

Towards Implementation Whole Genome Sequencing as a First Tier Test in Genomic Testing



Ruby Liu, Christin Collins, Arul Duraisamy, Andrea Behlmann, Leah Stansberry, Abhinav Mathur, Zeqiang Ma, and Madhuri Hegde

BACKGROUND

- Whole genome sequencing (WGS) becomes the first-tier diagnostic tool with an assumed diagnostic yield ranging from 38% to 48% depending on the patient cohorts studied.
- WGS greatly reduced the time and psychological suffering of the diagnostic odyssey for individuals with complex undiagnosed diseases due to genetic and clinical heterogeneity, wide-range of nonspecific phenotypes, and variable progression and severity.
- WGS has surpassed single gene testing, multi-gene panel testing and exome sequencing due to the near complete genome wide coverage including deep intra- and inter-genic coverage and unbiased sequencing.
- WGS added benefits of detecting small copy number variant (CNV), nucleotide repeat expansion and variants in pseudogenes.
- We are presenting 5 interesting cases to demonstrate the power of WGS

RESULTS

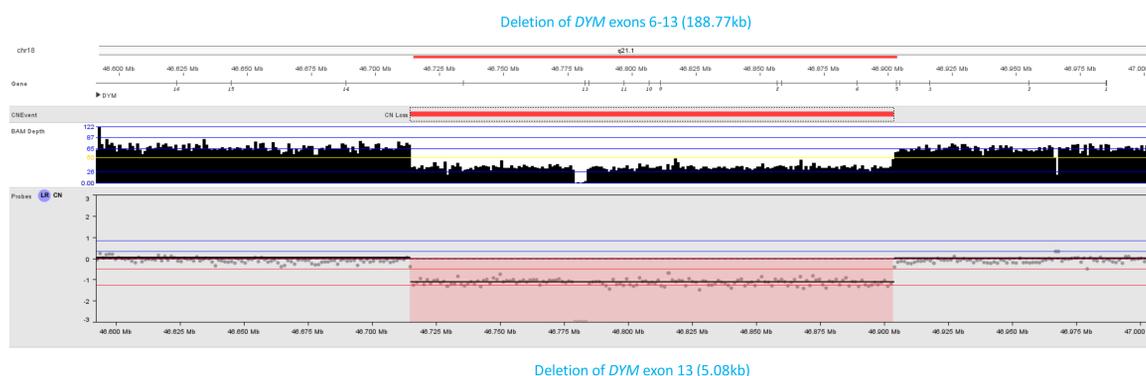
Case 1: 5 years old male

Suspected Hunter syndrome (MPS II)

- Reduced iduronate 2-sulfatase levels
- Negative Sanger sequencing and MPLA testing of the *IDS* gene
- WGS identified an *IDS* c.880-72A>G variant of uncertain.

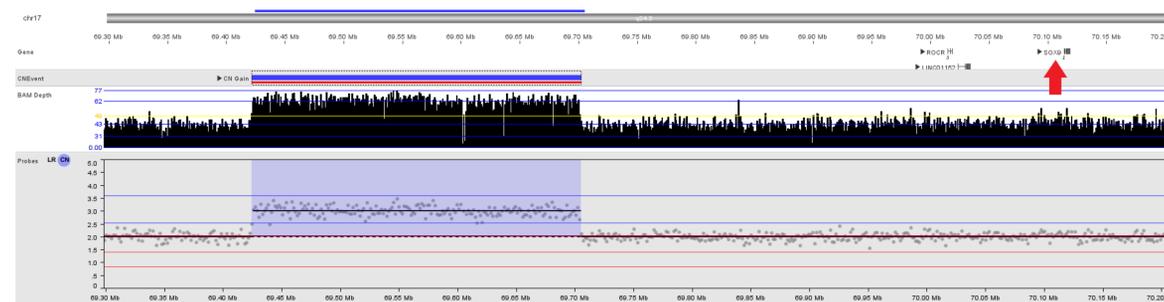
Case 2: 6 years old male

- Intellectual disability, speech problem
- large stem, abnormal hands and legs
- Negative family history
- WGS revealed a 5.08 kb pathogenic homozygous deletion of exon 13 in *DYM* associated with Dyggve-Melchior-Clausen (DMC) disease.



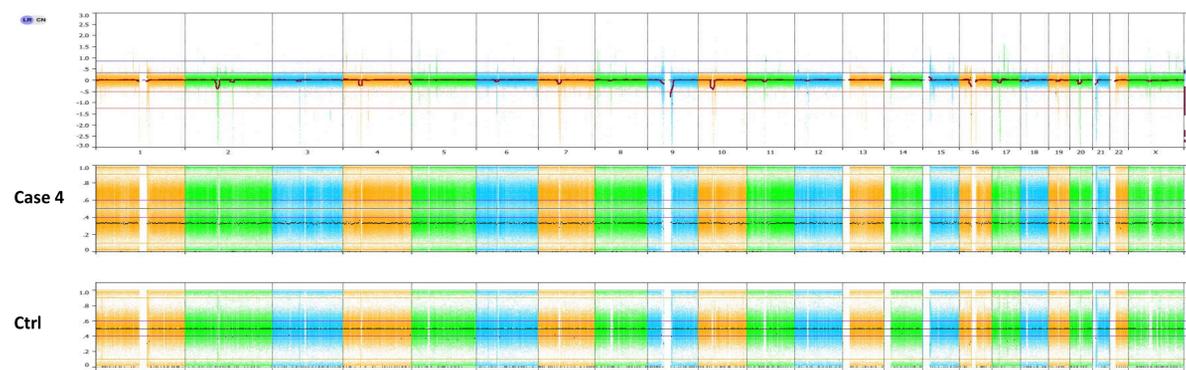
Case 4: 9 months old male

- Ambiguous genitalia, female pseudohermaphroditism, perineal hypospadias
- Clinical suspicion of ovotesticular sex development disorder.
- Karyotype and FISH showed 46, XX and SRY-negative.
- Family history: old brother and paternal uncle present similar features.
- WGS quint testing detected a paternally inherited pathogenic 281 kb duplication including XYSR region approximately 0.4Mb upstream of the *SOX9* gene on chromosome 17 which also showed in affected brother and paternal uncle.



Case 4: 3 months old female

- Microcephaly, dysmorphic facial features, abnormal skin pigmentation, abnormal limb morphology
- Biliary atresia, hepatomegaly, atrial septum defect, respiratory failure
- Failure to thrive, extremely low birth weight, IUGR, premature birth
- WGS identified pathogenic triploidy, confirmed by SNP array



Case 5: 2 years old male

- Hirschsprung disease, intramuscular hemorrhage, soft tissue edema, multiple fractures
- Maternal family history of Hirschsprung disease
- WGS identified a 46-48 GCN repeat expansion in the *PHOX2B* gene.
- GCN repeat expansion in *PHOX2B* associated with central hypoventilation syndrome, congenital, with or without Hirschsprung disease. Unaffected individuals have 20 GCN repeats.
- Confirmatory testing by an orthogonal method is pending

CONCLUSION

- The implementation of WGS ascertained the provider's clinical diagnosis, provided insights for genetic counseling and useful information for future family planning.
- With the advancement of technology and bioinformatics as well as decline in cost, WGS is moving to the direction of replacing most of the other sequencing tests in the laboratories and becomes a one-time genetic test that would provide the basis for lifelong follow-up. The differences would be the set of genes analyzed appropriate to the specific clinical indications and requests.