News Release

Title

Mutational landscape and clonal architecture in grade-II and III gliomas.

Key Points

1. **Over 700 samples of grade II or III gliomas were analyzed by next-generation sequencer.**
2. **Regardless of histology types, LGGs are grouped into three distinct subgroups (Type I, II, and III tumors) with different clinical/biological behaviors, according to sets of genetic lesions characteristic to each subtype.**
3. **Major driver alterations showed strong positive and negative correlations with each other and temporal orders to occur, suggesting strong functional interplay between these mutations, which were also supported explicit serial/multi-regional sampling analysis.**
4. **Heterogeneity within a tumor and between tumors at different time points was prominent in grade II and III gliomas. Nevertheless, common occurrence of parallel mutations found in TP53/ATRX, CIC, FUBP1 genes indicated central roles of these mutations in glioma development,**
5. **Multi-regional sampling delineated how grade II and III glioma originated and propagated to generate extensive intratumor heterogeneity through acquiring new mutations in a complex but still ordered fashion.**

Summary

Dr. Atsushi Natsume, Department of neurosurgery, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), and colleagues elucidated Mutational landscape and clonal architecture in grade-II and III gliomas. This study was reported online April 13th, 2015 in *Nature Genetics*.

Grade II/III gliomas account for approximately one third of all gliomas. Although grade II/III gliomas are typically slowly progressive, their clinical course is invariably indolent and most patients ultimately succumb to death. In contrast to glioblastoma (GBM), our knowledge about the genetic lesions and clonal evolution in grade II/III gliomas is still incomplete.

Main findings are as follow;

1. Over 700 samples of grade II or III gliomas were analyzed by next-generation sequencer.
2. Regardless of histology types, LGGs are grouped into three distinct subgroups (Type I, II, and III tumors) with different clinical/biological behaviors, according to sets of genetic lesions characteristic to each subtype.
3. Major driver alterations showed strong positive and negative correlations with each

other and temporal orders to occur, suggesting strong functional interplay between these mutations, which were also supported explicit serial/multi-regional sampling analysis,

4. Heterogeneity within a tumor and between tumors at different time points was prominent in grade II and III gliomas. Nevertheless, common occurrence of parallel mutations found in TP53/ATRX, CIC, FUBP1 genes indicated central roles of these mutations in glioma development,

5. Multi-regional sampling delineated how grade II and III glioma originated and propagated to generate extensive intratumor heterogeneity through acquiring new mutations in a complex but still ordered fashion.

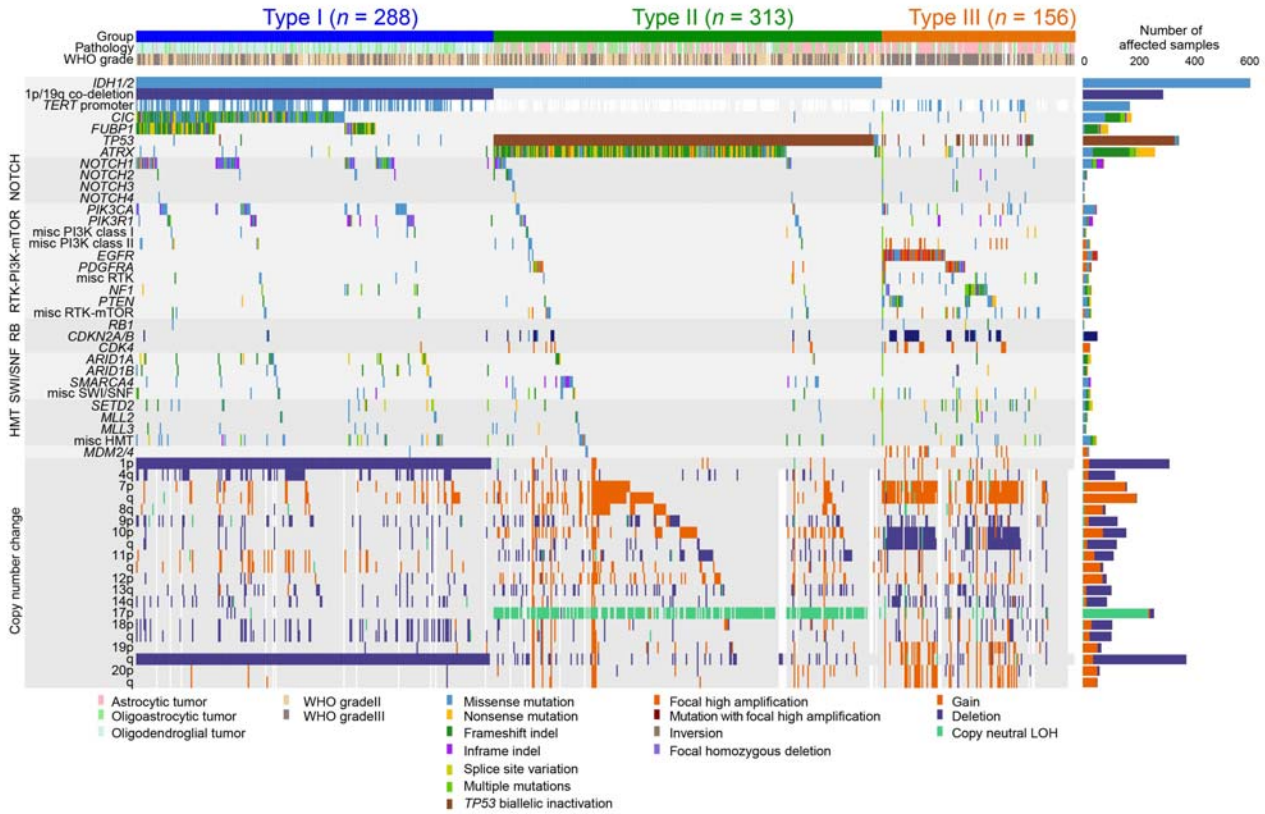
Research Background

Grade II/III gliomas account for approximately one third of all gliomas. Although grade II/III gliomas are typically slowly progressive, their clinical course is invariably indolent and most patients ultimately succumb to death. In contrast to glioblastoma (GBM), our knowledge about the genetic lesions and clonal evolution in grade II/III gliomas is still incomplete.

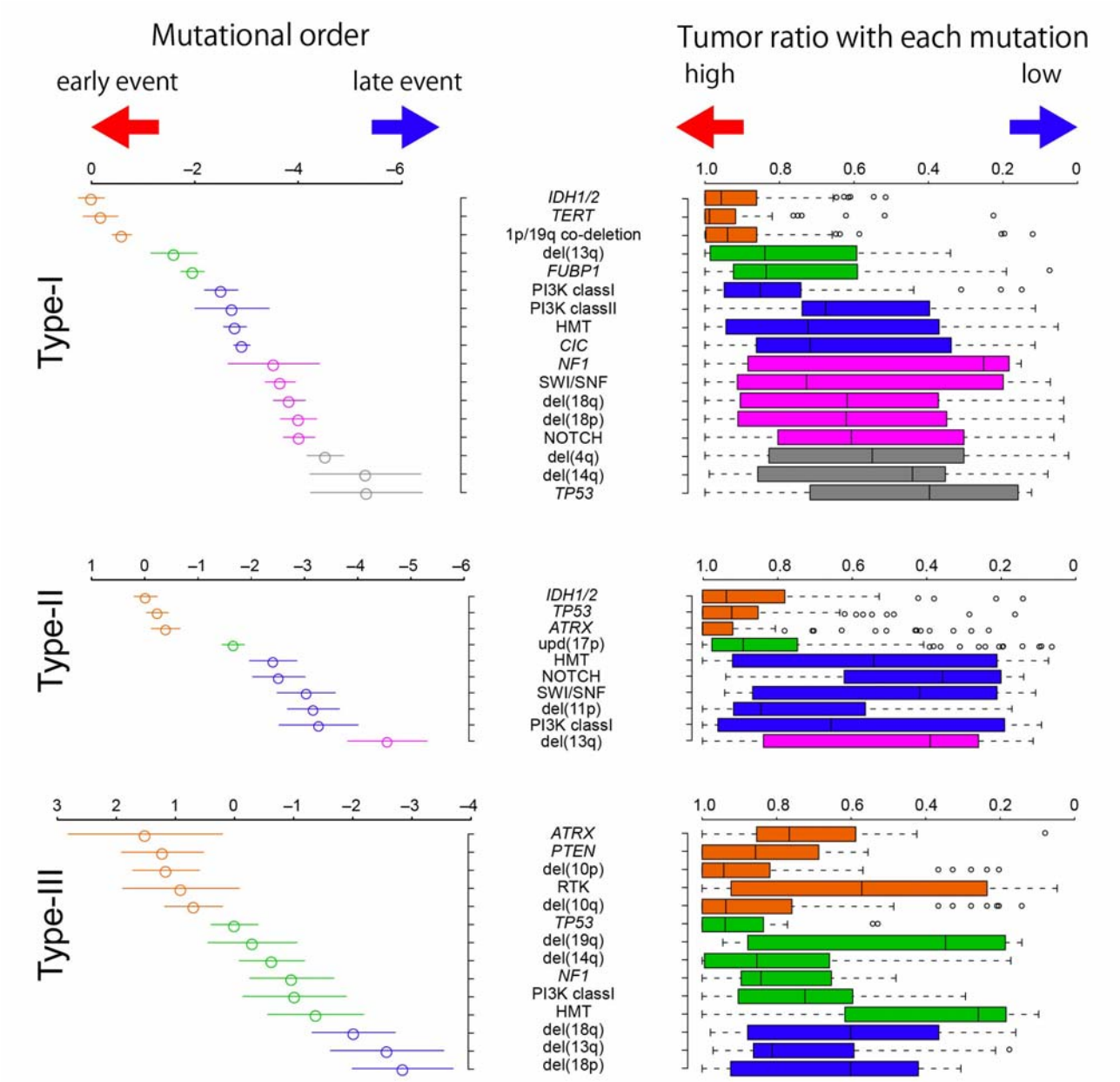
Dr. Atsushi Natsume, Department of neurosurgery, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), and colleagues analyzed over 700 grade II/III gliomas and revealed mutational landscape and clonal architecture.

Research Results

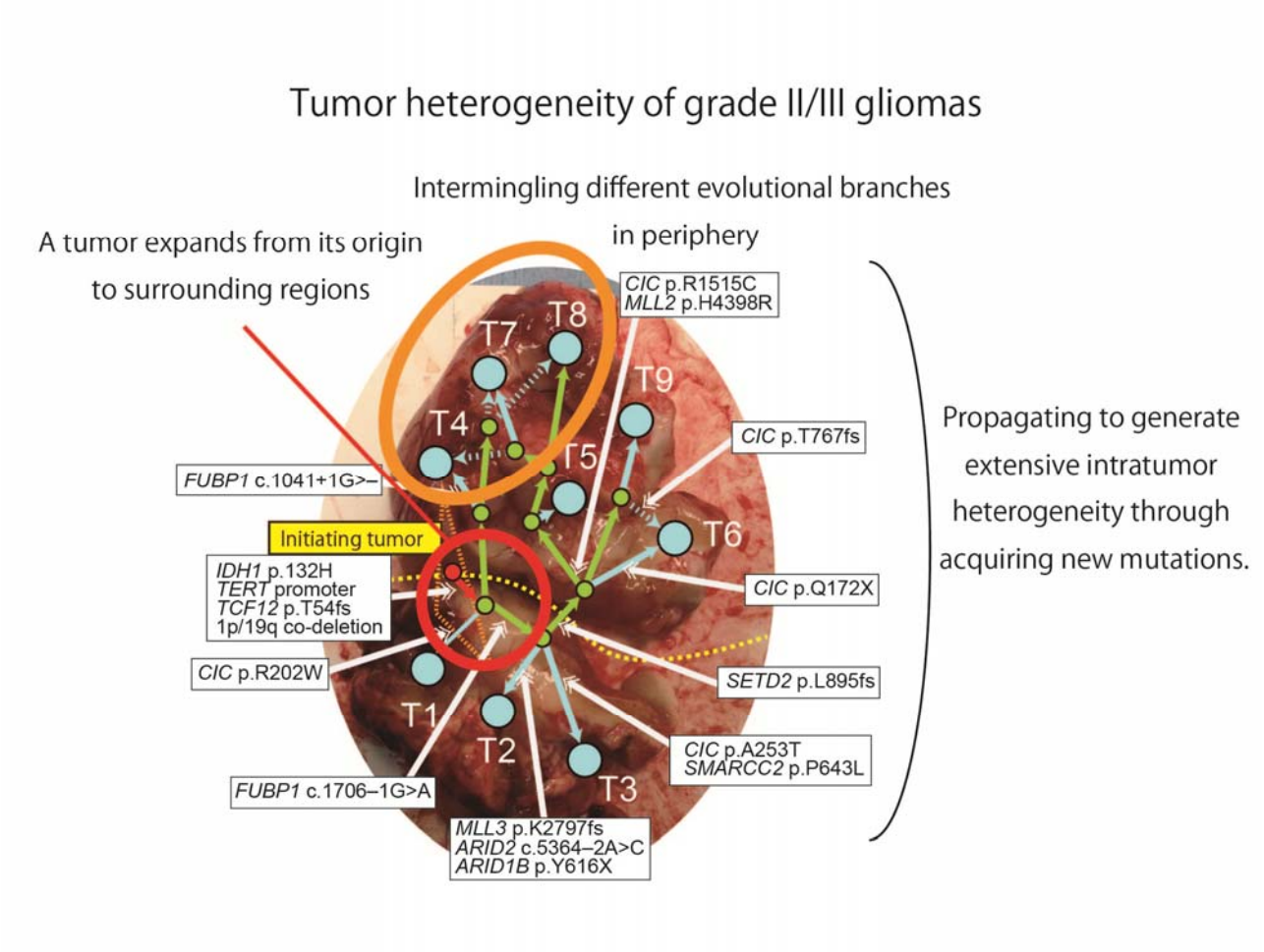
Including large data of whole exome/targeted sequencing and copy number analysis in 757 grade II/III glioma cases from combined Japanese (N = 332) and TCGA (N = 425) cohorts, this represents the largest genetic study ever performed for grade II/III gliomas, revealing an entire picture of grade II/III gliomas. Massive parallel sequencing revealed grade II/III gliomas were clearly grouped into three subgroups with or without *IDH1/2* mutation and 1p/19q co-deletion (Figure 1).



Mutations showed significant positive/negative correlations and chronological hierarchy as inferred from different allelic burdens among coexisting mutations (Figure2). All mutations in *IDH1* and *TERT* promoter as well as 1p/19q co-deletion in Type-I tumors and most *TP53* in Type-II tumors were found as early event. Multi-/serial sampling analyses supposed these mutational orders.



Extensive serial/multi-regional sampling analyses further revealed high degrees of temporal/spatial heterogeneity generated during tumor expansion and relapse. Figure 3 is representative case.



Research Summary and Future Perspective

These finding provided the basic information of grade II/III glioma pathogenesis and will lead to the development of new therapy for grade II/III gliomas.

The authors and title of the paper

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http://www.med.nagoya-u.ac.jp/medical/dbps_data/_material_/nu_medical/_res/topix/2015/gliomas_20150414jp.pdf