The top CNV component has the followinfg trio-states. Where '1' indicates a deletion and order is F, M, O.

```
000 001 010 011 100 101 110 111
326   3  14  35  14  32   1  20
```

```
> est.list.beaty <- lapply(binom.list.beaty, FUN = trioClasses:::get.est)
> ci.list.beaty <- lapply(binom.list.beaty, FUN = trioClasses:::get.ci)
> testable.beaty <- !is.na(ci.list.beaty)
> ci.mat.beaty <- matrix(unlist(ci.list.beaty[testable.beaty]),
      nrow = sum(testable.beaty), ncol = 2, byrow = TRUE)
> est.vec.beaty <- as(est.list.beaty, "numeric")[testable.beaty]
> gr.cnp.beaty <- cnv.beaty.obj$cmp.gr[testable.beaty]

> est.list.pitt <- lapply(binom.list.pitt, FUN = trioClasses:::get.est)
> ci.list.pitt <- lapply(binom.list.pitt, FUN = trioClasses:::get.ci)
> testable.pitt <- !is.na(ci.list.pitt)
> ci.mat.pitt <- matrix(unlist(ci.list.pitt[testable.pitt]),
      nrow = sum(testable.pitt), ncol = 2, byrow = TRUE)
> est.vec.pitt <- as(est.list.pitt, "numeric")[testable.pitt]
> gr.cnp.pitt <- cnv.pitt.obj$cmp.gr[testable.pitt]
```

The CNV components with signiifcant p-values (Bonferroni) are given below.

```
GRanges with 17 ranges and 0 metadata columns:
          seqnames                  ranges strand
             <Rle>               <IRanges>  <Rle>
  comp1883     chr7 [141435189, 141439888]      *
  comp1994     chr8 [ 39356825,  39370186]      *
  comp1995     chr8 [ 39370187,  39379683]      *
  comp1996     chr8 [ 39379684,  39393417]      *
  comp1997     chr8 [ 39393418,  39401865]      *
       ...      ...                     ...    ...
  comp2005     chr8   [39450168, 39457081]      *
  comp2006     chr8   [39457082, 39460087]      *
  comp2007     chr8   [39460088, 39469612]      *
  comp2008     chr8   [39469613, 39476658]      *
  comp2009     chr8   [39476659, 39497557]      *
  ---
  seqlengths:
          chr1   chr1_random         chr2 ...         chrY         chrM
     247249719       1663265    242951149 ...     57772954        16571
```
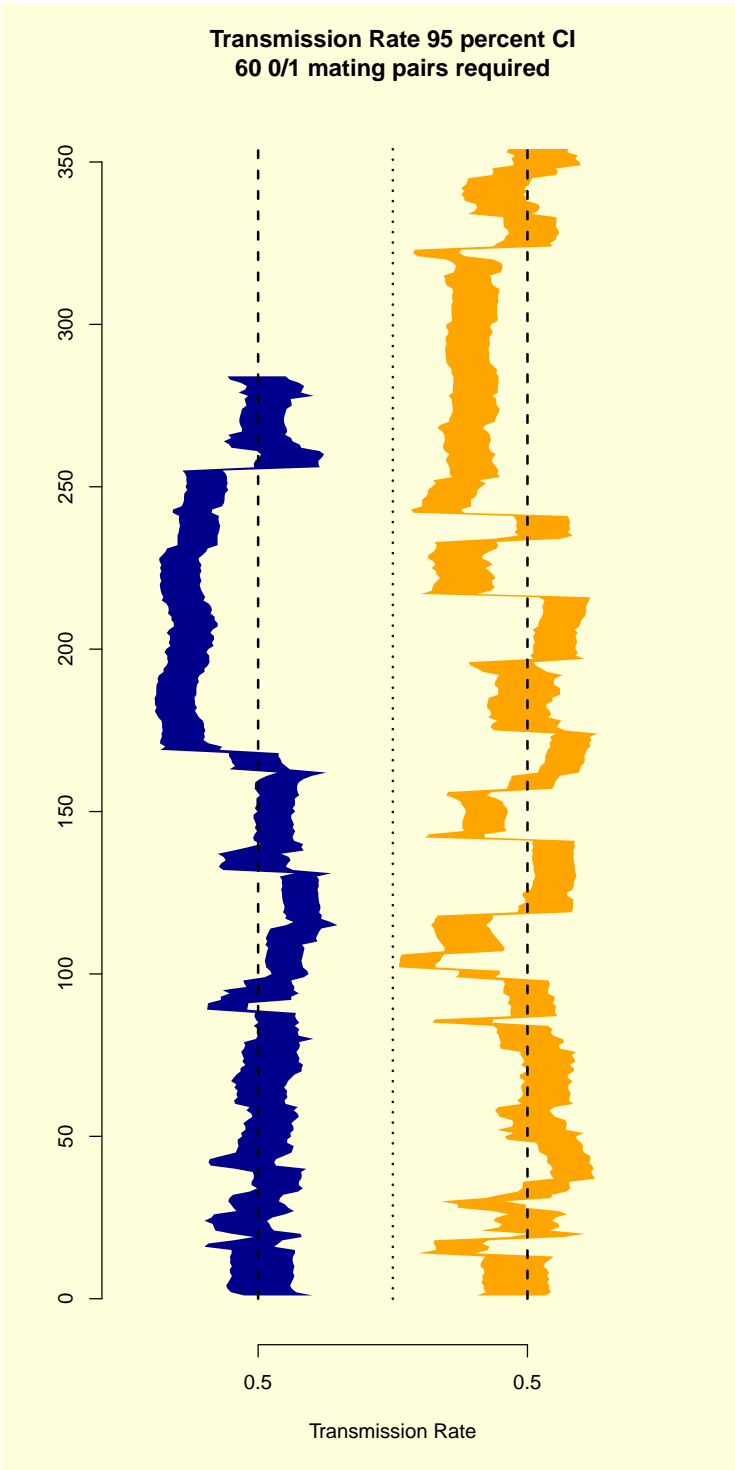
All CNV components are contiguous and the total width is 4.7 kB.

Transmission Rate 95 percent CI
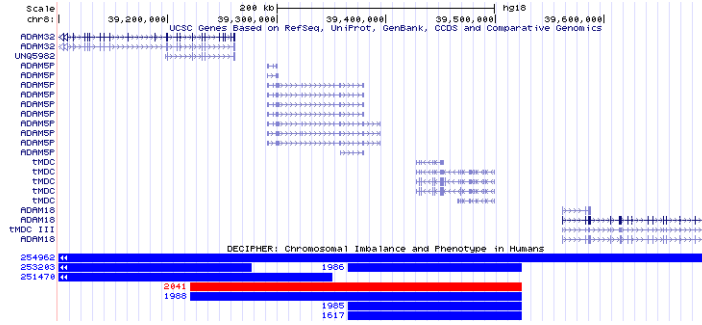**60 0/1 mating pairs required**

Transmission Rate

Figure 1: UCSC Genome Browser at chromosome 8 locus.

```
function (object)
{
    if (sum(object[c("101", "011", "100", "010")], na.rm = TRUE) >=
        60) {
        T <- sum(object[c("101", "011")], na.rm = TRUE)
        U <- sum(object[c("100", "010")], na.rm = TRUE)
        return(binom.test(x = T, n = T + U, p = 0.5, alternative = "greater")$p.value)
    }
    else {
        return(NA)
    }
}
<environment: namespace:trioClasses>

> gr.deletion.pitt <- gr.pitt[values(gr.pitt)$numsnp >= 10 &
      values(gr.pitt)$cn %in% 0:1]
> sum(countOverlaps(gr.deletion.pitt, reduce(locus)))

[1] 649
```
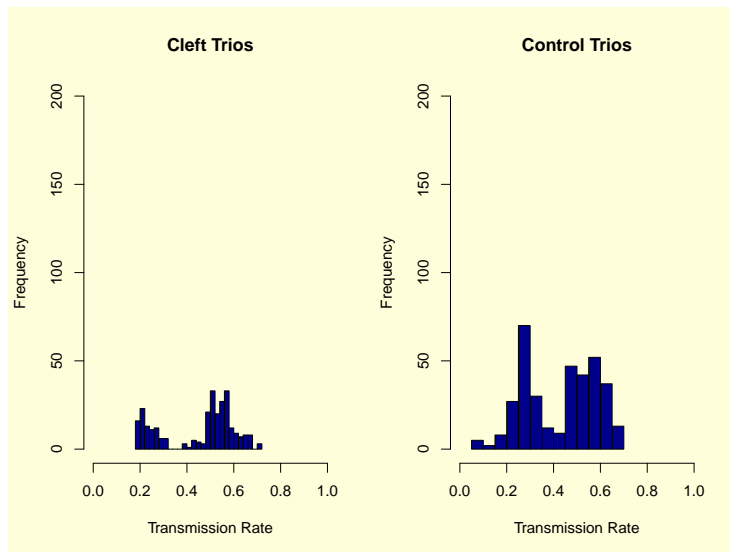
Methods

Cleft Data Description

- Performed 284 tests. Bonferroni significant locus has width 4.7 kB.

- *PennCNV* joint HMM

- european, MAD < 0.3, non-WGA, aux $\neq 1$

- coverage > 10

- 13140 hemi/homozygous deletions identified in 445 trios

3

- 4288 CNV components

    Common (> 0.01): 954

    Rare: 3334

- Construct trio-states for all CNV components

    recall that we use indicator variable for hemi/homozygous deletions

- must be at least 5 informative mating pairs

    01x and 10x

- count transmissions and perform binom.test (See "trans.tab")

```
> mean(est.vec.beaty[subjectHits(findOverlaps(reduce(locus),
    cnv.beaty.obj$cmp.gr))])

[1] NA

> mean(est.vec.pitt[subjectHits(findOverlaps(reduce(locus),
    cnv.pitt.obj$cmp.gr))])

[1] NA

> mean(-log10(trans.vec[subjectHits(findOverlaps(reduce(locus),
    cnv.beaty.obj$cmp.gr))]))
```
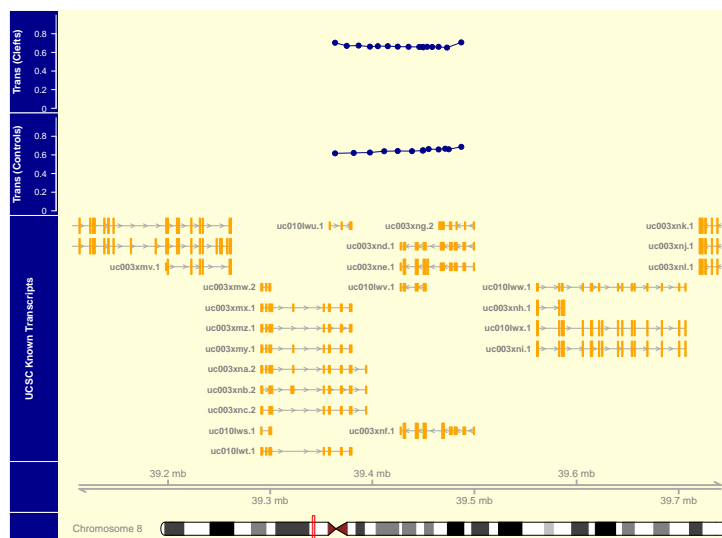
Figure 2: Cleft Trios — Red: $-\log_{10} p$-values for each CNV component that has at least **five** "0/1" mating pairs. Null hypothesis is transmission rate of $\frac{1}{2}$, and alternative hypothesis is "one-sided." Blue: The frequency of CNV component in the parents. Yellow: Gene tracks, labeled by transcript.

```
[1] 5.784253

> mean(-log10(trans.vec.pitt[subjectHits(findOverlaps(reduce(locus),
    cnv.pitt.obj$cmp.gr))])))

[1] 3.907709

> freq.pitt.vec[subjectHits(findOverlaps(reduce(locus), cnv.pitt.obj$cmp.gr))]

 comp1670  comp1820  comp1821  comp1822  comp1823  comp1824  comp1825
0.1914062 0.2675781 0.2910156 0.2929688 0.2949219 0.2988281 0.3027344
 comp1826  comp1827  comp1828  comp1829  comp1830  comp1831  comp1832
0.3027344 0.3007812 0.2890625 0.2871094 0.2792969 0.2792969 0.2617188

> freq.vec[subjectHits(findOverlaps(reduce(locus), cnv.beaty.obj$cmp.gr))]

 comp1883  comp1994  comp1995  comp1996  comp1997  comp1998  comp1999
0.1534155 0.4445689 0.4960806 0.5039194 0.5139978 0.5139978 0.5162374
 comp2000  comp2001  comp2002  comp2003  comp2004  comp2005  comp2006
0.5207167 0.5218365 0.5229563 0.5251960 0.5218365 0.5139978 0.5083987
 comp2007  comp2008  comp2009
0.4848824 0.4792833 0.4232923
```