ABSTRACT

Neuro Oncol. 2022 Jul 29:noac187. doi: 10.1093/neuonc/noac187. Online ahead of print.

Genetic predisposition & evolutionary traces of pediatric cancer risk: A prospective 5-year population-based genome sequencing study of children with CNS tumors.

Stoltze UK(1)(2), Foss-Skiftesvik J(1)(3), van Overeem Hansen T(2), Byrjalsen A(2), Sehested A(1), Scheie D(4), Mikkelsen TS(5), Rasmussen S(6), Bak M(2), Okkels H(7), Callesen MT(8), Skjøth-Rasmussen J(3), Gerdes AM(2), Schmiegelow K(1), Mathiasen R(1), Wadt K(2).

Author information:
(1)Department of Pediatrics and Adolescent Medicine; all Rigshospitalet University Hospital, Denmark.
(2)Department of Clinical Genetics; all Rigshospitalet University Hospital, Denmark.
(3)Department of Neurosurgery; all Rigshospitalet University Hospital, Denmark.
(4)Department of Pathology - all Rigshospitalet University Hospital, Denmark.
(5)Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Denmark.
(6)Novo Nordisk Foundation Center for Protein Research, Copenhagen University, Denmark.
(7)Department of Molecular Diagnostics, Aalborg University Hospital; Odense University Hospital, Denmark.
(8)Pediatrics and Adolescent Medicine, Odense University Hospital, Denmark.

BACKGROUND: The etiology of central nervous system (CNS) tumors in children is largely unknown and population-based studies of genetic predisposition are lacking.

METHODS: In this prospective, population-based study, we performed germline whole-genome sequencing in 128 children with CNS tumors, supplemented by a systematic pedigree analysis covering 3,543 close relatives.

RESULTS: Thirteen children (10%) harbored pathogenic variants in known cancer genes. These children were more likely to have medulloblastoma (OR 5.9, CI 1.6-21.2) and develop metasynchronous CNS tumors (p=0.01). Similar carrier frequencies were seen among children with low-grade glioma (12.8%) and high-grade tumors (12.2%). Next, considering the high mortality of childhood CNS tumors throughout most of human evolution, we explored known pediatric-onset cancer genes, showing that they are more evolutionarily constrained than genes associated with risk of adult-onset malignancies (p=5e-4) and all other genes (p=5e-17). Based on this observation, we expanded our analysis to 2 986 genes exhibiting high evolutionary constraint in 141 456 humans. This analysis identified eight directly causative loss-of-functions variants, and showed a dose-response association between degree of constraint and likelihood of pathogenicity - raising the question of the role of other highly constrained gene alterations detected.

CONCLUSIONS: ~10% of pediatric CNS tumors can be attributed to rare variants in known cancer genes. Genes associated with high risk of childhood cancer show evolutionary evidence of constraint.

DOI: 10.1093/neuonc/noac187
PMID: 35902210