

Abstract Title: Phenotypic 3D-organization of the human genome -inferred from the mapping of rare structural rearrangements

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Abstract: A systematic study of 406 sequence resolved balanced chromosomal rearrangements (BCR) associated with early developmental disorders (DD) and 304 control BCR carriers revealed a ~20% morbidity burden due to direct gene truncation. Enrichment of case breakpoints in specific topological associated domains (TADs) involving both known (SOX9, FOXP1) and novel (BCL11A, BCL11B) long-range-position-effect (LRPE) loci accounted for an additional 7% of the case morbidity. An excess of case breakpoints on chromosome 14 was due to breakpoint clustering within five TADs, which include one known (FOXP1) and four novel (BCL11B, LRFN5, FLRT2, GSC) candidate LRPE loci. The known LRPE-dysregulated genes are frequently embedded within large transposon-free regions and methylation free canyons/valleys and located near chromatin loop anchors. The latter explains the observed breakpoint polarity at known LRPE-loci and demonstrates that disruption of chromatin loops within specific TADs underly LRPE. We identified specific genomic features that discriminated TADs truncated by case and control breakpoints and used these features to rank TADs at risk for LRPE across the genome. The evolutionary and epigenetic features were also prevalent in the top300 ranked TADs, marking almost half of the homeobox genes in the human genome, along with many other transcription factor and key developmental genes that specify the body plan from worms to mammals. A significant excess of cases where both breakpoints truncated a predicted high-risk TAD, suggest that dual loss/gain/exchange of regulatory elements may be a common morbidity mechanism in BCRs that may likely lead to novel and potentially unique developmental disorders. Our study highlight that a continued effort to map BCRs from both affected and healthy carriers will have the power to link phenotype with genotype by disrupting the 3D-organization of these gene-poor, larger than average evolutionary conserved regulatory domains that constitute more than 20% of the human genome.

Area of expertise: Cytogenetics; balanced chromosomal rearrangements; 3D-genome organization; long-range position effects; Enhancer adoption/swapping