The genetic landscape of tumor predisposition syndromes in Chinese patients with glioma

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BACKGROUND

- Tumorigenesis is generally driven by a combination of inherited genetic alterations and acquired somatic cell mutations. Glioma usually manifests sporadically, while certain tumors are now known to be associated with tumor predisposition syndromes. The spectrum of syndromes that have glioma manifestations includes neurofibromatosis types 1 and 2, tuberous sclerosis complex, Li-Fraumeni syndrome, Cowden syndrome, Turcot syndrome.
- A comprehensive understanding of the genetics and molecular pathogenesis of glioma is critical in improving clinical care and promoting the development of molecularly targeted therapeutics. Herein, germline mutations were analyzed through NGS to investigate the molecular profiling and mutation frequency in Chinese glioma patients.

METHODS

- Germline mutations including SNV, small INDEL, and the corresponding somatic mutations from 805 glioma patients were analyzed with a 131-gene next-generation sequencing (NGS) panel.
- The pathogenicity of germline mutations was categorized based on American College of Medical Genetics and Genomics (ACMG) guidelines.

RESULTS

- In total 805 patients with glioma, 27(3.35%) patients were identified harboring 28 pathogenic (P)/likely pathogenic (LP) germline mutations, and the remaining 778 patients were carried non-pathogenic (Non-P) mutations.
- The P/LP mutation genes mainly involved DNA repair (*BRCA1* and *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *POLE*), cell cycle regulation (*ATM*, *CHEK2*), and tumor suppressor (*NF1*, *TSC2*). Most P/LP mutations were loss of function (LOF) variants.
- No significant differences were found between P/LP and Non-P groups with gender (p=0.167), age (p=0.734), IDH status (22/546 IDH wild-type vs. 5/259 IDH mutation, p=0.145). There was a significant statistical difference in MSI-H that the P/LP group was higher than the Non-P group (5/27 vs. 2/778, p<0.001), and all patients with MSI-H in the P/LP group carried MMR gene mutations.

Table 1: Pathogenic (P)/likely pathogenic (LP) germline mutations in glioma.

Gene	*MSH2*	*NF1*	*ATM*	*BRCA2*	*CHEK2*	*BRCA1*	*PMS2*	*POLE*	*TP53*	*PTPN11*	*MLH1*	*TSC2*	*APC*	*MSH6*
frequencies	17.86%	14.29%	10.71%	10.71%	10.71%	7.14%	3.57%	3.57%	3.57%	3.57%	3.57%	3.57%	3.57%	3.57%

CONCLUSIONS

- A proportion of germline variants of tumor syndromes was 3.35% in patients with glioma, which may be potentially linked to tumorigenesis, treatment, and prognosis. Integrative analysis in gliomas based on tumor syndromes and somatic variants needs to be further studied.

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