Meet James†

A 6-year-old male with autistic features, mild intellectual disability, ADHD, and short stature. He has an 18-month-old brother who has delayed developmental milestones.

Ordering exome as a first-tier genetic test for James' neurodevelopmental disorders would have:

Prevented

- A diagnostic odyssey
- The financial impact of running 3 tests vs 1

Provided

- An explanation for James' neurodevelopmental disorders and short stature
- A diagnosis for his brother, enabling early access to services

Chromosomal microarray (CMA) and *FMR1* testing for fragile X syndrome was initially ordered through a pediatrician and returned normal results.

James was eventually referred to a developmental pediatrician who ordered an autism panel of 241 genes, which returned a negative result. Following this negative result, James was offered whole exome sequencing (WES) as a trio with both of his biological parents.

Through exome testing, James was found to have a maternally inherited pathogenic variant in *CNOT1*. As a result, James' provider referred him and his family to a genetic counselor through GeneDx's patient counseling services to discuss the results, next steps, and familial implications.

During the appointment with a genetic counselor, it was disclosed that James' mother has a learning disability, short stature, and mild scoliosis, which are also features of this condition. This finding could also explain his brother's developmental delay, and testing for the familial variant was ordered for him.

Exome sequencing provided results that ended the diagnostic odyssey.

Heterozygous pathogenic variants in *CNOT1* are associated with Vissers-Bodmer syndrome, which has a highly variable phenotype.[1] Based on James' result, his younger brother subsequently received testing and was identified to have the same variant.

† - Fictionalized case study for illustrative purposes only

References

1. Vissers, L. E. L. M., Kalvakuri, S., de Boer, E., et al. De novo variants in CNOT1, a central component of the CCR4-NOT complex involved in gene expression and RNA and protein stability, cause neurodevelopmental delay. *Am. J. Hum. Genet.* 2020 Jul 2;107(1):164-172. doi: 10.1016/j.ajhg.2020.05.017.