

NextGen Sequencing of HEXA: A more sensitive assay

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Abstract:

Purpose: Tay-Sachs disease (TSD) is the prototype for ethnic-based carrier screening, with a carrier rate of ~1/25 in Ashkenazi Jews and French Canadians. *HEXA* enzyme analysis is the current gold standard for TSD screening (detection rate ~98%), but has technical limitations. We aimed to determine the utility of NextGen sequencing (NGS) versus enzyme screening for TSD.

Methods: *HEXA* enzyme analysis and DNA analysis (NGS + 7.6kb del) was performed on 74 samples collected at a TSD family conference.

Results: 51/74 participants had positive enzyme results (46 carriers, 5 LOTS). 42/51 enzyme positives had a pathogenic mutation, 7/ 51 had a previously reported VUS, 1/51 had a novel VUS, and 1/51 had the *HEXA* pseudoallele. 2 enzyme-negative individuals had the B1 pathogenic allele. Overall, NGS + 7.6kb del screening of *HEXA* found a pathogenic mutation, pseudoallele, or VUS in 100% of the enzyme-positive or obligate carrier/enzyme-inconclusive samples, detected 2 carriers missed by enzyme alone, and detected mutations in 7/51 not found in common mutation panels.

Conclusion: Our data suggest that NextGen sequencing in combination with enzyme may be used as an efficient screening technology for people of all backgrounds, and will provide a more sensitive test than enzyme alone or a mutation panel with enzyme.