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Original Article

Targeted massively parallel sequencing provides comprehensive genetic diagnosis for patients with disorders of sex development

Arboleda VA, Lee H, Sánchez FJ, Délot EC, Sandberg DE, Grody WW, Nelson SF, Vilain E. Targeted massively parallel sequencing provides comprehensive genetic diagnosis for patients with disorders of sex development.
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Disorders of sex development (DSD) are rare disorders in which there is discordance between chromosomal, gonadal, and phenotypic sex. Only a minority of patients clinically diagnosed with DSD obtains a molecular diagnosis, leaving a large gap in our understanding of the prevalence, management, and outcomes in affected patients. We created a novel DSD-genetic diagnostic tool, in which sex development genes are captured using RNA probes and undergo massively parallel sequencing. In the pilot group of 14 patients, we determined sex chromosome dosage, copy number variation, and gene mutations. In the patients with a known genetic diagnosis (obtained either on a clinical or research basis), this test identified the molecular cause in 100% (7/7) of patients. In patients in whom no molecular diagnosis had been made, this tool identified a genetic diagnosis in two of seven patients. Targeted sequencing of genes representing a specific spectrum of disorders can result in a higher rate of genetic diagnoses than current diagnostic approaches. Our DSD diagnostic tool provides for first time, in a single blood test, a comprehensive genetic diagnosis in patients presenting with a wide range of urogenital anomalies.