Genome Sequencing Diagnoses Atypical 7q11.23 Region Deletion in an Adult Patient

Madelyn A. Gillentine, PhD[1], Maruhen Datsch Silveria, PhD, FACMG[1,2], Nichole Owen, PhD, FACMG[1,2], Elizabeth Fieg, MS, CGC[1], Sydney A. Lau, MS, CGC[1], Robert Rigobello, MS, CGC[1], Huiya Gu, PhD[1], Gretchen MacCarrick, MS, CGC[3], Harry Dietz, MD[3]

1. Baylor Genetics, Houston, TX, USA
2. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA
3. Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

P561

Background

- Deletions in the 1.55–1.83 Mb critical gene region at 7q11.23 are associated with Williams syndrome (WS), a rare neurodevelopmental disorder that is characterized by mild to moderate developmental delay/intellectual disability, supravalvular aortic stenosis (SVAS) and other cardiovascular anomalies, characteristic facial features, a unique cognitive–behavioral profile, and connective tissue differences.[1,2]
- There can be wide clinical variability in the phenotype associated with WS, especially in cases with atypical deletions.[2,3]
- The WS deletion usually affects 25-27 contiguous genes, some of which are associated with specific disease features, such as the *ELN* gene and SVAS.[4]

Case Presentation and Methods

- Genome sequencing (GS) was performed for an adult patient with a medical history significant for SVAS and ADHD. The proband had no prior diagnostic genetic testing.
- Included in sequencing were two affected relatives - the proband's daughter, who also has SVAS, and the proband's niece, who has pulmonary artery stenosis.
- Data was aligned to the human reference genome build GRCh38 and variants were called using the Illumina Dragen BiolT Platform.
- Data was analyzed in the Emedgene platform.

Results

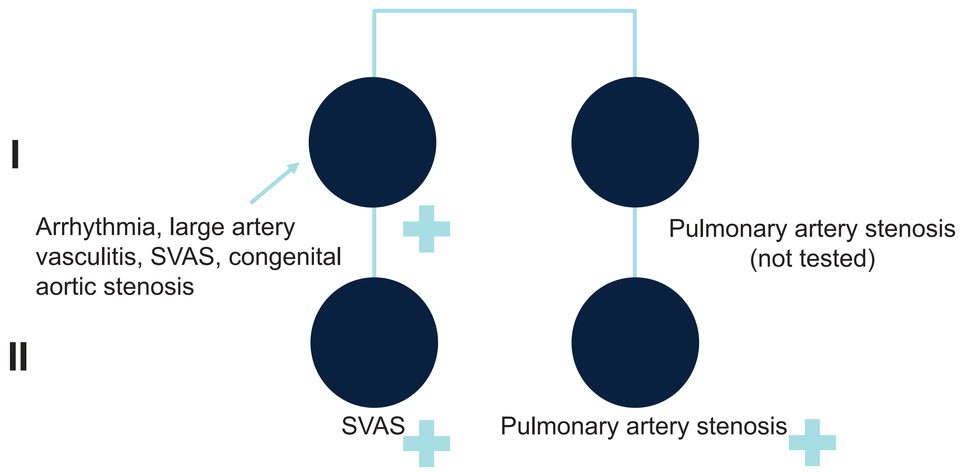


Figure 1. Family structure included in testing. The trio tested included the proband (indicated by arrow), her affected daughter, and her affected niece. A "+" indicates that this individual is positive for the deletion.

Table 1. Phenotypes of individuals with atypical 7q11.23 deletions upstream of *ELN*.

CASE	AGE (YEARS)	PHENOTYPE
I.1	70	Arrhythmia, large artery vasculitis, SVAS, congenital aortic stenosis
II.1	34	SVAS
II.2	38	Pulmonary artery stenosis
ClinVar_60243	NA	Developmental delay and/or other significant developmental or morphological phenotypes
DECIPHER_350066	NA	SVAS, pulmonary artery stenosis
ClinVar_154350	NA	Abnormality of cardiac morphology
Elastin Team at NIH	NA	4 families, mouse model

Figure 2. Deletion detected in proband, daughter, and niece, as well as similar deletions in ClinVar and DECIPHER. Atypical 7q11.23 deletions shown in red, typical WS deletion shown in black. The deletion reported in this family spans chr7:73766389-73999551 (223.2 kb) located approximately 28 kb upstream of *ELN*. This deletion likely affects a regulatory region impacting *ELN* gene transcription.

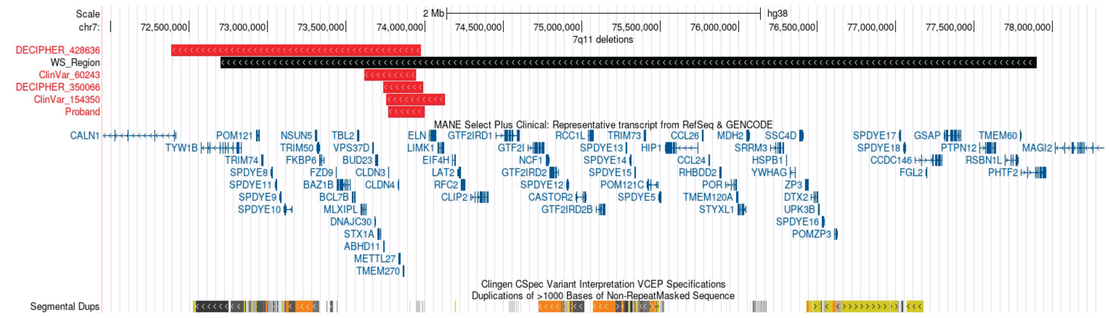
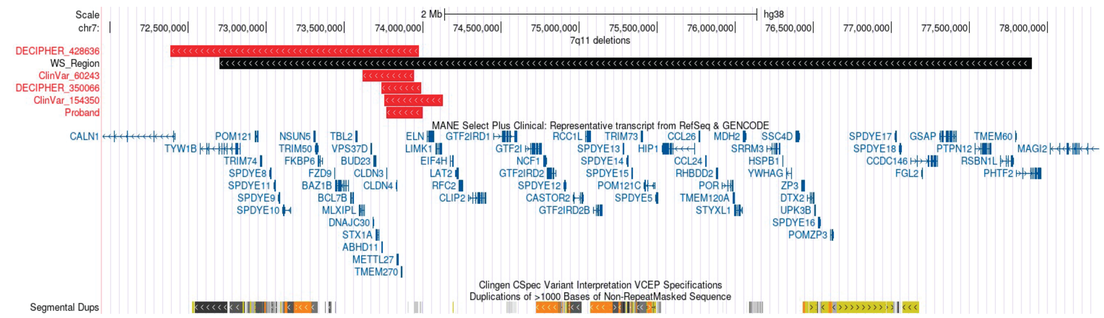


Figure 3. Figure 2, zoomed in on the proband's deletion and *ELN*. H3K4Me3 indicates potential active transcription start sites, H3K4Me1 indicates likely enhancers, and H3K4Ac indicates active promoters and enhancers, all supporting a regulatory impact of this region.



Discussion and Conclusion

- This case demonstrates that atypical deletions in the 7q11.23 region that do not include the *ELN* gene could still impact *ELN* gene function through regulatory mechanisms and may lead to associated cardiovascular phenotypes.
- This case also shows the diagnostic and clinical utility of GS in adult patients and the ability of GS to detect microdeletions in noncoding regions that may be otherwise missed on panel testing and/or exome sequencing. The capacity of GS to uncover variants impacting gene regulation indicates a need to expand genetic evaluation and testing methods traditionally made available to adult patients to enhance clinical care and outcomes.
- Clinical labs should consider the potential pathogenicity of atypical deletions in the 7q11.23 region as an etiology for cardiovascular phenotypes such as SVAS and other *ELN*-related cardiac defects, even if *ELN* is not directly included in the deletion.

Presented at the American College of Medical Genetics & Genomics (ACMG) Annual Meeting, Mar 10-14, 2026, Baltimore, MD USA.

References:

1. Delgado, L.M., Gutierrez, M., Augello, B., Fusco, C., Micale, L., Merla, G., & Pastene, E.A. (2013). A 1.3-mb 7q11.23 atypical deletion identified in a cohort of patients with Williams-Beuren syndrome. *Molecular Syndromology, 4*(3), 143-147. https://doi.org/10.1159/000347167
2. Alesi, V., Loddo, S., Orlando, V., Genovese, S., Di Tommaso, S., Liambo, M.T., Pompili, D., Ferretti, D., Calacci, C., Catino, G., & Falasca, R. (2021). Atypical 7q11.23 deletions excluding ELN gene result in Williams–Beuren syndrome craniofacial features and neurocognitive profile. *American Journal of Medical Genetics Part A, 185*(1), 242-249. https://doi.org/10.1002/ajmg.a.61937
3. Ferrero, G.B., Howald, C., Micale, L., Biamino, E., Augello, B., Fusco, C., Turturo, M.G., Forzano, S., Reymond, A., & Merla, G. (2010). An atypical 7q11.23 deletion in a normal IQ Williams–Beuren syndrome patient. *European Journal of Human Genetics, 18*(1), 33-38. https://doi.org/10.1038/ejhg.2009.108
4. Kozel, B.A., Knutsen, R.H., Ye, L., Ciliberto, C.H., Broekelmann, T.J., & Mecham, R.P. (2011). Genetic modifiers of cardiovascular phenotype caused by elastin haploinsufficiency act by extrinsic noncomplementation. *Journal of Biological Chemistry, 286*(52), 44926-44936. https://doi.org/10.1074/jbc.M111.274779