Uncertain Heritable Risk in Retinoblastoma Probands: Classification of Genetic Testing Results for Risk Stratification and Screening

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Introduction: Early diagnosis and prompt intervention is crucial to outcomes in retinoblastoma. Genetic testing for RB1 pathogenic variants is essential for the determination of germline mutations (heritable retinoblastoma) that places probands and relatives at risk for bilateral/multifocal disease and second cancers. All probands should undergo high-sensitivity genetic testing for RB1 variants in blood and, when available, tumour samples. Despite testing, there remain cohorts of retinoblastoma probands and/or relatives in which heritable risk remains uncertain and potentially leads to unnecessary screening. This study documented the number of retinoblastoma probands with uncertain heritable risk presenting to The Hospital for Sick Children (SickKids), and subclassified them on the basis of the nature of their uncertainty, with a view to the refinement of screening protocols for these probands and their first-degree relatives.

Methods: A 10-year retrospective observational case series with review of medical records and genetic testing results of all retinoblastoma probands that were seen as a new patient at SickKids during the study period (1st January 2014 – 31st December 2023). Variables collected included patient demographics, disease laterality and severity, type and results of genetic testing, pathogenic variants detected and family history.

Results: "There were 173 retinoblastoma probands identified (bilateral 45% (n=78), unilateral 55% (n=95)). Of these, 27.2% (n=47) were found to have uncertain heritable risk.

Of these probands with unilateral disease, 59.6% (n=28) were cases where tumour tissue was not tested and no RB1 pathogenic variant was detected in blood samples, 8.5% (n=4) had tumour tested with no mutation found, and no blood germline pathogenic variant detected, 8.5% (n=4) had only one tumour mutation detected, and no blood germline pathogenic variant detected, 4.3% (n=2) had a germline variant of uncertain significance, and (2.1% (n=1) had not had genetic testing performed.

Of the probands with bilateral disease and uncertain heritable risk (ie uncertain potential risk of disease in siblings/offspring), 12.8% (n=6) were diagnosed and/or tested outside of the province with no available genetic testing information, and 4.3% (n=2) had bilateral retinoblastoma with no germline mutation detected (low level somatic mosaicism).

Conclusion: These results provide a new descriptive subclassification system for probands with uncertain heritable risk. Further study to describe the long term follow up of unilateral probands, and relatives of all probands, to describe the risk of development of further primary retinoblastoma or second cancers is planned. This can inform the development of specific screening guidelines for probands and relatives with uncertain heritable risk.