IN THIS ISSUE

Phenotype-based search tools are ineffective for diagnosis

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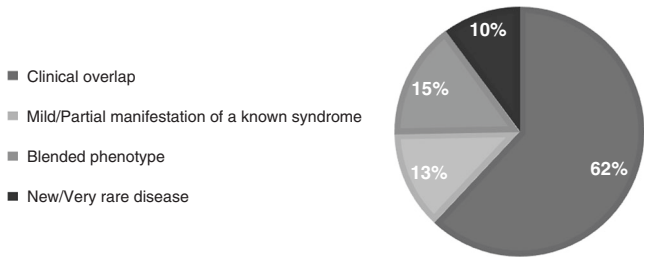

Medical genetics traditionally relies on observation and cataloging of phenotypic features to search for a genetic diagnosis of Mendelian conditions. However, varying degrees of specificity for clinical features as well as overlapping clinical features complicate the differential diagnosis. Phenotype-based search tools can facilitate the diagnostic process, but their effectiveness and yield remain unclear. In this issue, Fellner and colleagues report that searching public online databases for a molecular diagnosis based on patient phenotype is ineffective. Instead, the authors recommend a genotype-first approach with backward phenotyping. The researchers retrospectively analyzed 100 probands for whom exome sequencing and analysis yielded a molecular diagnosis. For most cases, the main indication for sequencing was cognitive abnormalities, intellectual disability, or developmental delay. The researchers then performed search queries for each case in three public online databases—OMIM, Phenolyzer, and Mendelian—using Human Phenotype Ontology terms reported by the referring medical geneticist. For a third of cases, search results from any of the databases did not include the actual molecular diagnosis (AMD). Search results from OMIM included the AMD for the highest percent of cases (58%), whereas search results from the Phenolyzer and Mendelian databases included the AMD in only 28 and 35% of cases, respectively. The top 10 search results from any of the databases included the AMD for only 21% of cases. The results demonstrate a low search yield. For the majority of cases, low search yield was attributed to clinical overlap among different disorders. The authors conclude that phenotype-based search using publicly available online databases does not effectively streamline diagnosing Mendelian disorders and instead suggest a genotype-first approach with deep backward phenotyping as a central diagnostic strategy. —*V. L. Dengler, News Editor*

Early hormonal treatment bolsters language development in Klinefelter syndrome

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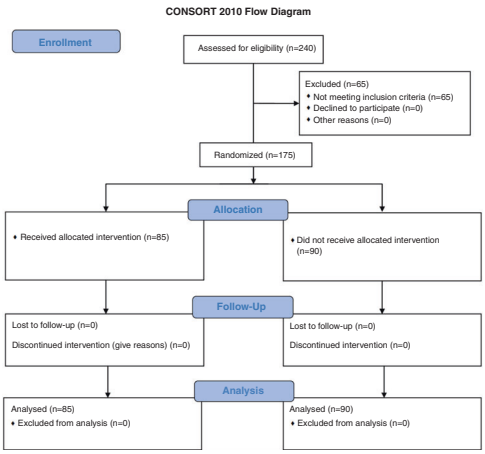

More than three-quarters of boys with Klinefelter syndrome (47, XXY) experience speech and language difficulties, particularly with expressive ability. Early hormonal treatment (EHT) in adolescents and young men has been shown to have a beneficial effect on physical, cognitive, and behavioral impairments. However, little research has investigated the impact of EHT on early speech and language capabilities in infants with Klinefelter syndrome. Samango-Sprouse and colleagues report a positive association between EHT and language development in 47,XXY boys. The researchers evaluated 175 prenatally diagnosed boys with Klinefelter syndrome ages 1–71 months using a battery of age-appropriate neurodevelopmental language assessments. Those who received EHT scored significantly higher on many of the language assessments than those who did not receive hormone treatment. For example, participants between 24 and 35 months of age who received EHT scored significantly higher than their age-matched peers who did not receive hormone treatment on auditory and expressive communication assessments, including the Early Language Milestone Scale 2 expressive language assessment and the Expressive One Word Picture Vocabulary Test. These boys also did better on an assessment for complexity of speech patterns. Although boys who did not receive EHT showed delayed expressive language capabilities, boys in the EHT group had no expressive language delays. In addition, the researchers did not observe any adverse effects in the EHT group, indicating that the treatment is safe and effective. Altogether, the findings demonstrate that early testosterone treatment is associated with improved auditory comprehension, expressive ability, and verbal intelligence. The researchers conclude that EHT may facilitate early language development in 47,XXY boys, a critical factor in promoting reading skills, academic success, and self-esteem. —*V. L. Dengler, News Editor*

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