Inherited deletions!

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Abstract

Copy number variants (CNVs) may play an important part in the development of common birth defects such as oral clefts, and individual patients with multiple birth defects (including clefts) have been shown to carry small and large chromosomal deletions. In this paper we investigate the transmission rates of deletions in cleft offspring-parent trios.

Background (from Manuscript #1)

Oral clefts are among the most common birth defects, and include three anatomical defects: cleft lip (CL); cleft lip and palate (CLP) and cleft palate (CP). Because there are similarities in embryological and epidemiological evidence, CL and CLP are often grouped together as cleft lip with/without cleft palate (CL/P), although there is debate about whether all three groups may have distinct etiologies [1, 2]. Collectively, oral clefts represent half of all craniofacial malformations and create a major public health burden for both affected children and their families. The overall prevalence of oral clefts is estimated at 1 per 700 live births worldwide, but there is dramatic variation across populations and between racial and ethnic groups, in particular for CL/P [3, 4].

Oral clefts show strong familial aggregation, and the recurrence risk among first degree relatives is approximately 32 times greater than the general population risk for CL/P, and approximately 56 times greater for CP [5]. Twin studies also suggest a major role for genes controlling risk to oral clefts with monozygotic twins showing much higher concordance rates than dizygotic twins, 31% versus 2% for CL/P, and 43% versus 7% for CP [6]. Normal development of craniofacial features is a complex process and disruption of any one of numerous steps can lead to development of oral clefts [7], further supported by mounting evidence that multiple genes, in addition to environmental influences, play a role in the etiology of oral clefts [8, 9, 10, 11, 12, 13].

Assessment of chromosomal anomalies such as microdeletions and translocations also played an important role in the identification of genes and genomic regions underlying facial disorders [14, 15, 16, 17, 18, 19, 20, 21, 22]. In particular, high throughput technologies such as CGH and SNP arrays have gained popularity in assessing chromosomal alterations [23, 24]. For example, Sivertsen et.al assessed the prevalence of duplications and deletions in the 22q11 region (DiGeorge syndrome region) in Norwegian offspring with open CP, but did not detect an association [25]. Shi et. al used SNP genotyping, DNA sequencing, high-resolution DNA microarray analysis, and long-range PCR to characterize deletions in 333 candidate genes for orofacial clefting using 2,823 samples from 725 two and three-generation families ascertained through a proband having CL/P [26]. The authors confirmed several de-novo deletions in some of these candidate genes, in particular SUMO1, TBX1, and TFAP2A, raising the possibility that genes or regulatory elements contained within deleted regions might play a role in the etiology of oral clefts. Further, high rates of Mendelian inconsistencies were observed in 11 different genes, suggesting the existence of additional micro-deletions.

Results and Discussion

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Conclusions

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Methods

Data Description

- *PennCNV* joint HMM
- european, MAD < 0.3, non-WGA, aux $\neq 1$
- coverage > 10
- 13140 hemi/homozygous deletions identified in 445 trios
- 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

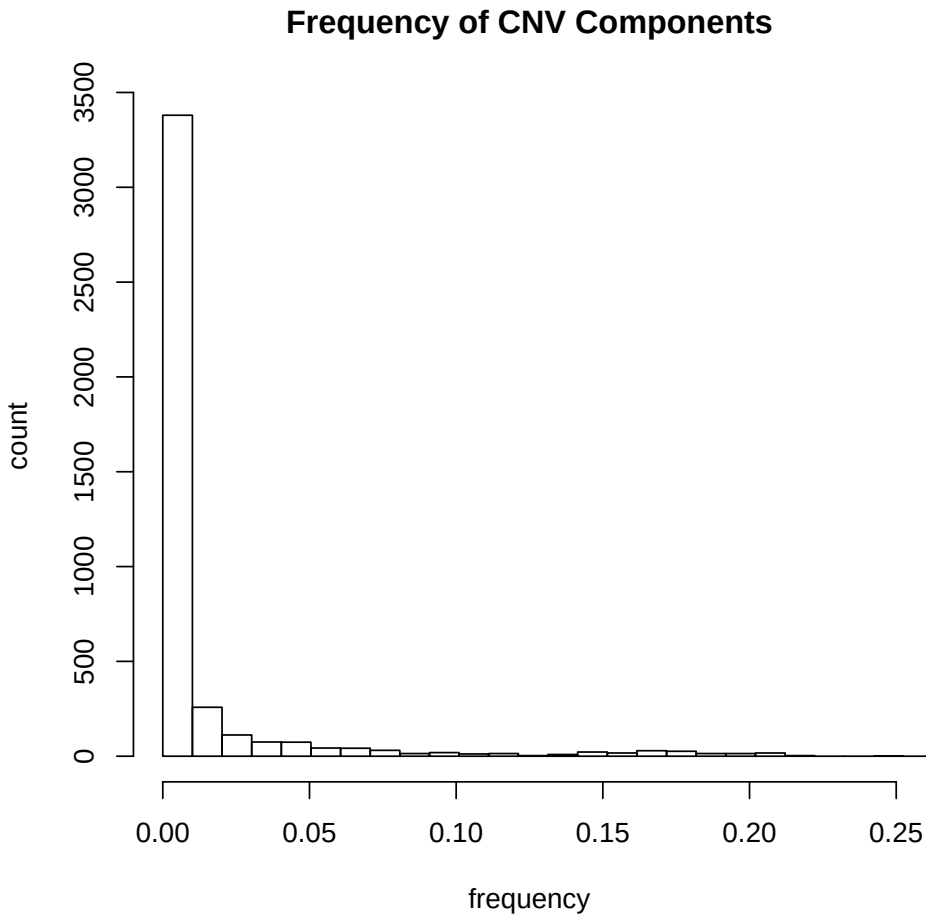
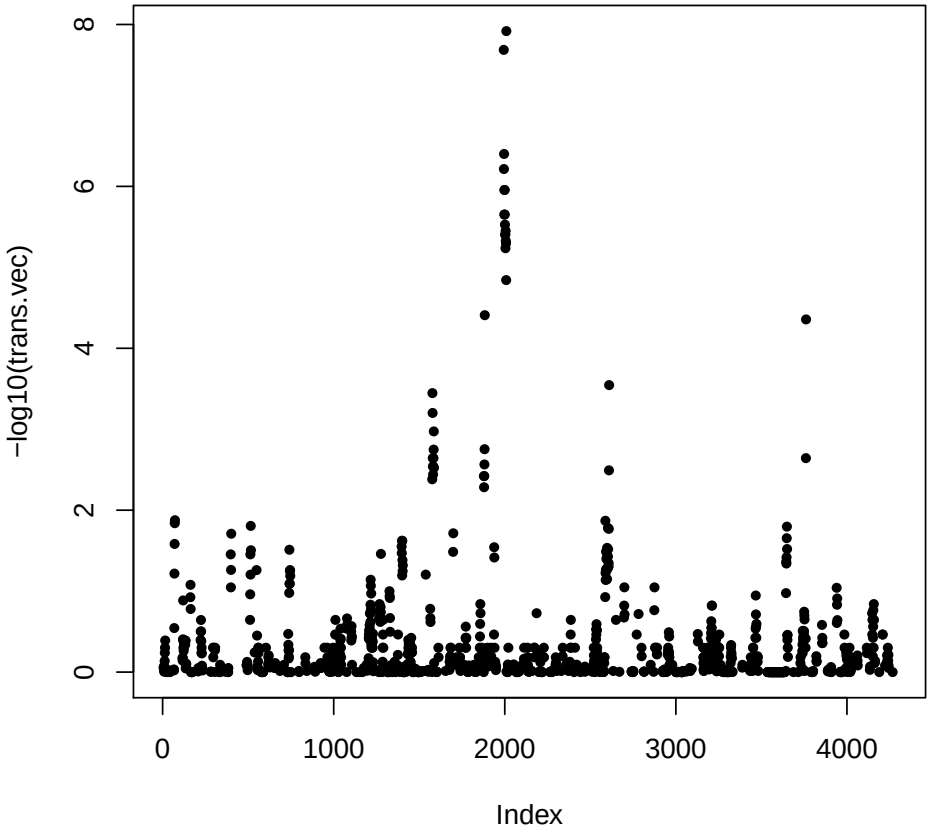


Figure 1: histogram



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

```
> summary(freq.vec)

    Min.  1st Qu.   Median
0.000000 0.001120 0.002240
    Mean  3rd Qu.     Max.
0.020640 0.007839 0.684200
```

Performed 1346 tests. Bonferroni significant locus has width 140.733 kB.

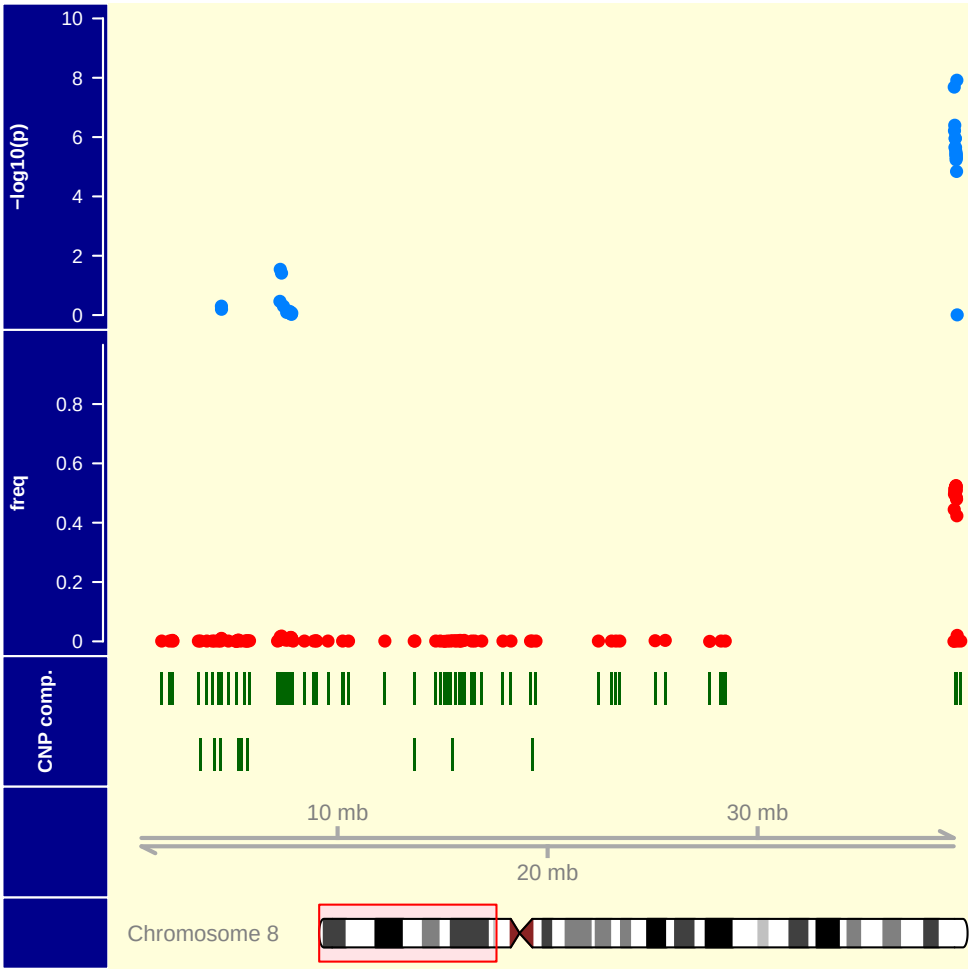


Figure 2: $-\log p$-values for Fisher's exact test (blue) for an increase in transmission rate among cleft and control groups. The transmission rate in the cleft group (red) is seen to increase around 20 MB with the $\log p$-value climbing to close to 3.

Authors contributions

Acknowledgements

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