00133 Clinical Relevance of Cancer Predisposition Syndrome Screening Tool for Detection of Genetic Susceptibility in a Singaporean Cohort of Childhood Tumors

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Aims: Detection of cancer predisposition syndromes is a challenge for paediatric oncologists, especially in an Asian cohort with unknown prevalence of germline mutations. We assessed the clinical utility of two checklists for screening cancer predisposition syndromes validated by genomic sequencing in a Singaporean cohort of paediatric solid tumors.

Methodology: We evaluated 102 patients recruited at our tertiary medical center over a period of 31 months.

Patient clinical records were reviewed against two published checklists and germline mutations in 100 cancer-associated genes were profiled through a combination of whole exome sequencing and multiplex ligation-dependent probe amplification analyses on blood-derived genomic DNA.

Result: Fifty-four patients met criteria for cancer predisposition syndromes on both clinical checklists, of which 10 (18.5%) harboured germline mutations in associated genes identified by sequencing.

Specificity of screening was markedly improved by combining criteria of both checklists without effect on sensitivity. Both checklists were able to detect all 10 children (9.8%) in the cohort with pathogenic germline mutations in six known cancer predisposition genes: TP53, DICER1, NF1, FH, SDHD and VHL. TP53 was most frequently mutated, affecting five children with adrenocortical carcinomas, sarcomas and diffuse astrocytoma. Multiple pathogenic germline mutations were found in two patients. Disparity in prevalence of germline mutations across tumor types suggested variable genetic susceptibility and implied potential contribution of novel susceptibility genes. A family history of cancer was observed in only 50% of children with pathogenic germline mutations.

Conclusion: Currently available cancer predisposition syndrome screening checklists are adequately sensitive to detect at-risk children and relevant for clinical application. Our study showed that 9.8% of Asian paediatric solid tumors have a heritable component, consistent with cohorts of other populations.