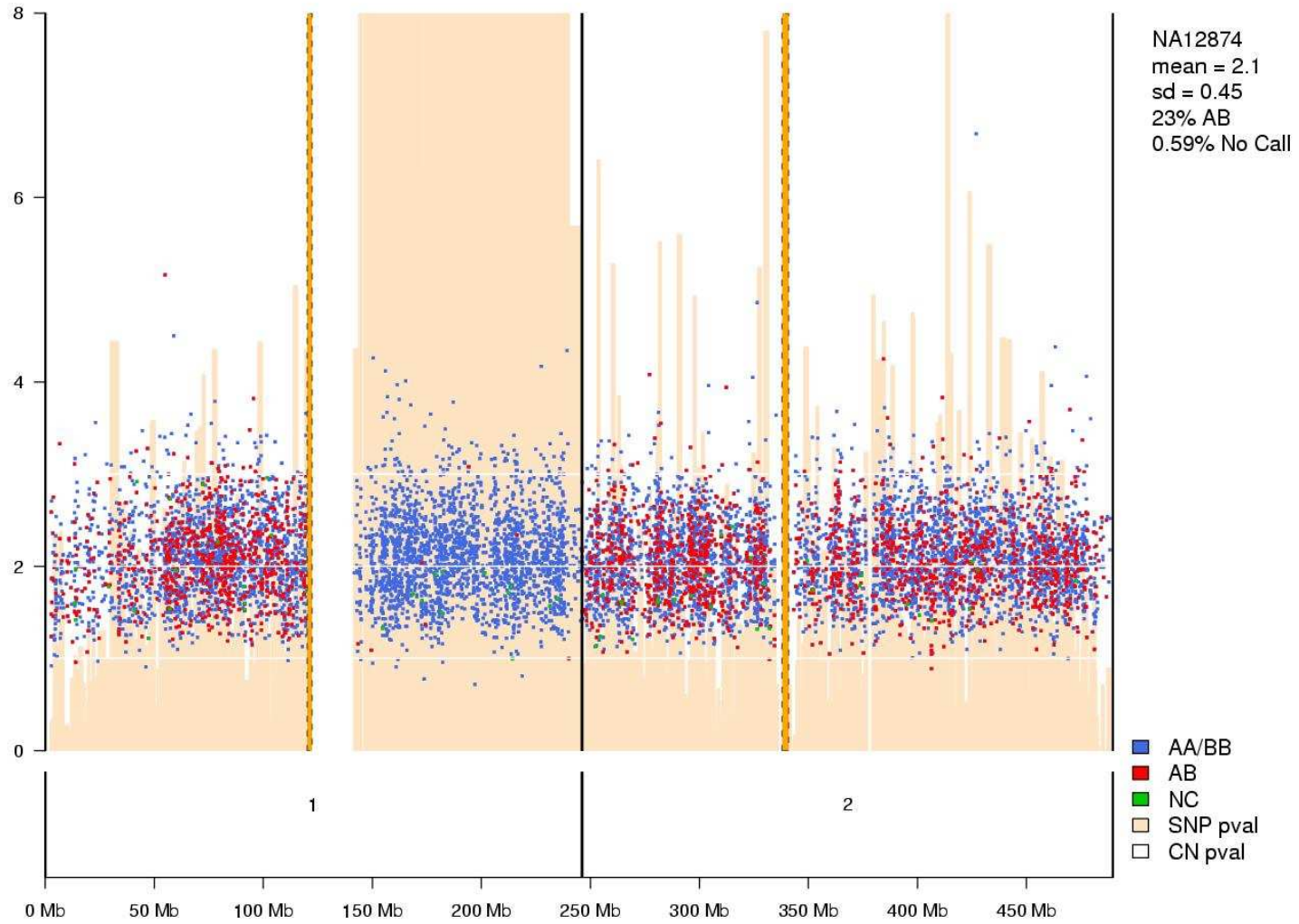
   Comparison between normal and disease populations to find chromosomal alterations associated with disease.

Deletion

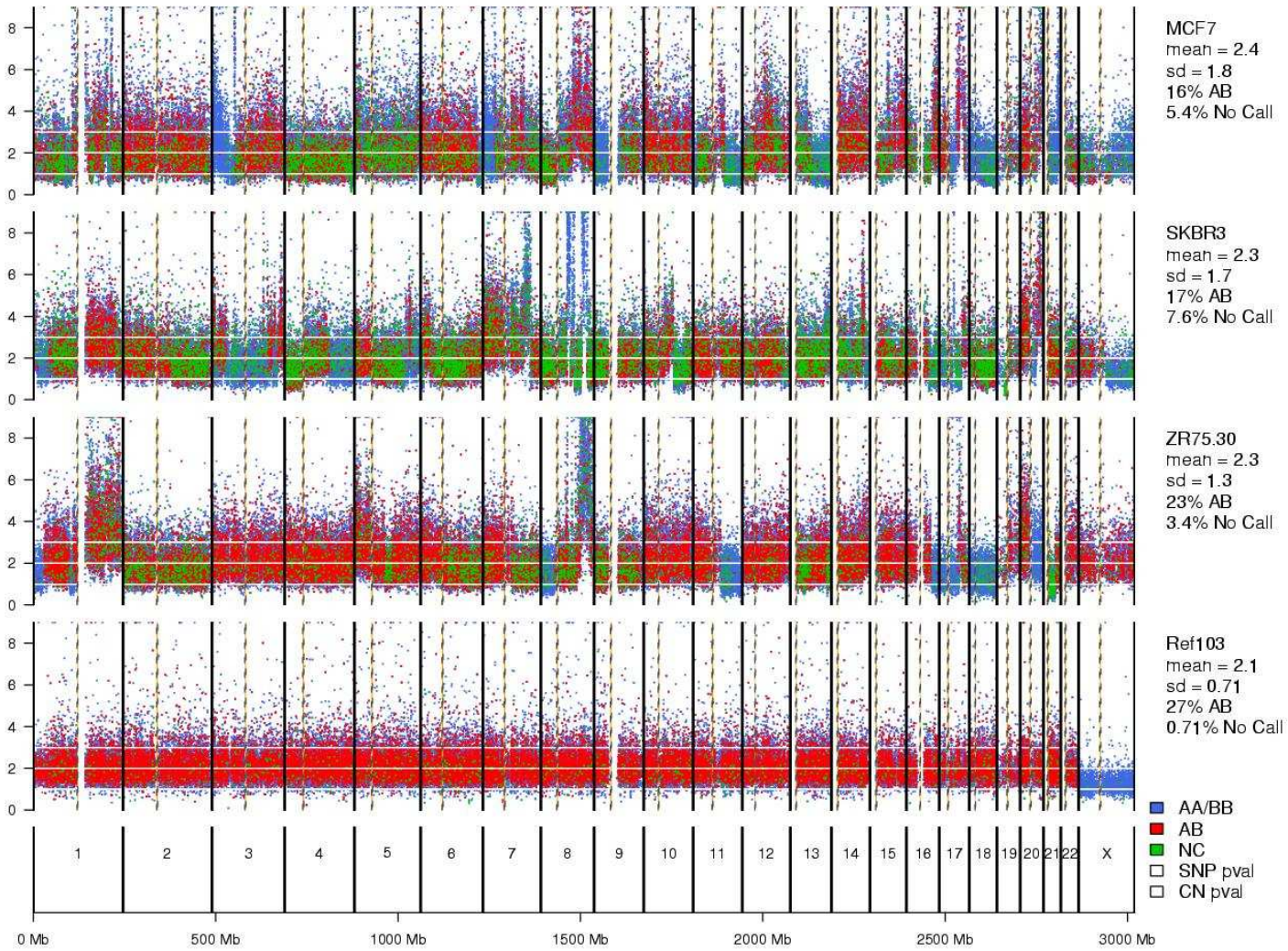

ZR75.30
mean = 2.1
sd = 0.91
21% AB
1.8% No Call
8
6
4
2
0
11
12
1820 Mb
1860 Mb
1900 Mb
1940 Mb
1980 Mb
2020 Mb
2060 Mb
AA/BB
AB
NC
SNP pval
CN pval

Amplification

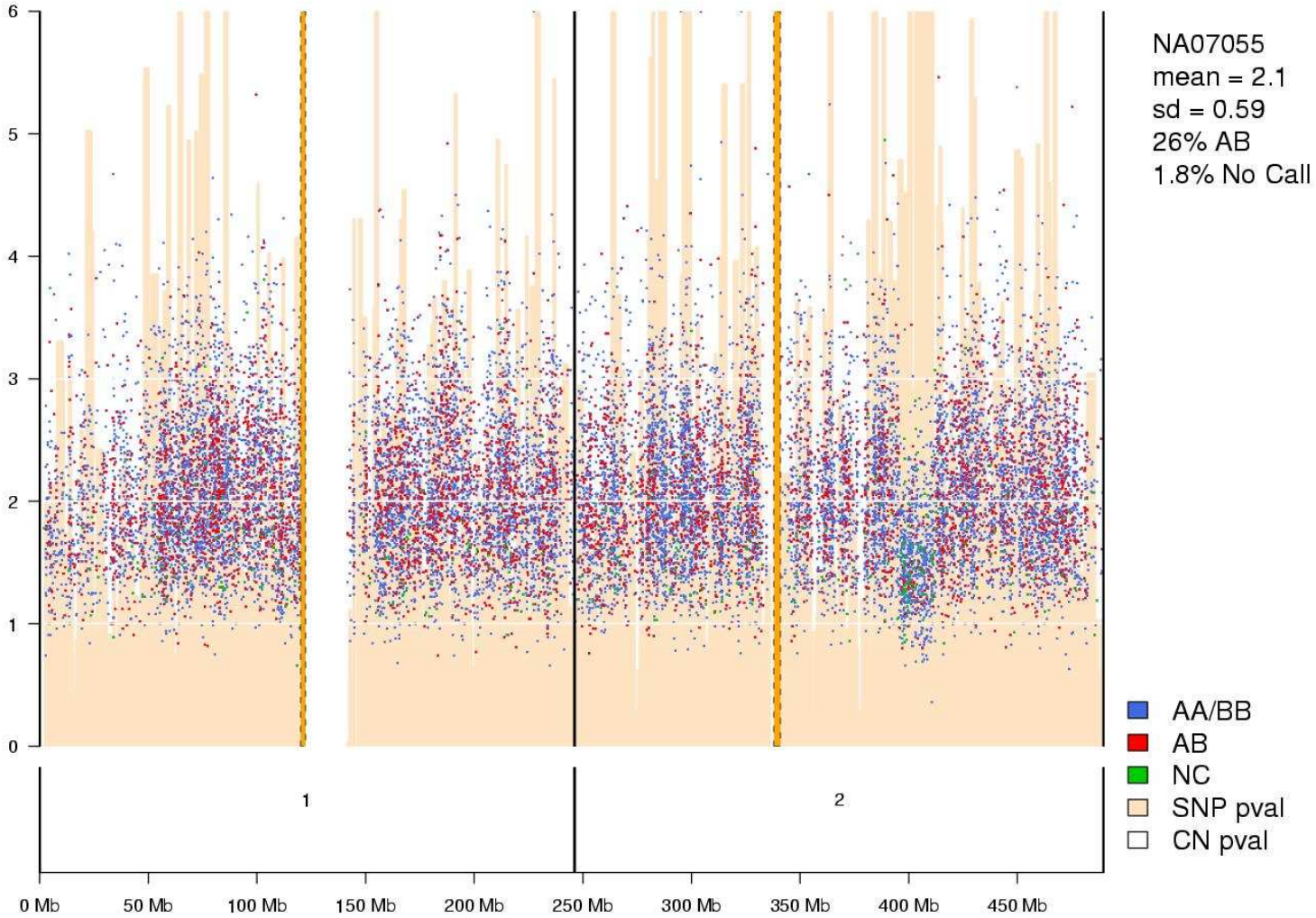
Uniparental Isodisomy



Cancer samples



Mosaicism


NA07055
mean = 2.1
sd = 0.59
26% AB
1.8% No Call
AA/BB
AB
NC
SNP pval
CN pval
0
1
2
3
4
5
6
1
2
0 Mb
50 Mb
100 Mb
150 Mb
200 Mb
250 Mb
300 Mb
350 Mb
400 Mb
450 Mb

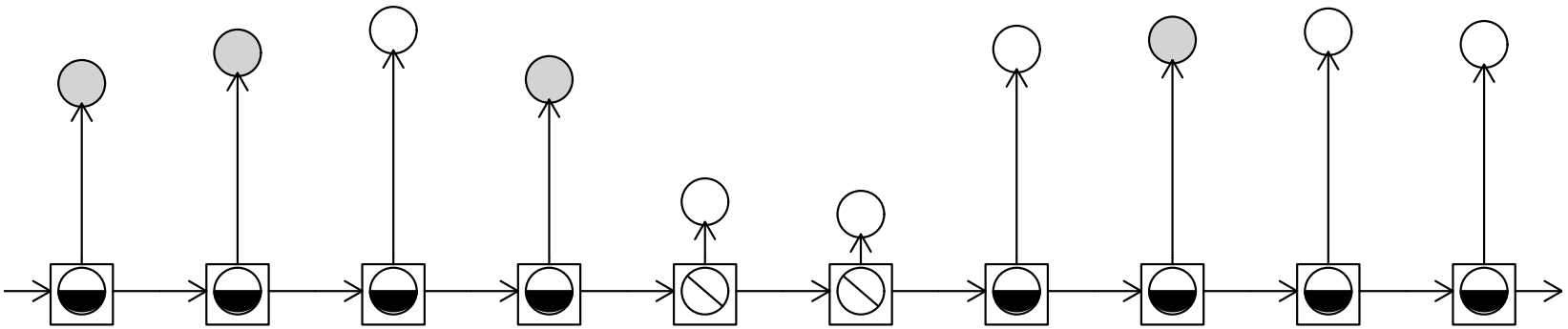
SNPchip S4 classes and methods

```
> merged <- subset(merged, samples = 1)
> summary(merged)
$NA06985
                        Chr 1 Chr 2 Chr 3 Chr 4 Chr 5 Chr 6 Chr 7 Chr 8 Chr 9
mean copy number         2.06  2.07  2.09  2.15  2.08  2.09  2.09  2.06  2.06
sd copy number           0.45  0.45  0.43  0.46  0.45  0.46  0.45  0.43  0.45
% heterozygous calls     0.26  0.26  0.27  0.27  0.27  0.29  0.28  0.28  0.27
% homozygous calls       0.73  0.72  0.72  0.73  0.72  0.69  0.71  0.71  0.72
% no calls               0.01  0.01  0.01  0.01  0.01  0.01  0.01  0.01  0.01
                        Chr 10 Chr 11 Chr 12 Chr 13 Chr 14 Chr 15 Chr 16 Chr 17
mean copy number          2.04   2.06   2.06   2.11   2.09   2.02   2.00   1.98
sd copy number            0.45   0.45   0.46   0.46   0.46   0.43   0.44   0.44
% heterozygous calls      0.30   0.28   0.25   0.27   0.26   0.25   0.26   0.29
% homozygous calls        0.69   0.70   0.74   0.72   0.73   0.74   0.72   0.70
% no calls                0.01   0.01   0.01   0.01   0.01   0.01   0.01   0.01
                        Chr 18 Chr 19 Chr 20 Chr 21 Chr 22 Chr X Total (autosomes)
mean copy number          2.09   1.98   1.98   2.10   1.92  2.13               2.07
sd copy number            0.46   0.44   0.43   0.47   0.44  0.44               0.45
% heterozygous calls      0.26   0.24   0.30   0.27   0.26  0.26               0.27
% homozygous calls        0.73   0.74   0.68   0.72   0.72  0.73               0.72
% no calls                0.01   0.02   0.01   0.02   0.02  0.01               0.01

>
```

The structure of the data we observe

⟶ At each SNP, we observe a noisy measure of the true copy number and genotype (and possibly also measures of confidence in those estimates).



Another HMM...?

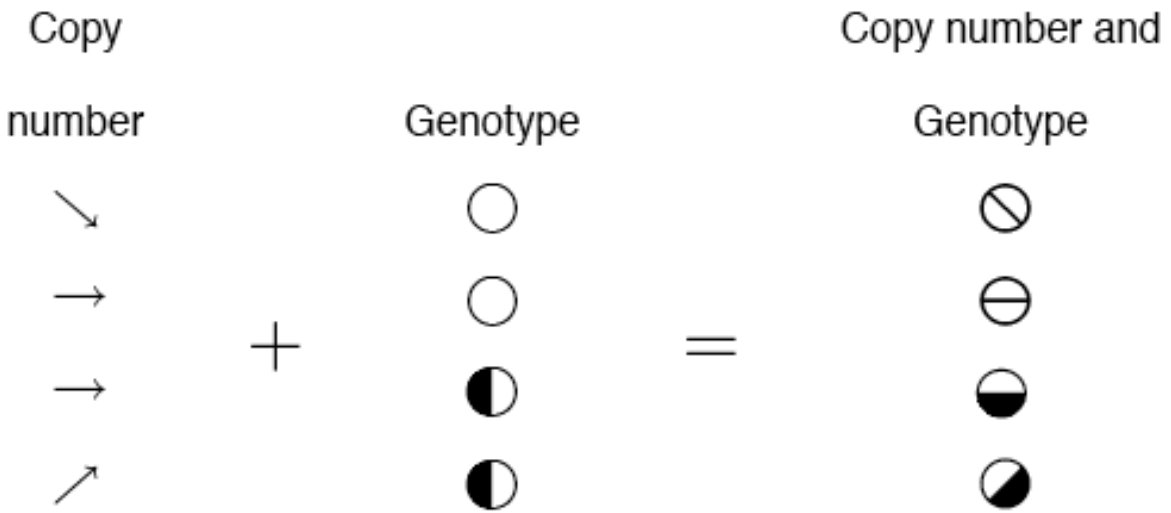
Novel (and we believe, important) HMM features:

1. Model the observation sequence of genotype calls and copy number jointly (Vanilla)
2. Integrate confidence estimates of the genotype calls and copy number estimates (ICE)

The Vanilla HMM components

- Observations $\widehat{\text{CN}}$ and $\widehat{\text{GT}}$
- Hidden states
- Initial state probability distribution
- Transition probabilities
- Emission probabilities

Hidden states



Transition probabilities

Following suggestions in the literature, we model the transition probabilities as a function of the distance d between SNPs.

Specifically, let $\theta(d) \equiv 1 - e^{-2d}$ denote the probability that SNP i is not informative (I^c) for SNP at $i+1$.

For example:

$$
\begin{aligned}
\tau_{\blacklozenge|\oslash}(d) &= P\{\blacklozenge_{i+1} \mid \oslash_i, d\} \\
&= P\{\blacklozenge_{i+1}, I \mid \oslash_i, d\} + P\{\blacklozenge_{i+1}, I^c \mid \oslash_i, d\} \\
&= P\{\blacklozenge_{i+1} \mid I, \oslash_i, d\} \times P\{I \mid \oslash_i, d\} + \\
&\quad P\{\blacklozenge_{i+1} \mid I^c, \oslash_i, d\} \times P\{I^c \mid \oslash_i, d\} \\
&= P\{\blacklozenge\} \times \theta(d).
\end{aligned}
$$

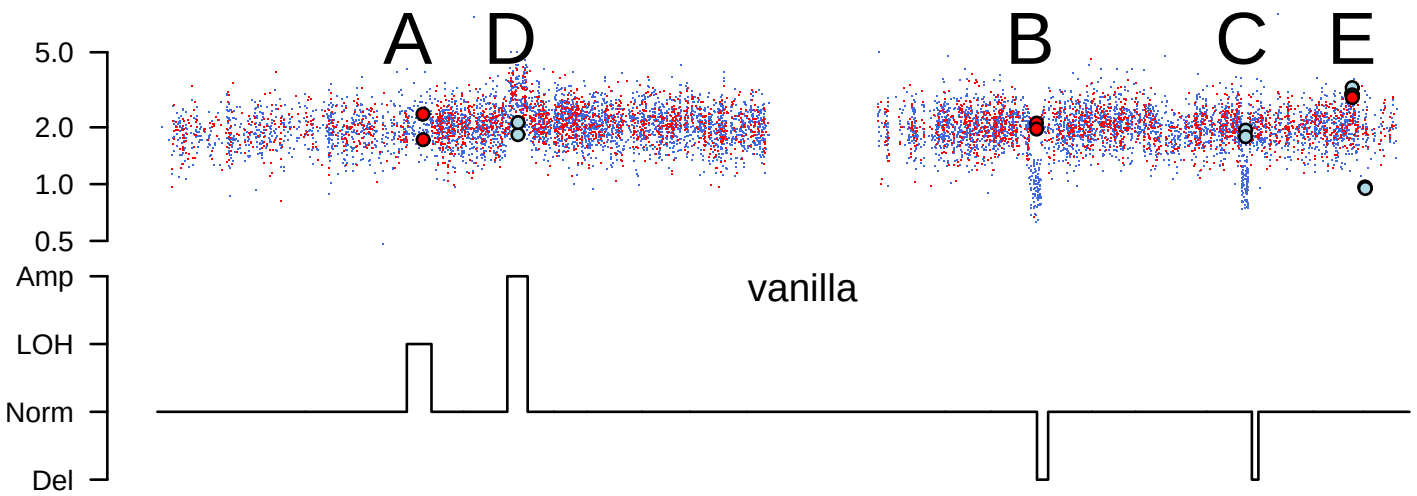
Emission probabilities

We assume conditional independence between copy number estimates and the genotype calls.

For example:

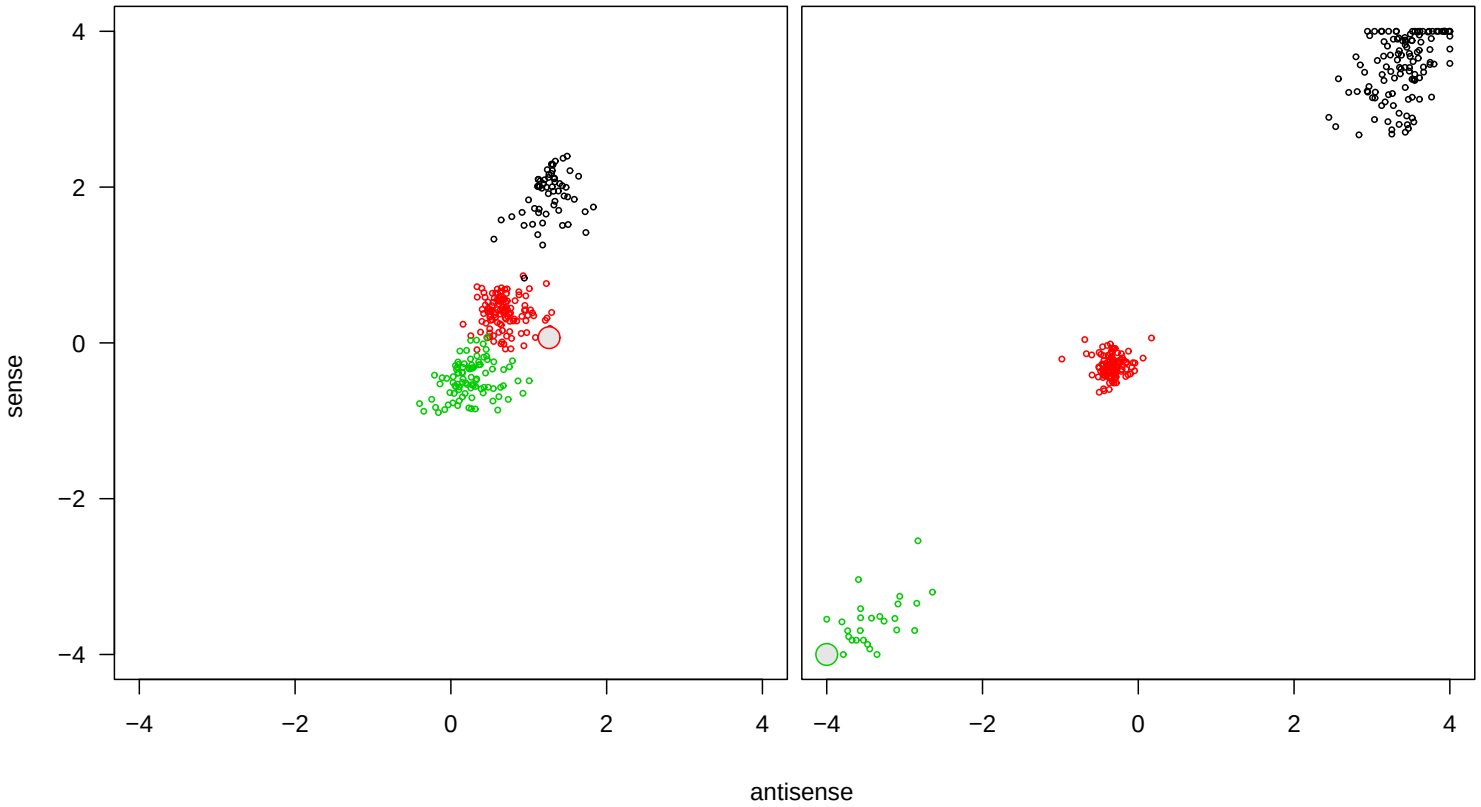
$$
\begin{aligned}
f(\widehat{\mathrm{CN}}, \widehat{\mathrm{GT}} | \oslash) &= f(\widehat{\mathrm{CN}} | \oslash) \times f(\widehat{\mathrm{GT}} | \oslash) \\
&= f\left\{ \widehat{\mathrm{CN}} \mid \searrow \right\} \times f\left\{ \widehat{\mathrm{GT}} \mid \bigcirc \right\} \\
&= \beta_{\searrow}\left\{\widehat{\mathrm{CN}}\right\} \times \beta_{\bigcirc}\left\{\widehat{\mathrm{GT}}\right\}.
\end{aligned}
$$

Vanilla HMM



More information

→ The confidence in genotype calls can differ substantially between SNPs!



Integrating confidence estimates for genotype calls

Let $S_{\widehat{GT}}$ be the confidence score for the genotype estimate.

We can estimate from Hapmap the following densities:

$$f\left\{ S_{\widehat{HOM}} \mid \widehat{HOM}, HOM \right\}, f\left\{ S_{\widehat{HOM}} \mid \widehat{HOM}, HET \right\}, f\left\{ S_{\widehat{HET}} \mid \widehat{HET}, HOM \right\}, f\left\{ S_{\widehat{HET}} \mid \widehat{HET}, HET \right\}.$$

$\longrightarrow$ Note:

$$f\left\{ S_{\widehat{HOM}} \mid \widehat{HOM}, \bigcirc \right\} \approx f\left\{ S_{\widehat{HOM}} \mid \widehat{HOM}, HOM \right\}$$

$$f\left\{ S_{\widehat{HET}} \mid \widehat{HET}, \bigcirc \right\} \approx f\left\{ S_{\widehat{HET}} \mid \widehat{HET}, HOM \right\}.$$

Emission Probabilities - Loss

Recall that

$$\begin{aligned} f(\widehat{\mathrm{CN}}, \widehat{\mathrm{GT}} | \oslash) &= f(\widehat{\mathrm{CN}} | \oslash) \times f(\widehat{\mathrm{GT}} | \oslash) \\ &= f\left\{ \widehat{\mathrm{CN}} \mid \searrow \right\} \times f\left\{ \widehat{\mathrm{GT}} \mid \bigcirc \right\} \\ &= \beta_{\searrow}\left\{\widehat{\mathrm{CN}}\right\} \times \beta_{\bigcirc}\left\{\widehat{\mathrm{GT}}\right\}. \end{aligned}$$

If the state for a particular SNP is *Loss*, we have

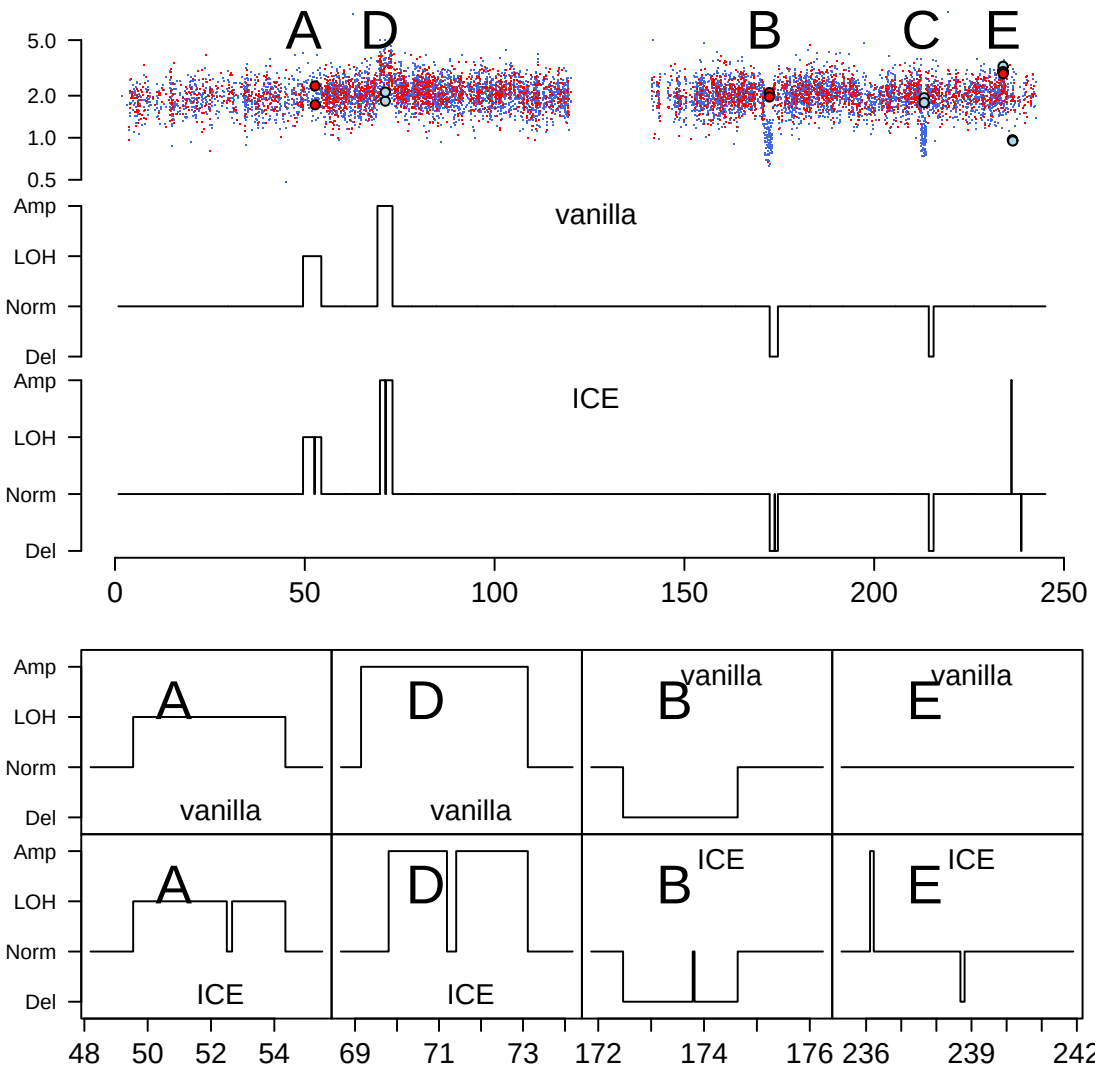
$$\beta_{\bigcirc}\left\{ \widehat{\mathrm{GT}}, \mathrm{S}_{\widehat{\mathrm{GT}}} \right\} = f\left\{ \widehat{\mathrm{GT}} \mid \bigcirc \right\} \times f\left\{ \mathrm{S}_{\widehat{\mathrm{GT}}} \mid \widehat{\mathrm{GT}}, \bigcirc \right\}.$$

Emission Probabilities - Retention

For retention, the true genotype can be HET or HOM:

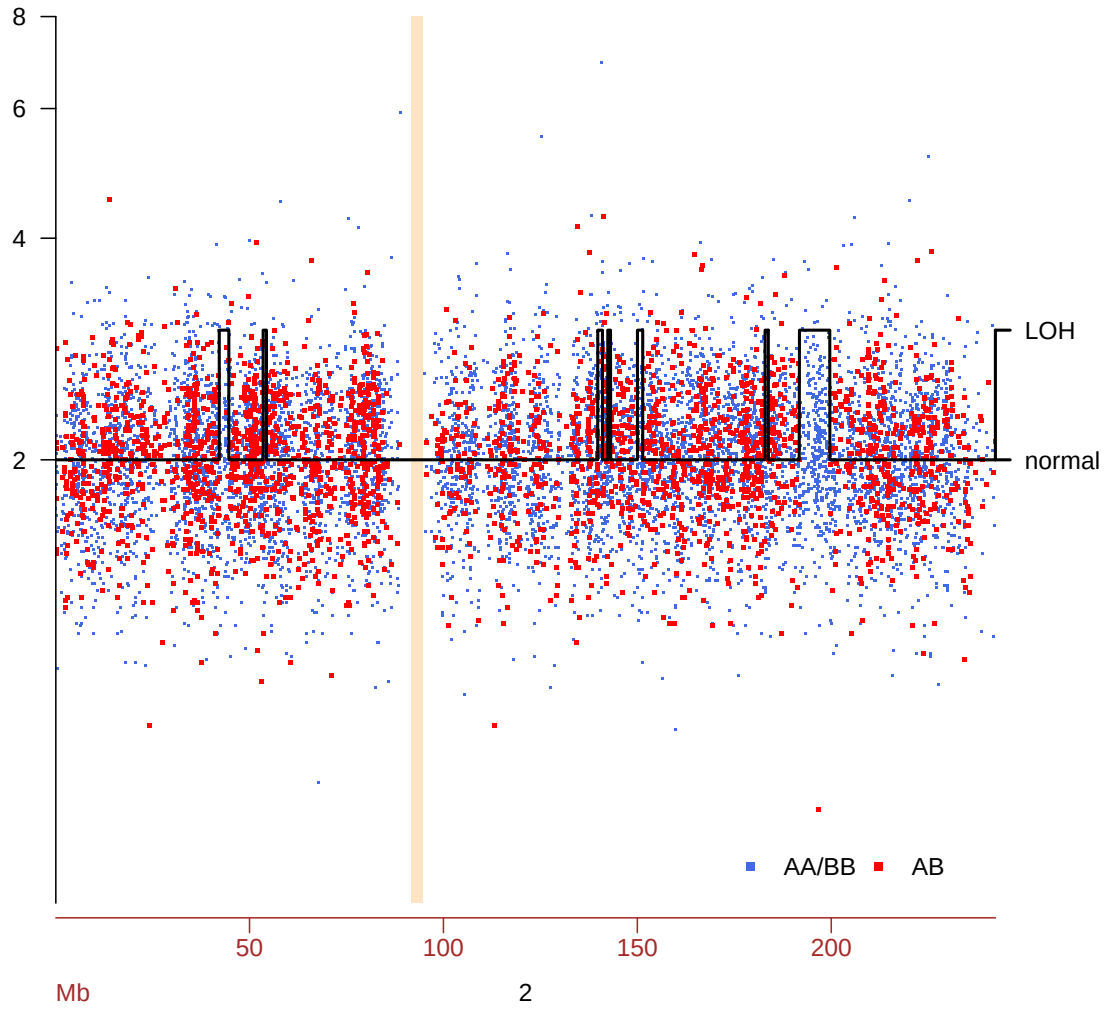
$$
\begin{aligned}
& \beta_{\textcolor{black}{\bullet}} \left\{ \widehat{\mathrm{GT}}, \mathrm{S}_{\widehat{\mathrm{GT}}} \right\} \\
= \quad & f \left\{ \widehat{\mathrm{GT}} \mid \textcolor{black}{\bullet} \right\} f \left\{ \mathrm{S}_{\widehat{\mathrm{GT}}} \mid \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} \\
= \quad & f \left\{ \widehat{\mathrm{GT}} \mid \textcolor{black}{\bullet} \right\} \left(f \left\{ \mathrm{S}_{\widehat{\mathrm{GT}}}, \mathrm{HOM} \mid \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} + f \left\{ \mathrm{S}_{\widehat{\mathrm{GT}}}, \mathrm{HET} \mid \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} \right) \\
= \quad & f \left\{ \widehat{\mathrm{GT}} \mid \textcolor{black}{\bullet} \right\} \left(f \left\{ \mathrm{S}_{\widehat{\mathrm{GT}}} \mid \mathrm{HOM}, \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} f \left\{ \mathrm{HOM} \mid \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} + f \left\{ \mathrm{S}_{\widehat{\mathrm{GT}}} \mid \mathrm{HET}, \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} f \left\{ \mathrm{HET} \mid \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} \right) \\
= \quad & f \left\{ \widehat{\mathrm{GT}} \mid \textcolor{black}{\bullet} \right\} \left(f \left\{ \mathrm{S}_{\widehat{\mathrm{GT}}} \mid \mathrm{HOM}, \widehat{\mathrm{GT}} \right\} f \left\{ \mathrm{HOM} \mid \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} + f \left\{ \mathrm{S}_{\widehat{\mathrm{GT}}} \mid \mathrm{HET}, \widehat{\mathrm{GT}} \right\} f \left\{ \mathrm{HET} \mid \widehat{\mathrm{GT}}, \textcolor{black}{\bullet} \right\} \right)
\end{aligned}
$$

Vanilla ICE comparison

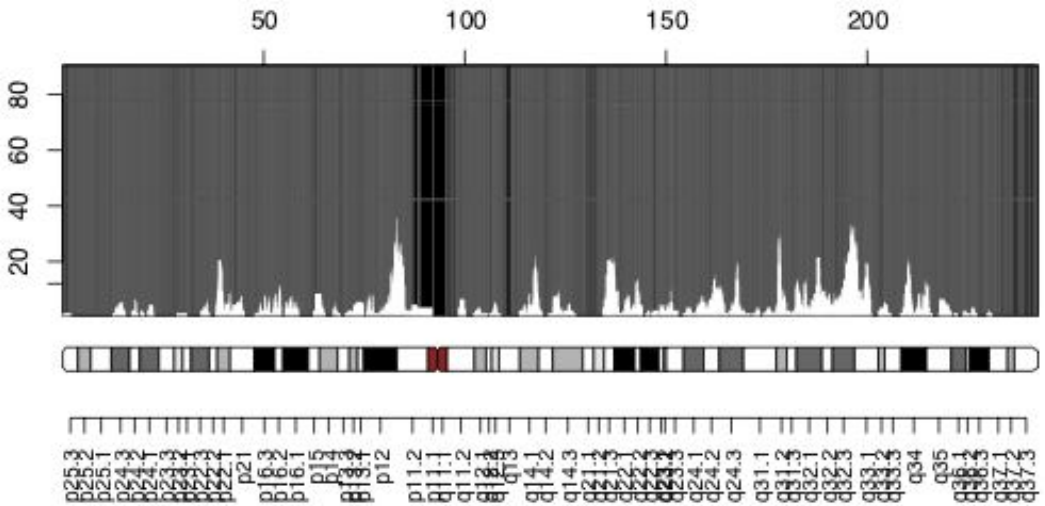


Bioconductor package: ICE

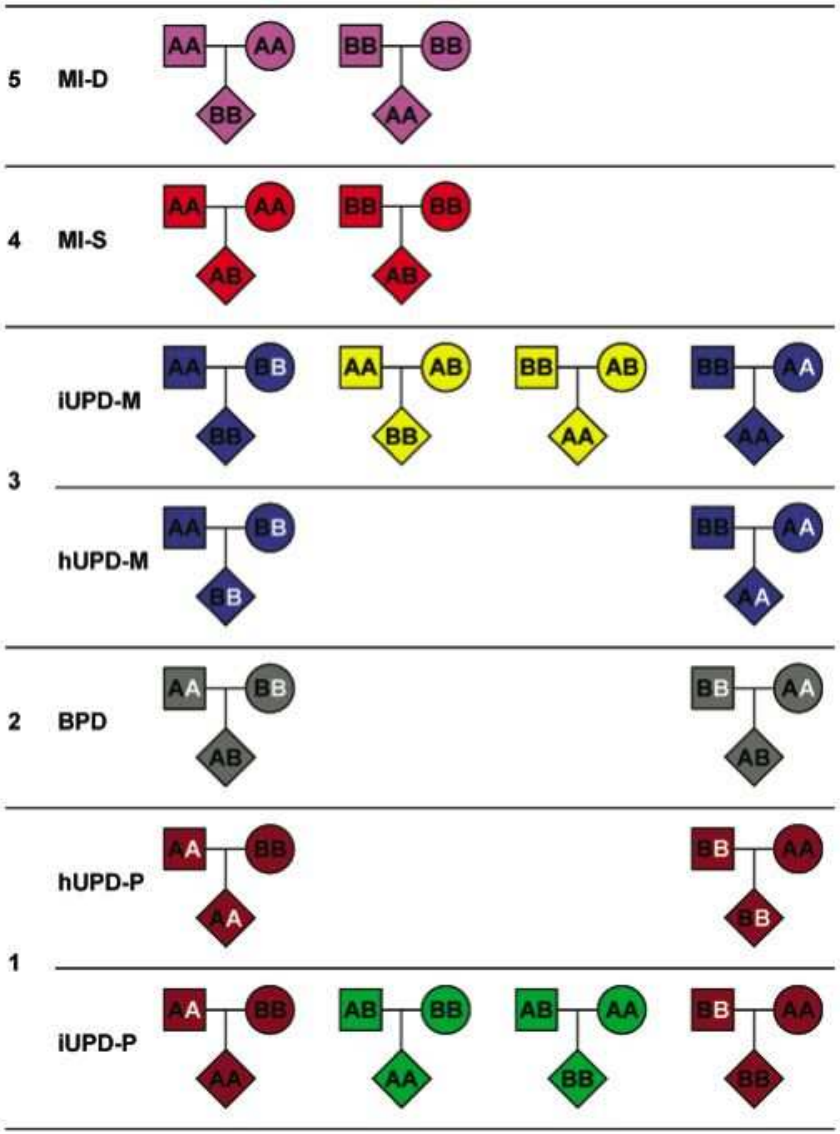
A HapMap sample



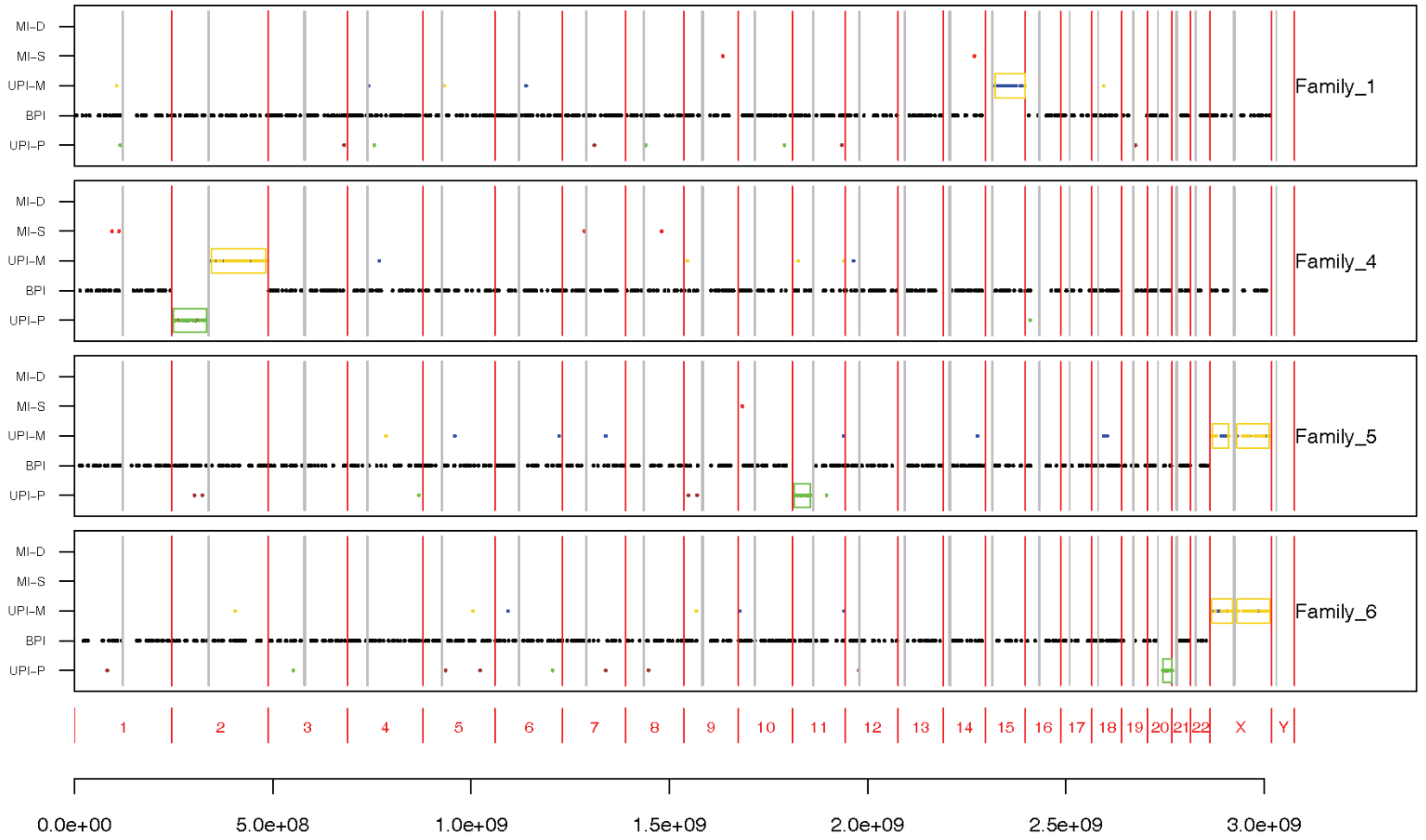
Many HapMap samples



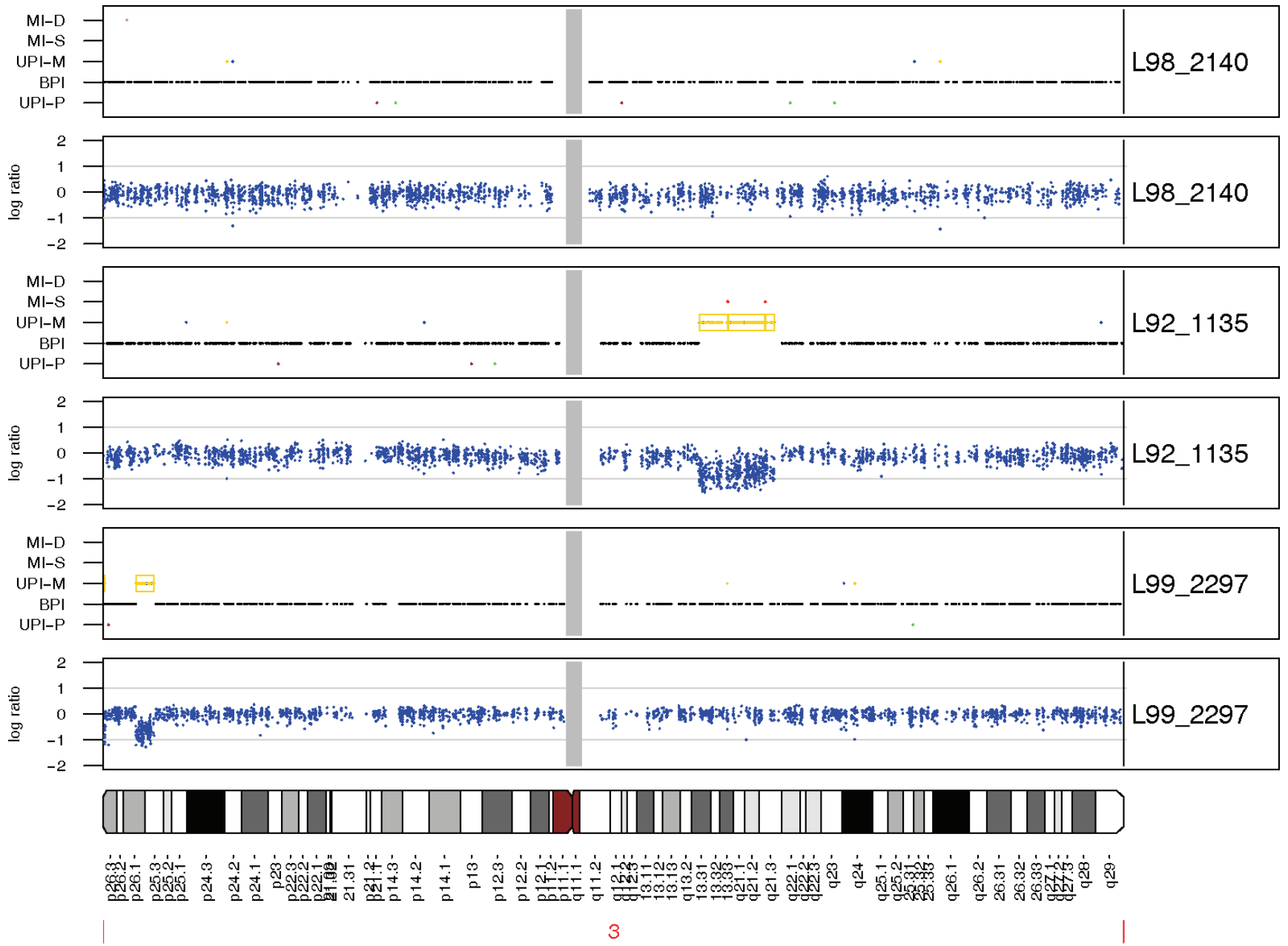
SNP Trio


5
MI-D
AA
AA
BB
BB
BB
AA
4
MI-S
AA
AA
AB
BB
BB
AB
3
iUPD-M
AA
BB
BB
AA
AB
BB
BB
AB
AA
BB
AA
AA
hUPD-M
AA
BB
BB
BB
AA
AA
2
BPD
AA
BB
AB
BB
AA
AB
1
hUPD-P
AA
BB
AA
BB
AA
BB
iUPD-P
AA
BB
AA
AB
BB
AA
AA
BB
AA
AB
BB
BB

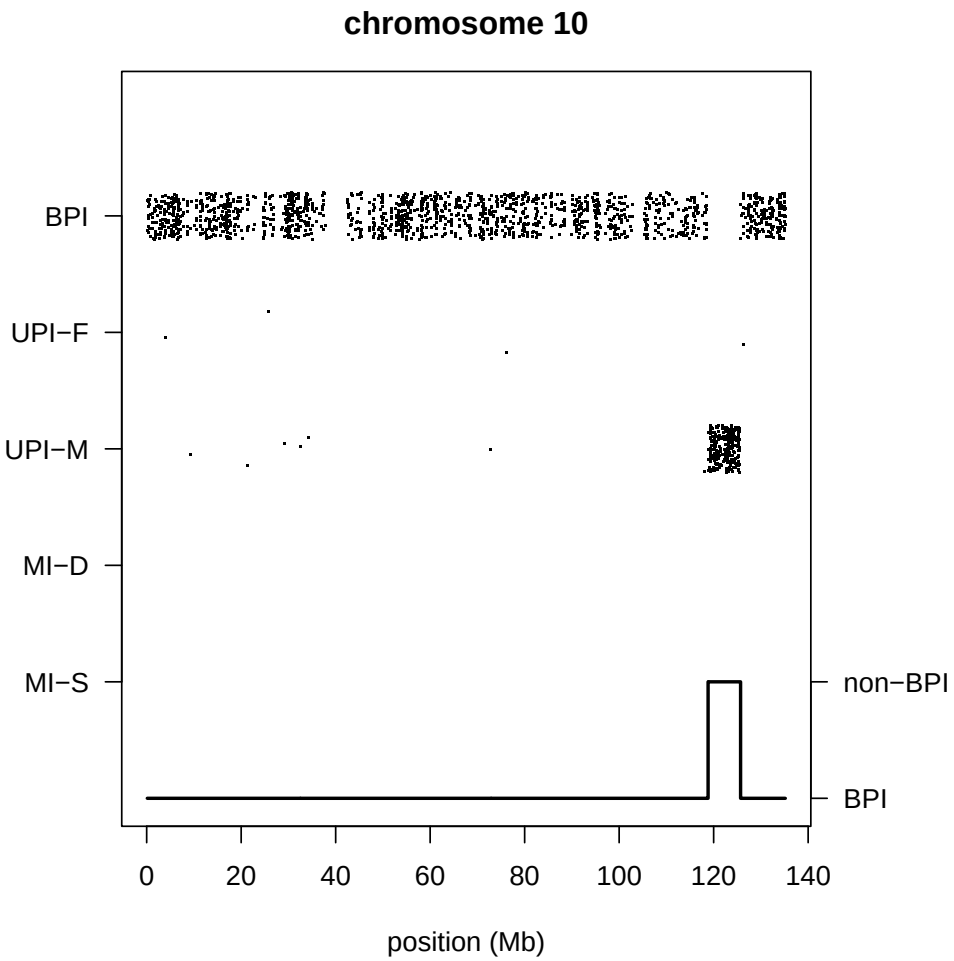
SNP Trio

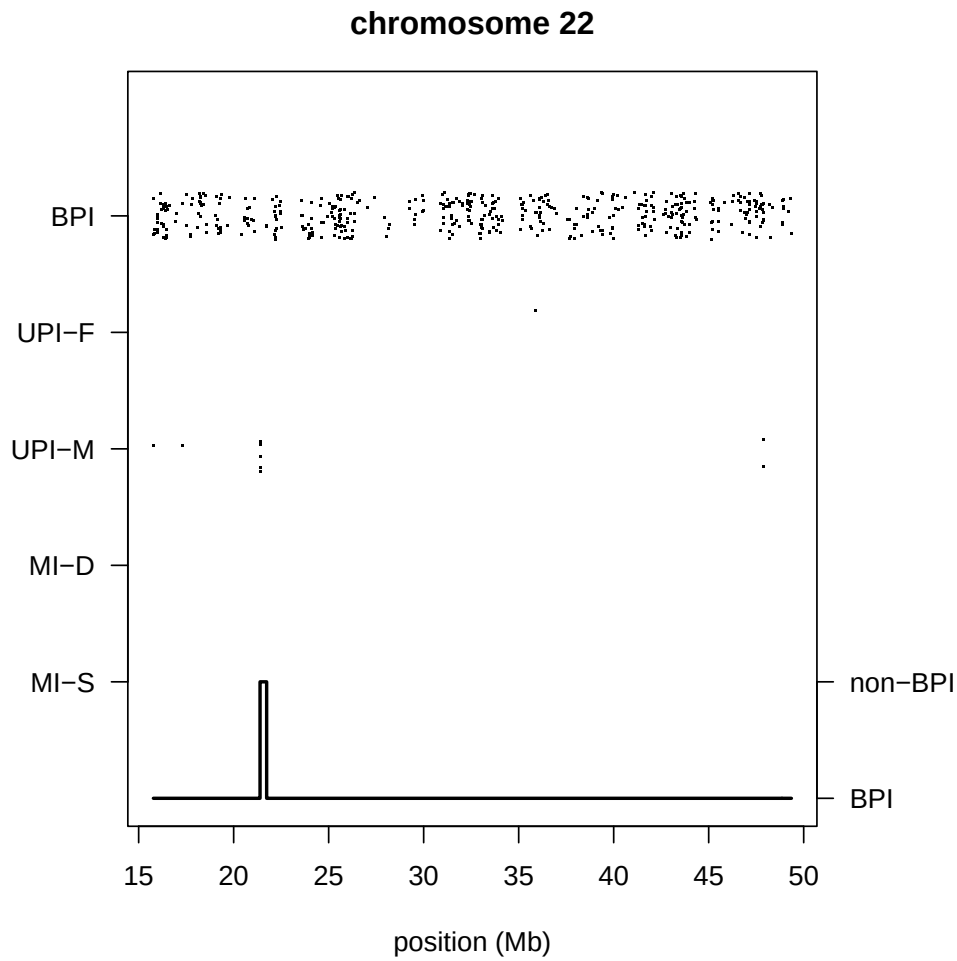

MI–D
MI–S
UPI–M
BPI
UPI–P
Family_1
Family_4
Family_5
Family_6
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y
0.0e+00
5.0e+08
1.0e+09
1.5e+09
2.0e+09
2.5e+09
3.0e+09

SNP Trio


MI–D
MI–S
UPI–M
BPI
UPI–P
L98_2140
log ratio
2
1
0
−1
−2
L98_2140
MI–D
MI–S
UPI–M
BPI
UPI–P
L92_1135
log ratio
2
1
0
−1
−2
L92_1135
MI–D
MI–S
UPI–M
BPI
UPI–P
L99_2297
log ratio
2
1
0
−1
−2
L99_2297
3

HMM for SNP Trio





Acknowledgments

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  Benilton Carvalho, Wenyi Wang
- Jonathan Pevsner

  Nate Miller, Eli Roberson, Jason Ting

References

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Exploration, normalization, and genotype calls of high-density oligonucleotide SNP array data. *Biostatistics*, 8(2):485-99.

Scharpf RB, Ting JC, Pevsner J, Ruczinski I (2007).
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Scharpf RB, Parmigiani G, Ruczinski I (2007).
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Ting JC, Ye Y, Thomas GH, Ruczinski I, Pevsner J (2006).
Analysis and visualization of chromosomal abnormalities in SNP data with SNPscan. *BMC Bioinformatics*, 7(1):25.

Ting JC, Roberson ED, Miller N, et al, Ruczinski I, Thomas GH, Pevsner J (2007).
Visualization of uniparental inheritance, Mendelian inconsistencies, deletions and parent of origin effects in single nucleotide polymorphism trio data with SNPtrio. *Human Mutation*, (in press).

Wang W, Caravalho B, Miller N, Pevsner J, Chakravarti A, Irizarry RA (2006)
Estimating genome-wide copy number using allele specific mixture models. *JHU Biostatistics Working papers*, #122.