Neurodevelopmental copy-number variants: A roadmap to improving outcomes by uniting patient advocates, researchers, and clinicians for collective impact

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Commission on Novel Technologies for Neurodevelopmental Copy Number Variants

Summary

- Copy-number variants and structural variants (CNVs/SVs) drive many neurodevelopmental-related disorders. While many neurodevelopmental-related CNVs/SVs give rise to complex phenotypes, the overlap in phenotypic presentation between independent CNVs can be extensive and provides a motivation for shared approaches. This confluence at the level of clinical phenotype implies convergence in at least some aspects of the underlying genomic mechanisms. With this perspective, our Commission on Novel Technologies for Neurodevelopmental CNVs asserts that the time has arrived to approach neurodevelopmental-related CNVs/SVs as a class of disorders that can be identified, investigated, and treated on the basis of shared mechanisms and/or pathways (e.g., molecular, neurological, or developmental).

- To identify common etiologic mechanisms among uncommon neurodevelopmental-related disorders and to potentially identify common therapies, it is paramount for interdisciplinary teams of scientists, clinicians, and patients to unite their efforts to help expedite therapeutic outcomes.

CNVs: Shared Stories, Common Challenges: The Patients behind the genes

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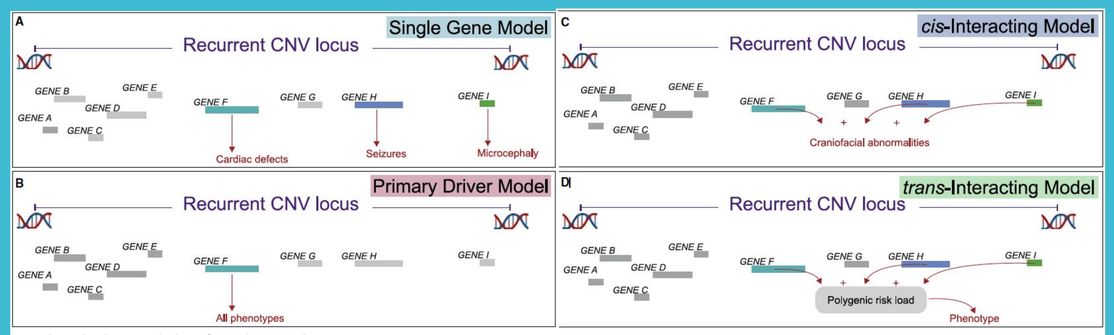
- CNVs are a major cause for NDD and birth defects ~10%
- CNVs are an under-investigated group with shared phenotypes
- "Modeling and potential therapeutics are likely common to many if not all CNV's"
  - Anthony Wynshaw-Boris



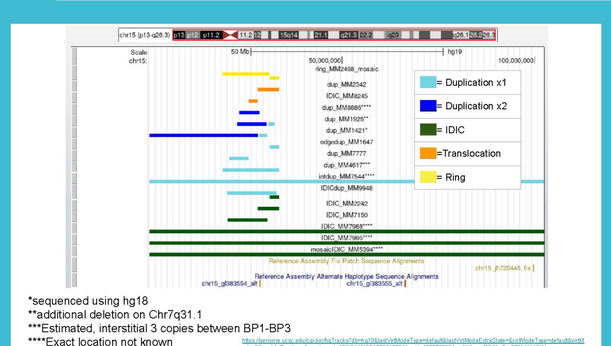
Mechanistic models of pathogenic CNVs

(A) Primary driver model: dosage sensitivity of a gene or genes encompassed within the CNV is the leading hypothesis underlying CNV pathogenicity. In the simplest scenario, altered dosage of a single gene may contribute to all or many phenotypes. For example, in 22q13 (Phelan-McDermid)18 and 15q11 (Angelman syndrome),19 the majority of defects seem to be due to haploinsufficiency of SHANK320 and UBE3A, respectively. Emerging data from a systematic approach testing constraints on haploinsufficiency and triplosensitivity across the genome suggests that the phenotypes associated with roughly 1/3 of recurrent CNVs are produced by a single primary driver gene.21

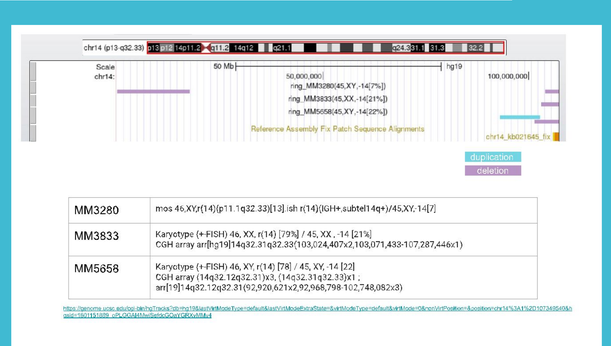
(B) Multiple driver model: one or more genes at a CNV locus are each responsible for discrete phenotypes. For example, in Williams syndrome (7q11.23Del), LIMK1 is proposed to be responsible for visuospatial deficits whereas ELN has been linked to cardiovascular phenotypes. 22,23 Importantly, in both this paradigm and the primary driver model, restoration of expression levels of only one gene should be sufficient to ameliorate acute phenotypes.

(C) Cis-interaction model: haploinsufficiency of multiple genes within a CNV locus may be required to produce a single given phenotype ("cis-interaction model").24 This seems to be the case at 16p11.2, where multiple genes are involved in craniofacial abnormalities. 35

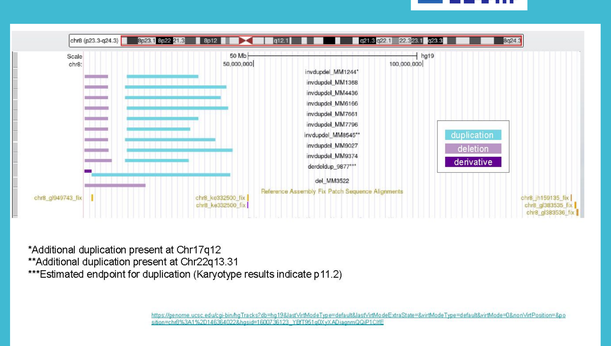
(D) Trans-interaction model: a fourth possibility is trans-interaction. In one scenario, trans-interactions could imply that phenotypes associated with a CNV only emerge in specific genetic backgrounds, most likely because of polygenic risk load or the presence of secondary rare disruptive gene variants.25 This scenario is observed in some cases of inherited CNVs where the full phenotype is not expressed and can even go undetected in the parent carrier. In another scenario, the change in dosage or arrangement of a gene regulatory element within the CNV locus impacts the expression of genes outside the locus. In this case, the manifestation of phenotypes is not dependent on a change in the dosage of a protein-coding gene. This model may explain ring chromosome or complex inversions and deletions/duplications found on chromosome 8p. These four models are not mutually exclusive, and it is likely that complex interactions are a feature of many CNVs that show variable phenotypic expressivity.



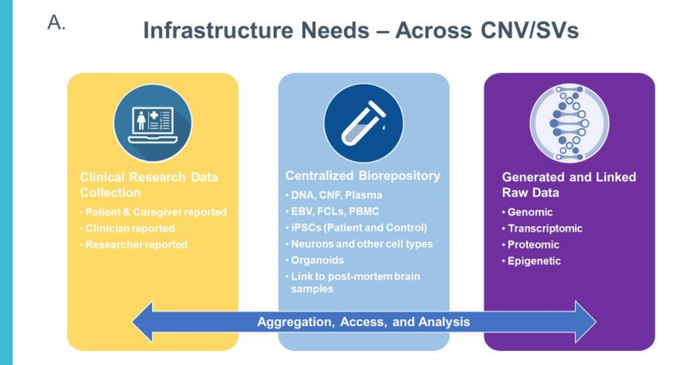
*sequenced using hg18
**additional deletion on Chr7q31.1
***Estimated, interstitial 3 copies between BP1-BP3
****Exact location not known



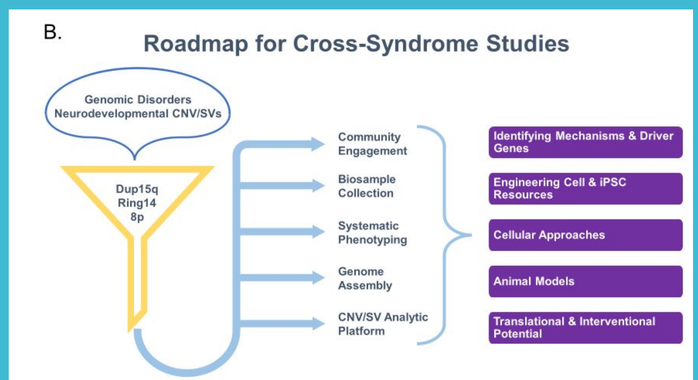
MM3280	mos 46,XY,r(14)(p11.1q32.33)[13].ish r(14)(IGH+,subtel14q+)/45,XY,-14[7]
MM3833	Karyotype (+FISH) 46, XX, r(14) [79%] / 45, XX, -14 [21%] CGH array arr[hg19]14q32.31q32.33(103,024,407x2,103,071,433-107,287,446x1)
MM5858	Karyotype (+FISH) 46, XY, r(14) [78] / 45, XY, -14 [22] CGH array (14q32.12q32.31)x3, (14q32.31q32.33)x1 ; arr[19]14q32.12q32.31(92,920,621x2,92,968,798-102,748,082x3)



*Additional duplication present at Chr17q12
**Additional duplication present at Chr22q13.31
***Estimated endpoint for duplication (Karyotype results indicate p11.2)



Shared infrastructure and roadmap to facilitate cross-syndrome studies and support aggregation, access, and analysis of shared data through open access.



Research roadmap to translation for neurodevelopmental-related CNVs/SVs starting with three distinct yet similar CNVs/SVs (dup15q, 8p, and ring 14). Abbreviations include EBV (Epstein-Barr virus DNA), FCLs (fibroblast cell lines), and PBMCs (peripheral blood mononuclear cells).

Please see for a full list of references

Conclusions

- CNVs/SVs Impose a significant burden on affected individual.
- We believe that the time is ripe to investigate CNVs with the same urgency used to analyze single-gene disorders. Unfortunately, funding agencies have not yet prioritized such studies.
- In this perspective, the CNV Commission provides a roadmap for cross-disorder CNV/SV research while keeping the patient voice at the center by supporting dynamic relationships between researchers and the patient/family community.
- As more stakeholders engage, a major goal should be to define knowledge and resource gaps, share the latest research, and identify a shared approach motivated by focusing on the convergence of clinical phenotypes.
- This roadmap provides a strategic direction to address neurodevelopmental-related CNVs/SVs (as exemplified by dup15q, 8p, and ring 14) but with tools and methods that encourage expansion to all other CNV disorders.
- In addition, we have created critical infrastructure (neurogenetics data platform, biorepository, and a CNV/SV portal) that is scalable, interoperable, and provides value for patients, families, clinicians, and researchers.
- Converging molecular pathways underlying diverse CNVs/SVs may suggest common solutions or therapies with broader impact for more than one CNV/SV. Recent advances in genome engineering, sophisticated in vitro and animal-based disease modeling, and clinical phenotyping protocols can help address these syndromes.
- The CNV Commission hopes to inspire and enable more collaborative, synergistic team-science approaches to CNV/SV research that will ultimately improve the health and well-being of patients and their

Open Data and Samples are Available!

- Large biosample collection of family trios/quads and iPSC models
- Systematic phenotyping with patient-reported and clinically observed
- WGS, RNAseq, and DNA methylation raw data

Consortia Members

- The members of The Commission on Novel Technologies or Neurodevelopmental Copy Number Variants are Elizabeth Buttermore, Stormy Chamberlain, Jannine Cody, Gregory Costain, Louis Dang, Andrew DeWoody, Yssa DeWoody, Kira Dies, Evan Eichler, Santhosh Girirajan, Marie Gramm, Alycia Halladay, Dennis Lal, Matthew Lalli, Tess Levy, Glennis Logsdon, Daniel Lowenstein, Heather Mefford, Jennifer Mulle, Alysson Muotri, Melissa Murphy, Eduardo Perez Palma, Stefan Pinter, Rebecca Pollak, Ryan Purcell, Rodney Samaco, Bina Shah*, Karun Singh, Joyce So, Maria Sundberg, Surabi Veeraragavan, Vanessa Vogel- Farley, and Anthony Wynshaw-Boris.