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Genetic counseling for carrier screening and prenatal diagnosis involving a Tay-Sachs disease variant of uncertain significance and possible pseudodeficiency allele in the East Asian population

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I. Introduction

Tay-Sachs carrier screening began in the 1970's and focused on the Ashkenazi Jewish population, where the carrier risk of Tay-Sachs disease is approximately 1 in 27, compared to 1 in 250 to 1 in 300 in the general population.[1] The disorder results from a deficiency of the enzyme beta-hexosaminidase A (HexA) and can be diagnosed biochemically via enzyme analysis or molecularly with the identification of two pathogenic variants in the *HEXA* gene. Conventional *HEXA* panels target alleles common in certain populations and may result in a false negative, while sequencing may identify variants of uncertain significance (VUS). Carrier screening may be further complicated by *HEXA* pseudodeficiency alleles, which affect enzyme testing but do not cause Tay-Sachs disease. Furthermore, due to the decreased *a priori* carrier risk, carrier screening in low risk populations can be significantly more complex and time consuming than screening in at-risk populations.

II. Case Report

A couple presented for genetic counseling at 11.7 weeks gestation in conjunction with routine first trimester screening. The patient was of Ashkenazi Jewish ancestry and was found to be a carrier of Tay-Sachs disease by both HexA enzyme analysis in leukocytes and DNA analysis (1278insTATC). Her partner, of Chinese ancestry, was screened, resulting in conflicting enzyme activity interpretations for serum, leukocytes, and plasma. Full gene sequencing of *HEXA* identified a VUS, c.548T>A (p.L183H), in the partner. Fetal diagnostic testing was pursued, and molecular analysis on amniocytes revealed that the fetus inherited the maternal 1278insTATC pathogenic variant, while the paternal c.548T>A VUS was not detected. Postnatal enzyme analysis of the infant was in the unaffected range.

Table 1. Enzyme interpretation results on partner

Draw #	Leukocytes	Serum	Plasma
1	Carrier	—	—
2	—	Non-carrier	—
3	Carrier	Inconclusive	—
4*	Inconclusive	—	Inconclusive

*performed at an outside laboratory

Significance of c.548T>A (p.L183H)

The c.548T>A variant is most frequently found in the East Asian population, with an allele frequency of 0.005.[2] A thorough literature search failed to identify reports of an individual affected with Tay-Sachs disease carrying this variant. One laboratory performing expanded carrier screening shared unpublished findings of homozygosity for the c.548T>A variant in three individuals. In the absence of clinical information with which to correlate these results, it was assumed that these adult individuals were unaffected with Tay-Sachs disease, though the late-onset form cannot be excluded. A second laboratory reported to us that they detected a single copy of the c.548T>A variant in 53 individuals, the majority of whom were Asian. This laboratory had biochemical results on 31 of these individuals: 12 had enzyme results in the non-carrier range, 4 were positive for carrier status, 12 were indeterminate, and 3 were atypical. A third laboratory reported that they, too, have identified this variant in carrier screening specimens that tested positive or inconclusive for carrier status by means of enzyme analysis. This information collectively suggests that this variant may be a pseudodeficiency allele, presenting with varying enzyme results in different specimen types, and is likely benign, though more data is needed to make any strong conclusions.

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III. Discussion

Genetic counseling and interpretation of prenatal testing was complex in this case; it required explanations of inconclusive and discrepant results, as well as explanations of variants of uncertain clinical significance. Furthermore, detailed descriptions of the various carrier screening methods and limitations of current technologies were necessary. This time consuming process underscores the value of offering carrier screening preconception or early in the pregnancy. It also highlights the limitations of genetic carrier screening in low risk populations and supports proposals by others for protocols, guidelines, and specific criteria that will aid in the efficiency of follow-up testing, counseling, and usefulness to the patient.[3] Given the diversity of our population, this will not be a simple task.

IV. Acknowledgements

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V. References

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