DES is uniquely useful in the identification of multi-gene alterations: Oligogenic findings make up a significant portion of previously undiagnosed patients

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Abstract:

Diagnostic exome sequencing (DES) has been instrumental in discoveringthe pathogenic etiology in patients in whom traditional molecular methods were uninformative. In addition to establishing a molecular diagnosis, enhancing genetic counseling, and aiding in clinical management, DES is uniquely useful in overcoming limitations posed by traditional molecular diagnostic strategies in the identification of multi-gene findings. Often complicating the interpretation of genetic variants are factors such as reducedpenetrance and variable expressivity, frequently attributed to the effects of genetic modifiers. Herein, we examined the first 100 reported DES cases with positive gene alteration findings. Among them, 17 (17%) containedmutations in more than one reported gene of either positive or uncertainsignificance. The majority of the multi-gene cases (15) reported two genefindings, while two cases each reported three gene findings. All reportedgenes were associated with high penetrance disease as DES does not include the interpretation or reporting of disease-association risk alleles withlow penetrance. The clinical spectrum of the patients with multi-gene findings was wide with 23% presenting with multiple congenital anomalies, 19%metabolic disease, 19% musculoskeletal phenotypes, and 15% childhoodonset neurological disease. A minority of patients also presented with hematologic, cancer predisposition, cardiologic, and immunologic/infectious phenotypes. Interestingly, oligogenic findings were not identified among thecohort of positive results from patients presenting with autism spectrumdisorder, which is typically considered multi-factorial. Virtually all patients had not previously received a clinical diagnosis consistent with our DESresults and less than half had been provided with a consistent differential diagnosis. Among the 17 multi-gene cases, 11 (65%) contained at least one alteration classified as a deleterious mutation. If single gene testinghad been performed for these patients, the pursuit of further molecular testing in the context of a single deleterious alteration in a well describedgene would have been unlikely. Overall, these results reveal that oligogenic findings make up a significant portion of previously undiagnosed patients highlighting the value of DES in providing the most comprehensive molecular diagnosis available. Moreover, these data have significant implications for genetic counseling and clinical management.