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Diagnosis of X-linked Intellectual Disability in an adult female by exome sequencing: A collaborative diagnosis between clinician & laboratory

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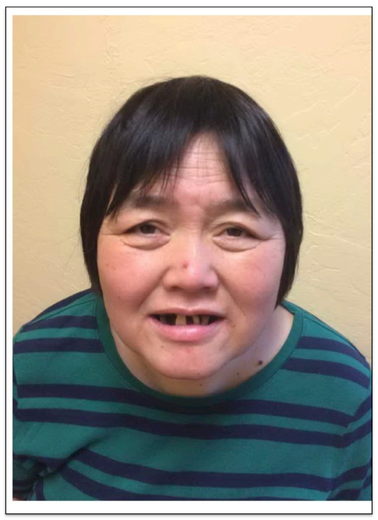
Case Presentation

Figure 1. Patient photo

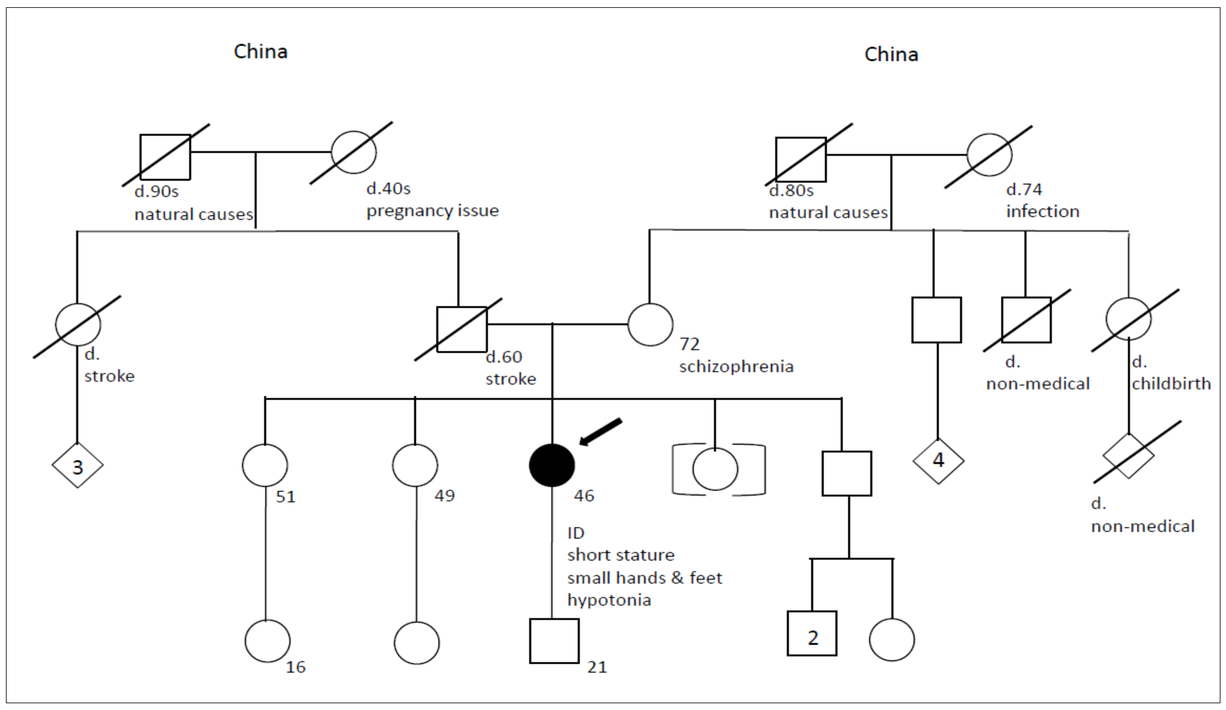


A 46-year-old Asian female was assessed in Medical Genetics at the Kaiser Permanente Genetics Department. Relevant clinical features included **severe intellectual disability (ID), short stature, hypotonia, small hands and feet, and self-stimulatory behaviors.**

There was **no reported family history** of ID in the patient's adult son, brother, two sisters, parents, or other relatives.

Previous testing was unremarkable, and included metabolic studies which were unremarkable and array comparative genomic hybridization, which showed a 15q13.3 duplication of unknown significance.

Figure 2. Family history



Exome Sequencing Results & Interpretation

The ACE Clinical Exome Test™ was performed on the patient. A **heterozygous likely pathogenic variant in *KIAA2022*, c.1441C>T, p.Arg481* (NM_001008537.2) was identified on the X chromosome.**

At the time of analysis, KIAA2022-related ID had only been reported in males; female carriers were reported to be unaffected. Given the inconsistent mode of inheritance of an affected female carrier with a X-linked recessive disorder, a diagnosis of KIAA2022-related ID in this patient initially seemed less likely.

Targeted Sanger sequencing did not identify the variant in both of the patients' unaffected siblings.

Additional Follow-Up Testing

A report published concurrently with the issuing of these results described an affected female patient with a *KIAA2022* variant and similar phenotype, shedding additional light on the potential impact of this finding.

Follow-up testing was performed in consultation with the Kaiser Permanente Medical Genetics Team in an effort to further characterize this diagnosis:

- **Targeted Sanger sequencing of the *KIAA2022* variant was performed on a specimen from the patient's mother and was negative.**
- X-inactivation studies were performed on the patient and showed **highly skewed x-inactivation (90:10 ratio)**.

In addition**, a recent study published in May 2016 described 14 females with *KIAA2022* variants, one of which carried the same variant as our patient**. Functional studies performed in this patient showed absent expression.

Conclusions

- This case emphasizes the **utility of WES in identifying potential novel disease** etiologies by expanding our understanding of disease pathogenesis.
- Personalis Clinical Laboratory (PCL) utilizes a rigorous screening, classification and interpretation process which includes manual review by experienced genetic counselors, variant scientists and geneticists. This **manual review enables PCL to identify non-traditional mechanisms of disease that may go undetected by traditional automated filters**.
- **This case illustrates the limitations of fixed variant filtering approaches based on presumed modes of inheritance**. Improvements to variant screening and filtering are needed to incorporate additional mechanisms including skewed X-inactivation, mosaicism, and reduced penetrance.
- Last but certainly not least, **this case highlights the importance of post-reporting collaborations with the ordering providers** on a case-by-case basis in an effort to maximize chances of making a diagnosis in a family.

Personalis @ NSGC:

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