Complexities in the neurodevelopmental presentation and psychiatric management of a child with multiple inherited chromosomal abnormalities

Amandeep Jutla, MD[1], Ashley M. Smith, Ph.D[2], Stephen Sai Folmsbee, Ph.D[1]

[1]Department of Psychiatry & Behavioral Sciences, Northwestern University Feinberg School of Medicine;
[2]Department of Psychology, University of California, Los Angeles

Northwestern Medicine®
Feinberg School of Medicine

Background

- Copy number variations (CNVs) are genetic deletions and duplications that involve at least 50 nucleobase pairs[1].
- Once thought rare, they have in recent years been recognized as the most common cause of structural variation in the human genome[2,3].
- As associations have repeatedly been found between specific CNVs and atypical neurodevelopmental phenotypes[4,5], chromosomal microarray-based CNV analysis is considered standard-of-care for all children with unexplained developmental delay[6].
- Chromosomal microarray results can, however, be difficult to interpret in the clinical setting. CNV risks often overlap and cross traditional diagnostic boundaries[7].
- Testing may also identify "variants of unknown significance": CNVs that, because they do not have an established relationship with pathology, could be incidental findings in a developmentally delayed youth[8].
- We describe the case of a youth with inherited CNVs affecting three chromosomes.
- A neurodevelopmental phenotype associated with this combination of CNVs has not, to our knowledge, previously been described.
- Our case illustrates challenges in interpretation of genetic testing, caregiver psychoeducation, and clinical treatment particular to youth with variants of unknown significance.

1. Zarrei M, MacDonald JR, Merico D, Scherer SW. A copy number variation map of the human genome. *Nat Rev Genet*. 2015;16(3):172-183.
2. Iafrate AJ, Feuk L, Rivera MN, et al. Detection of large-scale variation in the human genome. *Nat Genet*. 2004;36(9):949-951.
3. Freeman JL, Perry GH, Feuk L, et al. Copy number variation: New insights in genome diversity. *Genome Res*. 2006;16(8):949-961.
4. Torres F, Barbosa M, Maciel P. Recurrent copy number variations as risk factors for neurodevelopmental disorders: Critical overview and analysis of clinical implications. *J Med Genet*. 2016;53(2):73-90.
5. Takumi T, Tamada K. CNV biology in neurodevelopmental disorders. *Curr Opin in Neurobiol*. 2018;48:183-192.
6. Muhle RA, Reed HE, Vo LC, et al. Clinical diagnostic genetic testing for individuals with developmental disorders. *J Am Acad Child Adolesc Psychiatry*. 2017;56(11):910-913.
7. Kim YS, State MW. Recent challenges to the psychiatric diagnostic nosology: A focus on the genetics and genomics of neurodevelopmental disorders. *Int J Epidemiol*. 2014;43(2):465-475.
8. Tsuchiya KD, Shaffer LG, Aradhya S, et al. Variability in interpreting and reporting copy number changes detected by array-based technology in clinical laboratories. *Genet Med*. 2009;11(12):866-873.
9. Sagar A, Bishop JR, Tessman DC, Guter S, Martin CL, Cook EH. Co-occurrence of autism, childhood psychosis, and intellectual disability associated with a de novo 3q29 microdeletion. *Am J Med Genet*. 2013;161(4):845-849.
10. Saviouk V, Hottenga J-J, Slagboom EP, et al. ADHD in Dutch adults: Heritability and linkage study. *Am J Med Genet B Neuropsychiatr Genet*. 2011;156(3):352-362.
11. Quintela I, Eirís J, Gómez-Lado C, et al. Copy number variation analysis of patients with intellectual disability from North-West Spain. *Gene*. 2017;626:189-199.
12. Grayton HM, Fernandes C, Rujescu D, Collier DA. Copy number variations in neurodevelopmental disorders. *Prog Neurobiol.* 2012;99(1):81-91.
13. Constantino JN. Deconstructing autism: From unitary syndrome to contributory developmental endophenotypes. *Int Rev Psychiatry*. 2018;0(0):1-7.

Case

- "E." was a 12-¬year-¬old girl referred to a day treatment program for management of aggressive behavior manifesting both at home and at school.
- E.'s mother was her primary caregiver, as her parents had separated when she was 7.
- At program admission, E. carried diagnoses of attention-deficit/hyperactivity disorder, oppositional defiant disorder, and intellectual disability (with a full-scale IQ of 57).
- E.'s mother understood her to have "genetic abnormalities" that she "got from her father."
- Review of prior chromosomal microarray testing showed three CNVs: a 2.2 million base pair (megabase, or Mb) interstitial deletion of 2p25.1, a 2.7 Mb duplication of 3q29, and a 1.7 Mb deletion of 5p15.33. All were classified in E.'s case as variants of unknown significance.
- Review of parental testing showed that E.'s father, but not her mother, shared these CNVs. Father's history of neuropsychiatric symptoms was unknown.
- E.'s mother did not share these genetic variants, but described a personal history of "learning disabilities" and in family sessions was observed to have apparent cognitive imitations, as evidenced by concrete thinking and easy distractibility.
- On physical exam, E. had dysmorphic facies, microcephaly, astigmatism, oculomotor apraxia, and short digits bilaterally.
- On mental status exam, she was well-related but impulsive, irritable, and with limited distress tolerance. Reportedly her behavioral issues had begun in early childhood, and had improved only partially with stimulant medication.
- Given pharmacotherapy's limitations, the focus of treatment was on psychoeducation and behavioral parenting strategies. Both proved challenging given mother's apparent cognitive limitations.
- At discharge, mother reported having a more nuanced understanding of the role her inherited CNVs may have played in her behavior.

Conclusions

- The diversity of behavioral phenotypes across genetic syndromes represent a challenge in psychiatric diagnosis and treatment. Although E met descriptive diagnostic criteria for ADHD, ODD and intellectual disability, awareness of E.'s underlying CNVs contributed to our understanding of her presentation and informed our work with her mother.
- 3q29 deletion has been associated with intellectual disability and microcephaly[9], 2p25.1 CNVs are thought to be associated with ADHD symptoms[10], and 5p15.33 is associated with autism spectrum disorder and more generally developmental delay[11].
- It should equally be noted that de novo CNVs are more often associated with disease than those that are inherited[12]. It may therefore be that E.'s inherited CNVs raised her "background" risk[13] and interacted with epigenetic changes or de novo CNVs too small to be detected by standard chromosomal microarray.
- •The relationship between genotype and neuropsychiatric phenotype is ultimately complex, and in E.'s case could not be reduced to a handful of "bad genes" inherited from her father. Emphasizing this to E.'s mother proved important to mother's understanding of E.'s disease, and hence E.'s treatment.
- As our understanding of the relationship between genotype and phenotype improves, psychiatrists will be better able to serve E and youth like her.

Contact

- Amandeep Jutla
- 225 E Chicago Avenue, Box 10, Chicago, IL 60611
- ajutla@northwestern.edu