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TEMPORAL AND SPACIAL EVOLUTION OF CLONES IN 400 LOW GRADE GLIOMAS IN JAPAN

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BACKGROUND: Low grade gliomas (LGGs) account for approximately half of all gliomas. Although LGGs typically show slower tumor progression and generally better clinical outcomes than high-grade gliomas, their clinical course is invariably indolent and most patients ultimately succumb to death. In contrast to high-grade tumors, our knowledge about the genetic lesions and clonal evolution in LGG is still incomplete. **METHODS:** To obtain a complete registry of gene mutations involved in LGG pathogenesis and their role in clonal evolution, we performed whole exome sequencing (WES) of paired tumor/normal DNA from 54 cases with LGG. Clonal evolution in LGG was investigated using paired primary/relapsed tumor specimens from 9 cases as well as multiple tumor specimens (median 5) from 4 cases. We further performed deep-sequencing of common mutational targets identified by WES

and SNP array analysis among a large cohort of 327 LGG cases. **RESULTS:** Major mutational targets detected in WES included not only previously known mutational genes, including IDH1/2, TP53, ATRX, CIC, FUBP1 and NOTCH1, as well as multiple components of the PI3K pathway and the SWI/SNF complex. Multi-sampling analysis revealed regional and special heterogeneity of LGG. According to the observed variant allele frequencies (VAFs), mutations of IDH1/2 and 1p19q co-deletion were thought to exist in the major clone, representing truncal mutations in most cases. In contrast, mutations in TP53, ATRX, CIC and FUBP1 were more often identified in one or more phylogenetic branches in different subclones and involved in parallel evolution, where different mutations of the same genes were found at different time points in different locations. mutations in IDH1/2 were found in 78.6%. 1p19q co-deletion (43.1%), and TP53 mutations (34.6%) with or without ATRX mutations were mutually exclusive with common IDH mutations. VAFs of coexisting IDH1/2 and 1p19q co-deletion were approximately the same, whereas mutations in other genes tended to show lower VAFs than those of IDH1/2. **CONCLUSIONS:** Combined, our findings revealed two major, mutually exclusive patterns in clonal evolution in LGG; in some cases IDH1/2 mutations and 1p19q co-deletions were truncal events, followed by CIC, FUBP1, and other mutations in subsequent phylogenetic branches. In other cases, predated by the founder IDH1/2 mutations, mutations in TP53 and ATRX seemed to predominate tumor populations later. **SECONDARY CATEGORY:** Epidemiology & Cancer Control.