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Gliomas arising in the setting of Li-Fraumeni syndrome stratify into two molecular subgroups with divergent clinicopathologic features

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Li-Fraumeni syndrome (LFS) is a rare autosomal dominant tumor predisposition syndrome caused by heterozygous germline mutation or deletion of the *TP53* tumor suppressor gene on chromosome 17p13. The prevalence of deleterious *TP53* germline mutations in humans is estimated to range from 1 in 5000 to 20,000 [6]. These *TP53* germline alterations can either be inherited across generations or arise de novo, of which de novo acquisition is estimated to occur in 20% of affected patients [6]. LFS results in an increased risk of many different cancer types, including breast carcinoma, adrenocortical carcinoma, lymphoblastic leukemia, osteosarcoma, and brain tumors [6]. The three brain tumor types most commonly associated with LFS are choroid plexus carcinoma, medulloblastoma, and glioma [9]. Approximately one-third of choroid plexus carcinomas are known to arise in the setting of LFS [11], whereas LFS only accounts for a small fraction of childhood medulloblastomas. The majority of medulloblastomas arising in the setting of LFS occur in the second decade of life and are most commonly large cell/anaplastic tumors belonging to the SHH-activated and *TP53*-mutant molecular subtype [12]. However, the histologic,

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molecular, and clinical features of gliomas arising in the setting of LFS have not been well characterized to date.

Here we performed comprehensive genomic characterization and studied the clinicopathologic features of 14 gliomas arising in the setting of LFS (Table 1 and Supplementary Table 1). We identified that gliomas arising in the setting of LFS are diffuse astrocytic neoplasms that can be segregated into two molecular subgroups based on IDH mutation status that are associated with divergent clinicopathologic features and patient outcomes as described below (Fig. 1).

The IDH-mutant subgroup consisted of seven tumors from six patients, five female and one male, with median age at glioma diagnosis of 23 years (range 10–28). These seven tumors were uniformly located in the cerebral hemispheres and were all IDH-mutant diffuse astrocytomas lacking necrosis, microvascular proliferation, and significant mitotic activity. All seven tumors harbored *IDH1* mutations, three of which were p.R132H and four of which were the less common variant p.R132C (Supplementary Table 2). Six tumors harbored biallelic *TP53* inactivation due to a germline missense mutation accompanied by somatic loss of heterozygosity (four cases) or a somatic nonsense or missense mutation (two cases; Supplementary Table 3). The seventh tumor (patient LF-1) arose in the setting of constitutional mosaicism for a damaging *TP53* missense mutation that was acquired during post-zygotic development, with the glioma arising from a cell affected by the mosaicism that acquired a second somatic nonsense mutation inactivating the remaining *TP53* allele (Fig. 1a). Additionally, there were inactivating *ATRX* mutations in six of the seven tumors, with

Table 1 Clinicopathologic features of the 13 patients with gliomas arising in the setting of Li-Fraumeni syndrome

Patient	Sex	Age	Personal cancer hx	Family cancer hx	Tumor location	Histology	Clinical outcome	Follow-up
IDH-mutant								
LF-1	F	28	None	None reported	Cerebral hemisphere	Diffuse astrocytoma	Alive with progressive disease	24 months
LF-2A[a]	F	23	Breast DCIS	None reported	Cerebral hemisphere	Diffuse astrocytoma	Died of disease	79 months
LF-2B[a]		23			Cerebral hemisphere	Diffuse astrocytoma	Died of unrelated tumor	79 months
LF-3	F	22	None	Unknown	Cerebral hemisphere	Diffuse astrocytoma	Alive, no evidence of progression	25 months
LF-4	M	20	None	Unknown	Cerebral hemisphere	Diffuse astrocytoma	Alive, no evidence of progression	27 months
LF-5	F	24	None	Unknown	Cerebral hemisphere	Diffuse astrocytoma	Alive, no evidence of progression	23 months
LF-6	F	10	Osteosarcoma, multiple gliomas	Choroid plexus carcinoma (sister)	Cerebral hemisphere	Diffuse astrocytoma	Alive, no evidence of progression	6 months
IDH-wildtype								
LF-7	M	4	None	None reported	Thalami	Glioblastoma	Died of disease	2 months
LF-8	M	6	None	None reported	Cerebral hemisphere	Glioblastoma	Died of disease	12 months
LF-9	M	18	Medulloblastoma	None reported	Cerebellum	Anaplastic astrocytoma	Alive, no evidence of progression	15 months
LF-10	M	18	None	Adrenal cortical carcinoma (sister)	Cerebral hemisphere	Anaplastic astrocytoma	Alive with progressive disease	13 months
LF-11	F	4	None	Phyllodes tumor (mother); osteosarcoma (uncle); rhabdomyosarcoma (aunt); astrocytoma, colon carcinoma, liposarcoma (grandfather)	Cerebral hemisphere	Diffuse astrocytoma	Alive, no evidence of progression	7 months
LF-12	M	11	Osteosarcoma	Brain cancer (aunt); ovarian cancer (grandmother); rhabdomyosarcoma (uncle)	Cerebral hemisphere	Anaplastic astrocytoma	Alive, no evidence of progression	8 months
LF-13	M	6	None	None reported	Cerebral hemisphere	Glioblastoma	Alive with progressive disease	4 months

[a]Patient LF-2 had two spatially distinct gliomas that were synchronously resected and independently evaluated

an intact/wildtype *ATRX* gene in the youngest patient (LF-7). This absence of *ATRX* loss in patient LF-7 (10 years of age at time of glioma diagnosis) is similar to what has been previously reported in sporadic IDH-mutant astrocytomas in teenagers which lack the *ATRX* inactivation that is typical of their IDH-mutant astrocytoma counterparts in adults [3, 7]. Very few additional pathogenic alterations were identified beyond *IDH1*, *TP53*, and *ATRX*, with only one tumor harboring additional *CIC* nonsense and *ZBTB20* missense mutations (Fig. 1c). There were few, if any, chromosomal copy number changes in these seven tumors (Supplementary Table 4). The median progression-free survival for these patients with IDH-mutant astrocytomas arising in the setting of LFS was 57 months (Fig. 1d and e).

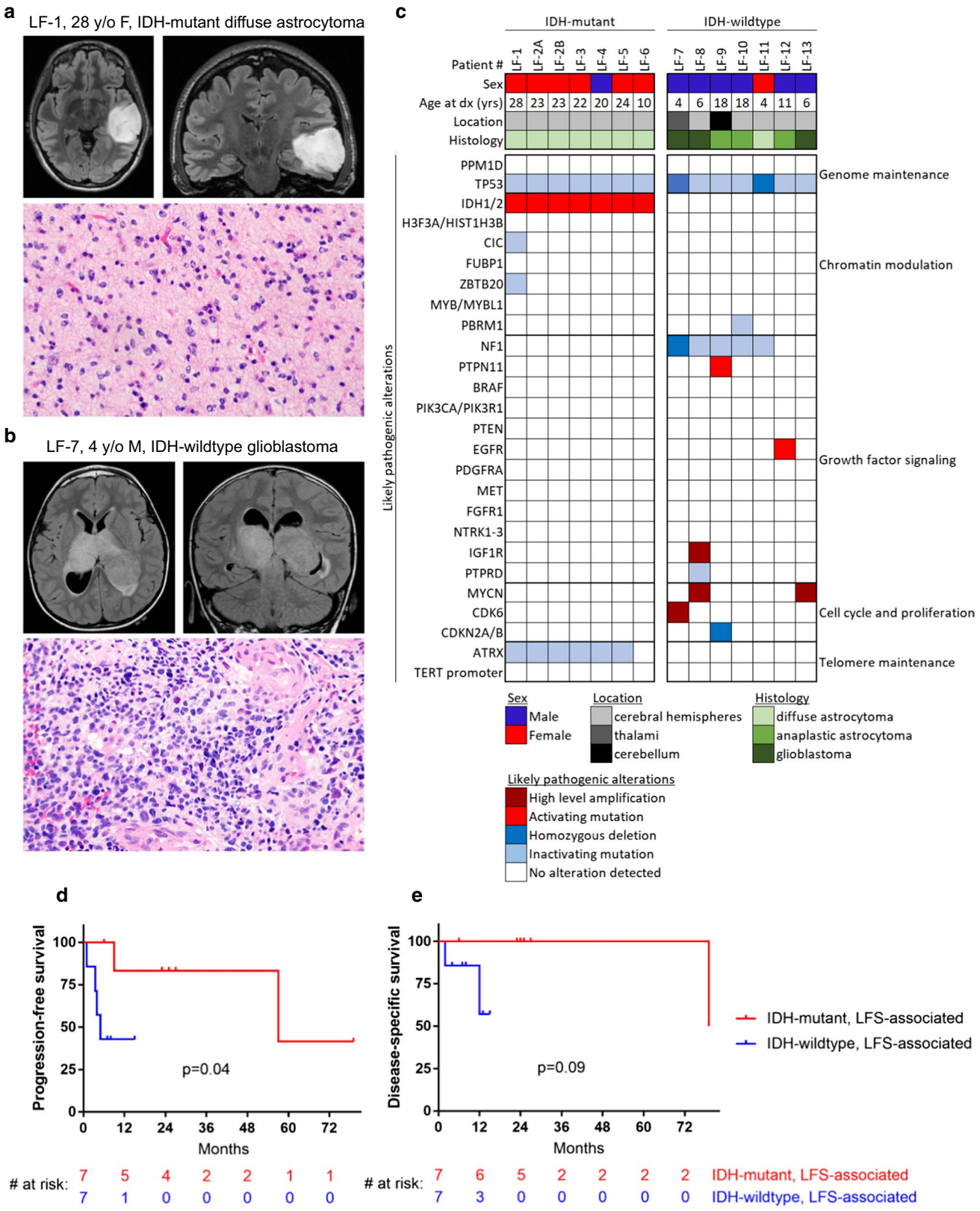
The IDH-wildtype subgroup consisted of seven tumors from seven patients, six male and one female, with median age at glioma diagnosis of 6 years (range 4–18). These seven tumors were located in the cerebral hemispheres (five), thalami (one), and cerebellum (one). Histologic diagnoses were glioblastoma (three), anaplastic astrocytoma (three), and diffuse astrocytoma (one). All seven tumors lacked hotspot mutations involving *IDH1*, *IDH2*, *H3F3A*, *H3F3B*, *HIST1H3B*, and *HIST1H3C*. Instead, five of the tumors harbored somatic biallelic inactivation of the *NF1* tumor suppressor gene and one harbored multiple *EGFR* activating missense mutations (p.L861Q and p.R252P) in the absence of *EGFR* gene amplification (Supplementary Table 2). Additionally, two tumors harbored focal high-level amplification of the *MYCN* oncogene, and individual tumors also harbored homozygous deletion of *CDKN2A/B*, focal high-level amplification of *CDK6* or *IGF1R*, an activating missense mutation in *PTPN11*, and inactivating mutations in *PBRM1* or *PTPRD* (Fig. 1c). All seven tumors harbored biallelic *TP53* inactivation due to a germline missense mutation (five cases) or gene deletion (two cases) accompanied by somatic loss of heterozygosity in all cases (Supplementary Table 3). All of the six histologically high-grade astrocytomas demonstrated numerous chromosomal copy number aberrations, whereas the one IDH-wildtype low-grade diffuse astrocytoma from patient LF-12 that was resected after identification on surveillance imaging lacked any chromosomal copy number changes (Supplementary Table 4). The median progression-free survival for these patients with IDH-wildtype astrocytomas arising in the setting of LFS was 5 months (Fig. 1d and e).

Together, these findings indicate that gliomas arising in the setting of Li-Fraumeni syndrome are diffuse astrocytic neoplasms that can be stratified into two molecular subgroups based on IDH status. Based on this cohort, IDH-mutant astrocytomas arising in the setting of LFS most often occur in females in the second and third decades of life, arise supratentorially in the cerebral hemispheres, have low-grade histologic features, harbor co-occurring *IDH* and *ATRX* mutations with a paucity of other pathogenic drivers, have near-diploid genomes, and are associated with favorable prognosis. In contrast, IDH-wildtype astrocytomas arising in the setting of LFS most often occur in males in the first and second decades of life, arise throughout the neuroaxis, have high-grade histologic features, harbor frequent *NF1* mutations/deletions along with a plethora of other pathogenic drivers including *MYCN* amplification, have aneuploid genomes, and are associated with unfavorable prognosis compared to their IDH-mutant counterparts. These IDH-wildtype astrocytomas appear to be heterogenous in their anatomic location and genetic drivers (in contrast to the homogeneity of their IDH-mutant counterparts), and therefore may likely represent a biologically diverse group of tumors.

Interestingly, the stepwise genetic progression that occurs in sporadic IDH-mutant astrocytomas starts with initial acquisition of *IDH1* mutation, followed by *TP53* mutation and then *ATRX* inactivation [1, 4]. This is in contrast to IDH-mutant astrocytomas arising in the setting of LFS where a germline *TP53* mutation is the initiating genetic driver, followed by somatic inactivation of the remaining *TP53* allele that occurs prior to acquisition of *IDH1* mutation and then *ATRX* inactivation (inferred based on variant allele frequencies, see Supplementary Table 2). Notably, our cohort confirms a high frequency of variant *IDH1* mutations (most commonly p.R132C) that has been previously identified in LFS-associated gliomas [13]. As has recently been appreciated for gliomas arising in the setting of neurofibromatosis type 1 [2], we speculate that gliomas arising in the setting of LFS may represent distinct glioma subtypes that should be distinguished from their sporadic counterparts for more informative diagnostic, prognostic, and therapeutic classification. We suggest the terminology "IDH-mutant [or IDH-wildtype] astrocytoma arising in the setting of Li-Fraumeni syndrome" along with a description of the histologic features (necrosis, microvascular proliferation, mitotic activity) and associated genetic alterations as the best integrated diagnostic framework for these syndromic gliomas pending further investigation.

Methods

The study cohort consisted of nine patients who underwent surgical resection of a glioma that had been prospectively clinically evaluated on the UCSF500 Cancer Panel, one patient who underwent surgical resection of two anatomically and genetically distinct gliomas that were evaluated by exome sequencing on a research basis that has been previously reported (patient 1 from reference 4), and three patients (TCGA-S9-A6U1, TCGA-DB-A64S, and TCGA-VM-A8CH) from the diffuse lower-grade glioma cohort of



The Cancer Genome Atlas Research Network with IDH-mutant astrocytomas found to harbor known pathogenic germline *TP53* mutations [1]. All of the thirteen patients included in this cohort were genetically confirmed to have

◂**Fig. 1** Clinicopathologic features of gliomas arising in the setting of Li-Fraumeni syndrome (LFS). **a** Imaging and histology from patient LF-1 (28-year-old woman) showing an expansile, nonenhancing, T2/FLAIR-hyperintense mass centered in the left temporal lobe with histologic features of a diffuse astrocytoma that was IDH-mutant. **b** Imaging and histology from patient LF-7 (4-year-old boy) showing an expansile and enhancing mass involving the thalami and left lateral ventricle with histologic features of a glioblastoma that was IDH-wildtype. **c** Oncoprint table of the clinicopathologic and molecular features of the 14 gliomas arising in the setting of LFS. **d**, **e** Kaplan–Meier analysis of progression-free survival (**d**) and disease-specific survival (**e**) stratified by IDH mutation status for the 14 gliomas arising in the setting of LFS. p value calculated by Log-rank (Mantel–Cox) test

Li-Fraumeni syndrome by identification of a known inactivating/pathogenic *TP53* mutation or deletion in a constitutional DNA sample via paired tumor-normal sequencing or via germline sequencing analysis at a commercial source. Methodology related to tumor genomic profiling via the UCSF500 Cancer Panel has been previously reported [5, 8, 10].

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Data availability Mutation and copy number data are available in the electronic supplementary material. Sequencing data files are available from the authors upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests related to this report.

Ethical approval This study was approved by the Committee on Human Research of the University of California, San Francisco, with a waiver of patient consent.

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