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The Clinicopathological and Genetic Characteristics of High-grade Gliomas with Histone H3.3 G34 Mutation in Teenagers and Young adults

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Chromatin is composed of nucleosomes, with each nucleosome consisting of an octamer of two copies each of histones H3, H4, H2A, and H2B. Chromatin is critical for the control of transcription, replication, DNA repair and other aspects of genomic stability. In humans, there are different histone H3 variants. H3.3 proteins are expressed thoughout the cell cycle as well as in quiescent cells [1], while H3.1 and H3.2 are expressed only during the S-phase [2].

In 2012, recurrent mutations in *H3F3A*, which encodes histone 3 variant H3.3, were firstly identified in pediatric and young adult high-grade gliomas (HGGs) [3,4]. Subsequent studies have extended the breadth of cancers known to carry mutations in histone H3, including chondroblastoma, giant cell tumors of bone, chondrosarcoma, pediatric soft tissue sarcoma, head and neck squamous cell carcinoma and leukemia [5-8]. In HGGs, *H3F3A* mutations lead to amino acid substitutions at two critical positions within the histone tail (K27M, G34R/V) involved in key regulatory post-translational modifications. HGGs with H3 K27M mutation almost exclusively occur in midline structures (thalamus, brain stem, or spinal cord) and have been designated as “diffuse midline gliomas (DIPGs), K27M-mutant” in the WHO classification of tumors of the CNS 2016 [9]. Otherwise, HGGs with H3.3 G34R/V mutation have not been defined as a separate entity in the WHO classification 2016.

HGGs with H3.3 G34R/V mutation occur most often in cerebral hemispheres of teenagers and young adults (age 10 to 25 years), with a generally poor prognosis [10-12]. Histologically, these HGGs typically show an undifferentiated phenotype with a small blue-cell component, a glioblastoma-like astrocytic component or a mixture of the two. Therefore, they have been diagnosed as glioblastoma (GBM) or primitive neuroepithelial tumor (PNET) in the past [10,13]. One case of astroblastoma [14] and two cases of neuro-epithelial tumors containing glial and dysplastic ganglion cell components [15] with H3.3 G34 mutation have been reported. We know that the histological spectrum of mutations associated with tumor entities is often wider than initially described. For example the list of brain tumors with BRAF-V600E is growing [16]. Hence, the morphologic spectrum of brain tumors with H3.3 G34 mutation may further extend in future studies. Maybe these tumors should be defined as neuro-epithelial tumors with H3.3 G34 mutation.

H3F3A encoding histone H3.3 is mutated at high frequency in pediatric brain and bone tumors. These *H3F3A* missense mutations affect three amino acids on the N-terminus of H3.3, K27, G34 and K36. K27 and K36 are mutated to methilnine (M) in pediatric DIPGs and chondroblastoma respectively [3,4,17]. G34 mutated to various amino acids, including arginine (R) and valine (V) in pediatric HGGs and tryptophan (W) and leucine (L) in giant cell tumors of the bone (GCTB) [5]. The K27M mutant competes for binding to EZH2, the H3K27-specific lysine methyltransferase (KMT), and thus effectively sequesters EZH2 and the PRC2 complex to prevent it from further propagating the repressive H3K27 methylation mark [18,19]. The K36M mutant inhibits KMTs specific to H3K36, including NSD1, NSD2 and SETD2 and reduces global H3K36 methylation [7,20]. It suggest that the lysine-to-methionine mutations inhibit H3 methylation pathways to promote tumorigenesis.

Somatic mutations at G34 in *H3F3A* were first identified in pediatric HGGs of the cerebral cortex. And the cortical

pediatric HGGs bear a more common G34R mutation than G34V mutation [21]. G34 lies towards the base of the H3 tail, close to the DNA entry and exit points of the nucleosome. G34 sits just 2 residues away from K36 and 4 residues from P38, a residue that can adopt distinct conformations to control K36 methylation [22]. G34R and V mutants have been investigated to diminish H3K36me2/3 in cis on the same histone H3 tail, but exhibit no dominant effect to block K36 methylation on WT H3 tails [23].

HGGs bearing G34R/V mutations are also frequently mutated for ATRX (α-thalassaemia/mental retardation syndrome X-linked), DAXX (death-domain associated protein) and *TP53* [3,24]. In addition, *MGMT* promoter methylation is frequently detected in G34-mutant HGGs(74%) and associated with a significantly better prognosis [10]. G34-mutant HGGs also display 2q loss (67%), 4q loss (70%), *PDGFRA* amplications (27%), *CDNK2A* detetion (14%) and *CDK6* amplification (10%) [10,25,26]. *H3F3A* G34 mutations cause profound upregulation of *MYCN*, a potent oncogene that is causative of GBMs [27].

In conclusion, HGGs with H3.3 G34 mutations are restricted in cerebral cortex of adolescence or young adulthood. These tumors display a divergent histopahtologic apperance, including GBM-like and PNET-like morphology. Glial and dysplastic ganglion cell components can also been found. Except the G34 mutation, other molecular features in G34-mutant HGGs include *ATRX* and *TP53* mutations, *MGMT* promoter methylation. However, how the G34 mutants exert dominant effects on histone H3 biology, remains unknown, which provides a novel avenue for targeted therapy in these HGGs.

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