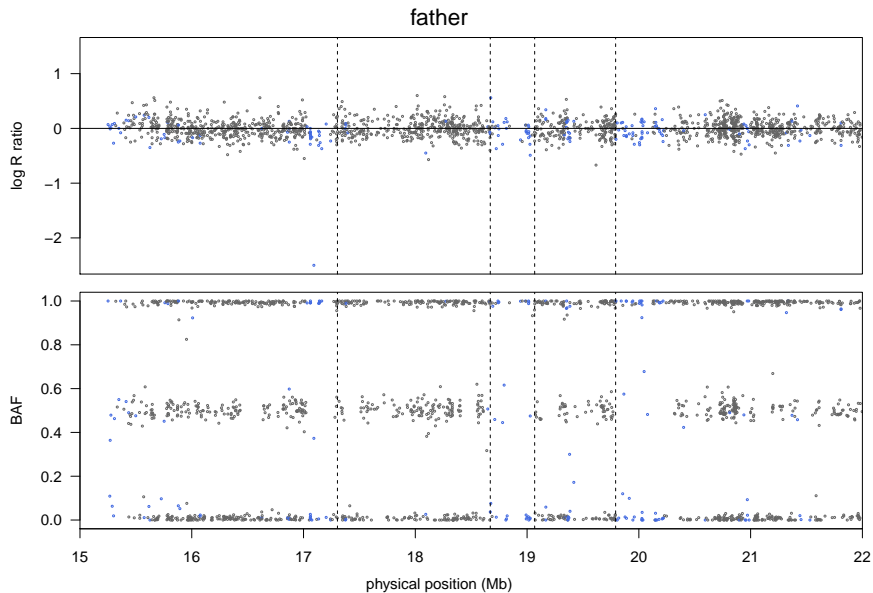


Association of De novo Copy Number Variants with Oral Clefts

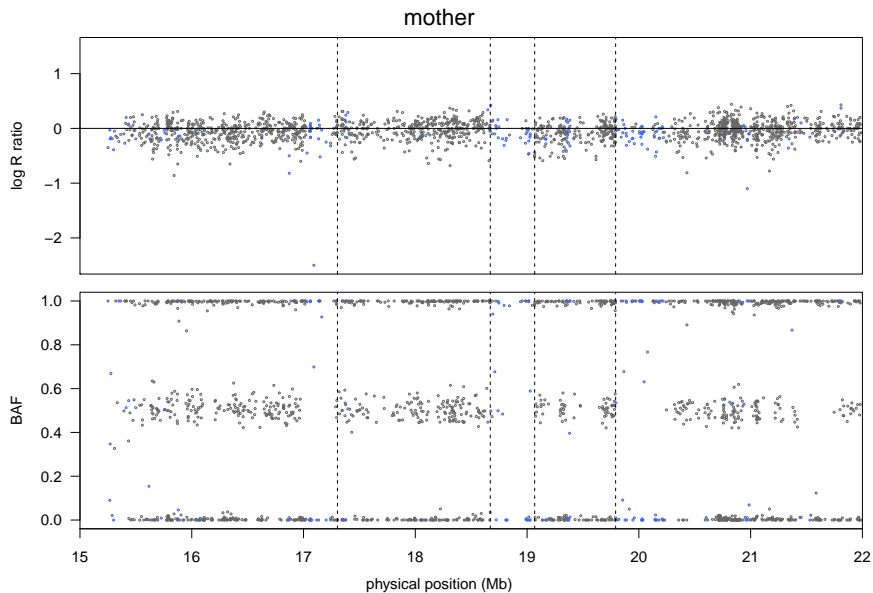
Rob Scharpf

June 25, 2012

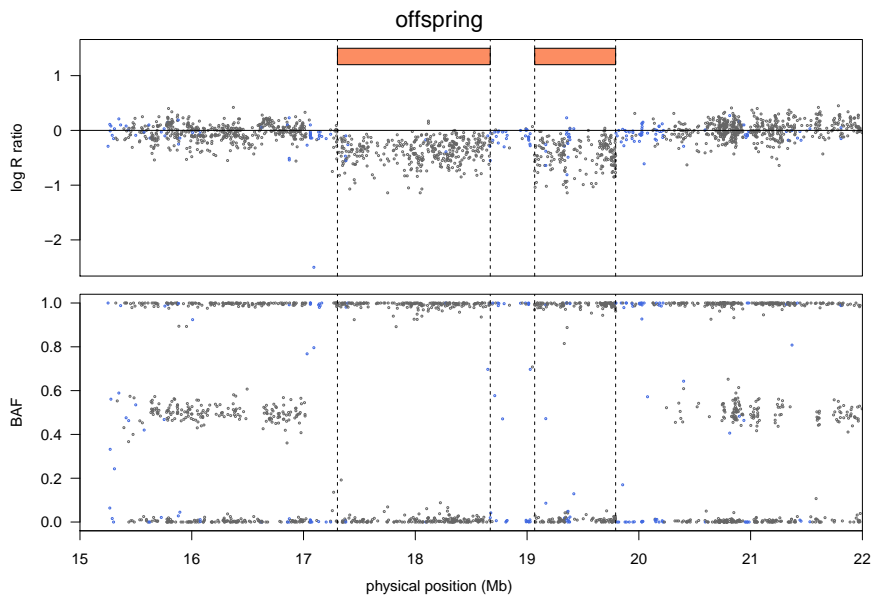
Low level data



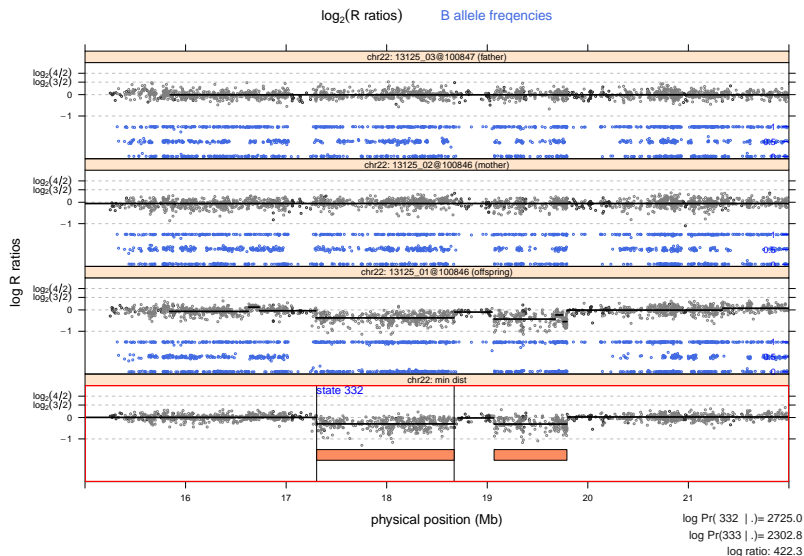
Low level data



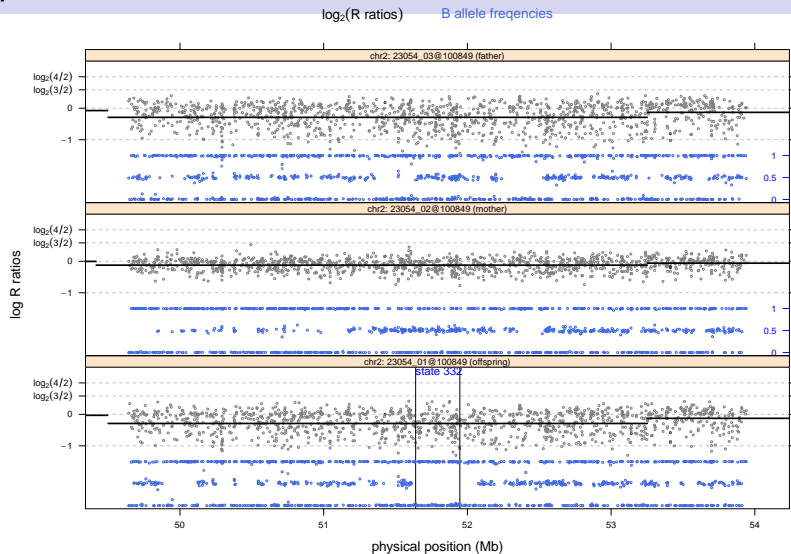
Low level data



Same data



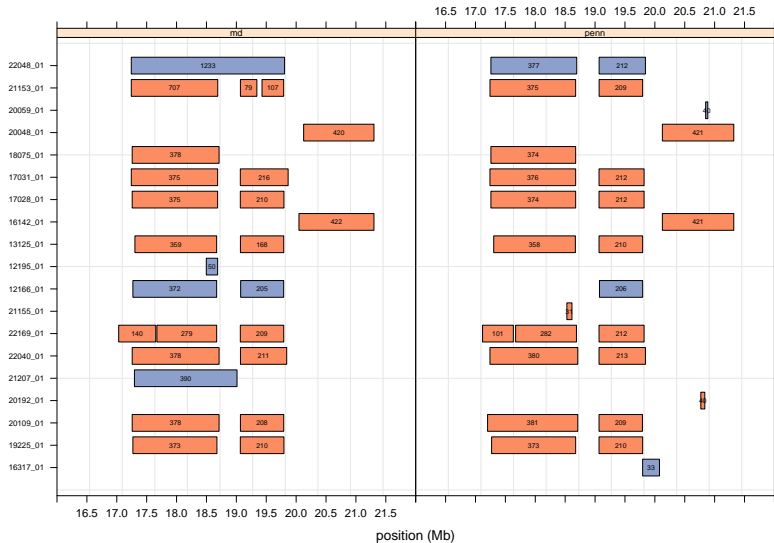
Oops!



The minimum distance

- 1 Calculate the signed, smallest absolute difference in copy number comparing parents to offspring (at each marker)
 - ▶ Removes probe-level heterogeneity due to shared biological *and* technical sources of variation
- 2 Segment the minimum distance as a function of physical position
- 3 For each minimum distance segment, calculate a posterior likelihood

Denovo CNV in the DiGeorge region



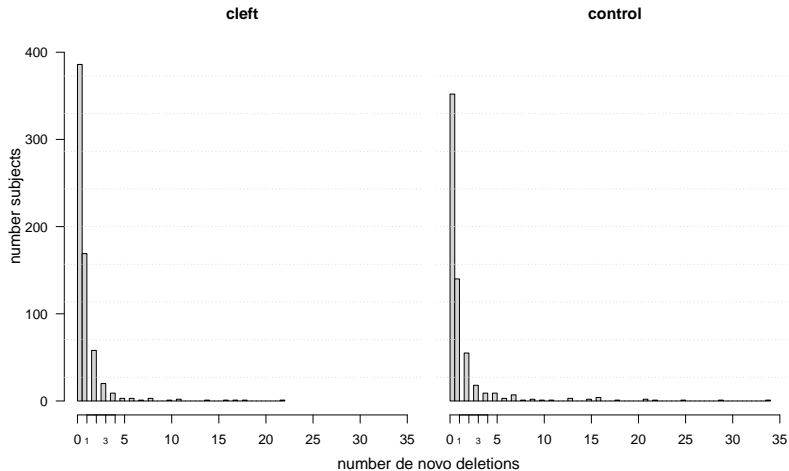
590 CPU hours for 2082 trios (versus 6420 CPU hours)

Sample size for association

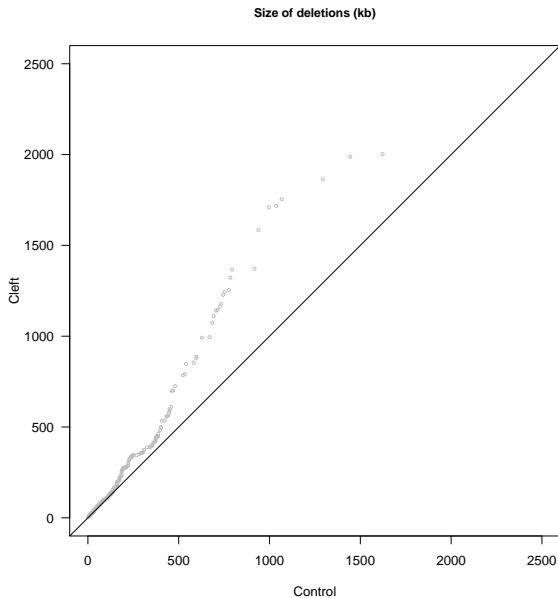
Discovery	2082	752
WGA	120	99
MAD > 0.3	212	138
non-EA	1090	-
n	660	515

- cell frequencies are the number of Father-Mother-Offspring trios
- The controls are trios with dental caries.

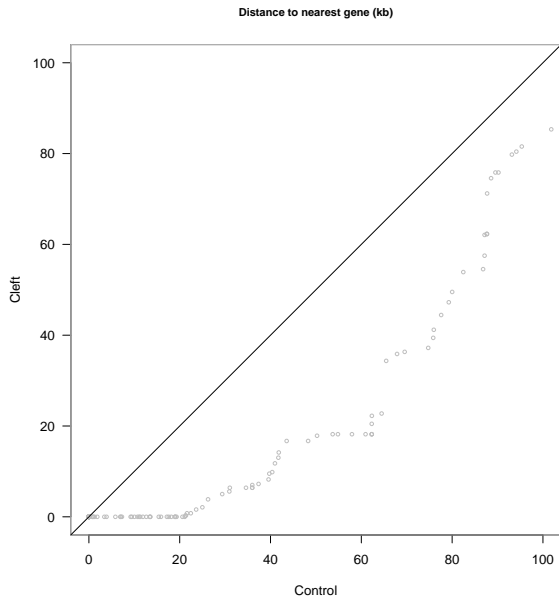
Frequency of de novo deletions



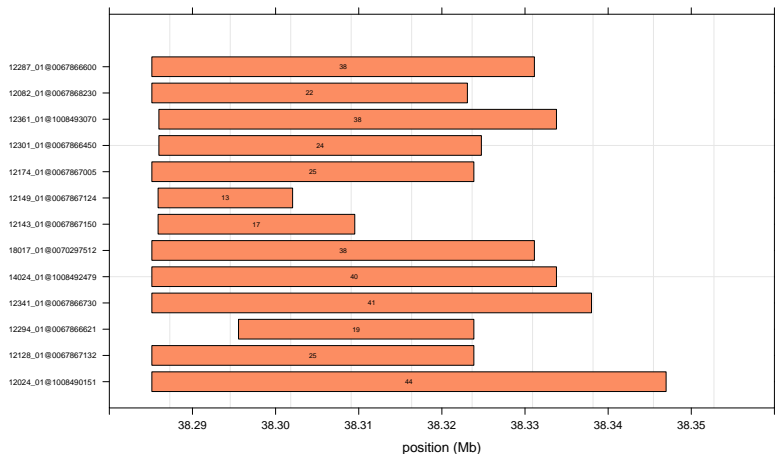
Quantile-quantile plot of deletion size



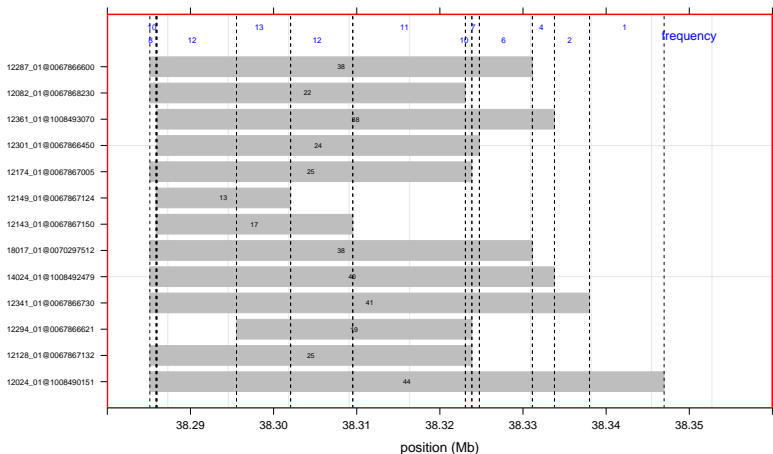
Quantile-quantile plot of distance to nearest tx site



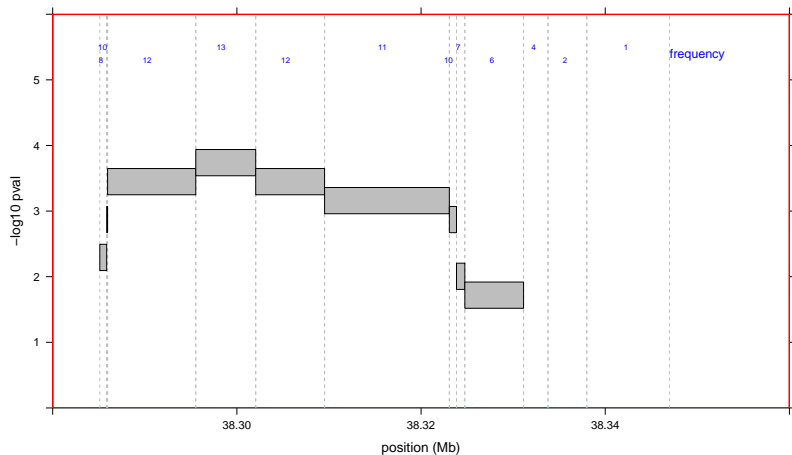
Recurrent denovo loss at chromosome 7 locus



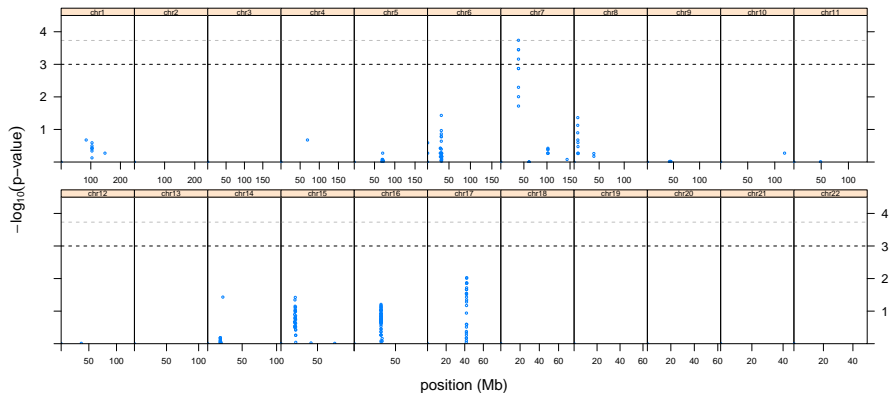
Assessing statistical significance



Assessing statistical significance

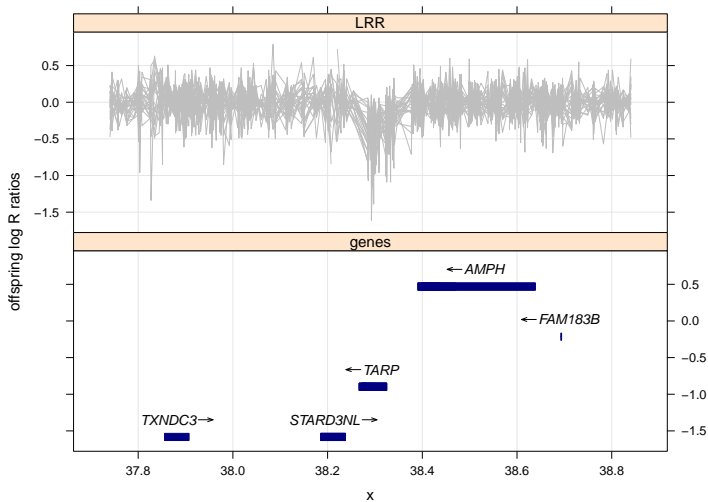


Manhattan plot for denovo CNV association

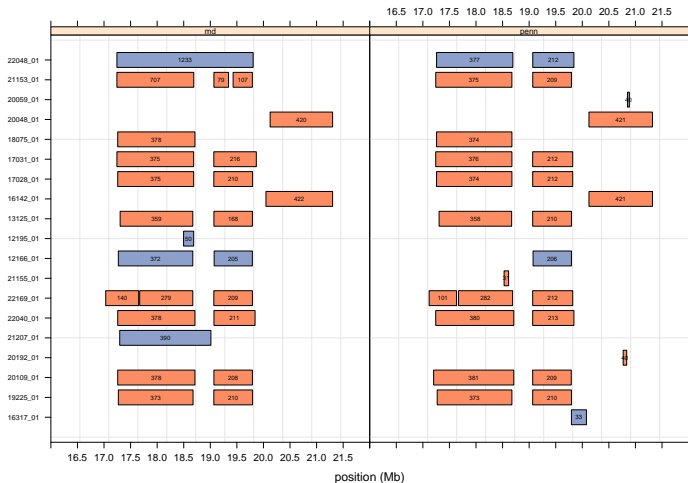


Each panel is a chromosome

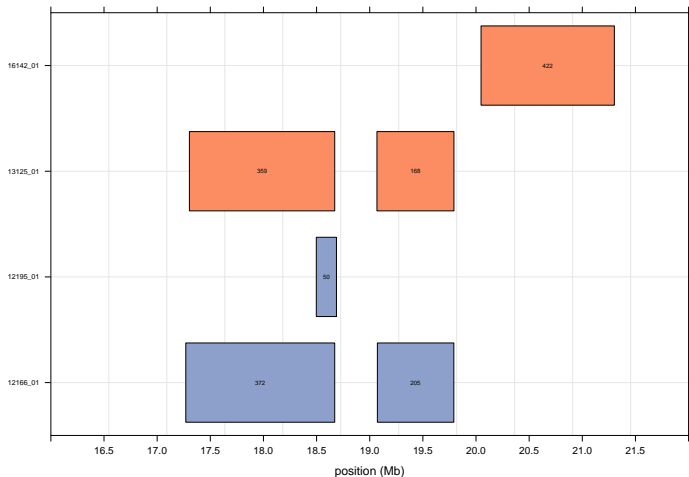
Chromosome 7



What about the DiGeorge region?



What about the DiGeorge region?



Only 2 de novo deletions among the offspring with European ancestry

- False positives are pervasive in denovo CNV discovery
- R package MinimumDistance at Bioconductor / Manuscript under review
- Oral cleft denovo CNV differ in both size and proximity to transcription start sites in comparison to controls
- Biological significance of Chr 7 locus not known
- We used a small fraction of the available oral cleft data, and only focused on denovo loss

Acknowledgements

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- Jackie Hetmanski
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