ASHG 2016 Abstract

Inheritance patterns may not always be as expected: Diagnostic exome sequencing (DES) uncovers alterations in X-linked genes in equal amounts in males and females with intellectual disability.

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Diagnostic exome sequencing (DES) uncovers a positive finding in a characterized gene in roughly 30% of patients with a broad range of underlying Mendelian disorders.

Among the first 2,000 patients undergoing DES, 1,364 (68.2%) patients were referred for intellectual disability (ID). Overall among patients with ID, a positive finding in a characterized gene was identified in 28.4% (388).

The rate of positive findings in characterized genes at the time of original analysis was higher in females (30.8%; 178/578) than in males (26.7%; 210/786) ($p = 0.01$, chi-square test). Interestingly and unexpectedly, the rate of positive findings in characterized X-linked genes was similar in males (4.3%; 34/786) vs females (4.7%; 27/578). All the heterozygous mutations on the X chromosome identified in females arose *de novo* (when both parents are available for testing) or are *bona fide* mutations (in which at least one parent was unavailable for testing). Recurrent causative XLID genes seen in females include *MECP2*, *HDAC8*, and *WDR45*. For males, a *de novo* occurrence accounts for 41.2% (14/34) of the detected mutations and the rest 58.8% (20/34) inherited the mutation from their mother. In the latter 20 male probands, there were no strong indications of an X-linked condition in any family.

It is possible that males with ID (and unlikely that females with ID) underwent testing for X-linked genes prior to DES and thus the most prevalent and best known XLID genes have already been excluded. Alternatively, these data may support the concept of a “female protective model” for neurodevelopmental disorders. For example, an increase in number of identifiable pathogenic CNVs and SNVs in female vs male probands with autism spectrum disorders has been observed, despite the increased prevalence in males (Jacquemont, *et al.* AJHG 2014).

Our data demonstrate that the chance to find an X-linked molecular etiology is similar in males and females undergoing DES and highlight the utility of DES to detect unanticipated inheritance patterns. The data have implications for genetic counseling; highlighting that pre-test counseling should include a review of all applicable inheritance patterns.