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CORRESPONDENCE

K27/G34 versus K28/G35 in histone H3-mutant gliomas: A note of caution

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The discovery of *H3F3A* mutations in pediatric gliomas [11] marked a milestone in understanding the pathogenesis of these tumors. Schwartzentruber et al. demonstrated that so-called H3.3K27M and H3.3G34R/V alterations serve as driver mutations in pediatric glioblastomas. Further investigations revealed that G34R/V mutations are seen mainly in hemispheric glioblastomas. In contrast, neoplasms with histone H3K27M mutations are often located in midline structures. An important example is the diffuse intrinsic pontine glioma (DIPG), with a median overall survival of less than 12 months [5]. The discovery of the above as well as H3.3K27I, H3.1K27M and H3.2K27M [2] mutations proved not only to be of major diagnostic and prognostic relevance [1] but also as a potential therapeutic target [9]. In fact, the correlation of H3K27M mutations with poor overall survival has led to the introduction of a new entity, the "diffuse midline glioma H3K27M-mutant", in the updated "WHO Classification of Tumours of the Central Nervous System" (2016) [8].

In our analyses, we have observed a discrepancy of the described mutation site and the DNA-based mutation within the mutant-protein. Figure 1 (a) depicts the first 15 amino acids of the coding *H3F3A* sequence. Molecular genetic analysis of a representative diffuse midline glioma (WHO grade IV) H3K27M-mutant is shown in (b), indicating that the amino acid 28 rather than 27 shows a conversion from lysine (K) into methionine (M). Furthermore, the amino acid sequence of a tumor from another patient (c) demonstrates that the discrepancy also applies to the H3.3G34R-mutation, which involves amino acid G35 rather than G34. One explanation for this discrepancy is that alterations in the histone protein typically do not follow the "standard mutation nomenclature in molecular diagnostics (2007)" [10], which states that the first nucleotide of a coding DNA sequence is the A of ATG and that the first amino acid of a protein is labeled with 1. Instead, the numeration of histone amino acids is based on initial papers that disregarded the first methionine, as it is cleaved in an early posttranslational state, and was, therefore, initially not detected. [4].

Maintaining separate nomenclatures for cancer-related mutations will certainly be a hopeless endeavor in times of whole-genome sequencing, which follow the standard nomenclature from 2007 [10]. In addition, standard references such as the "Catalogue of Somatic Mutations in Cancer" (COSMIC) or the NCBI database, as well as single publications follow this nomenclature and describe such alterations as K28M or G35 mutations [6, 7]. Exactness is particularly important in G34-related mutations, as the DNA-based 34th amino acid of *H3F3A* is also a glycine that could be converted into arginine. Therefore, it needs to be discussed, how the histone nomenclature by convention should be adapted. A precedent for a successful nomenclature change is the *BRAF*V600E mutation, which was formerly reported as *BRAF*V599E mutation [3]. We believe that this lack of clarity is prone to erroneous interpretation of the reported mutations and to diagnostic inaccuracy.

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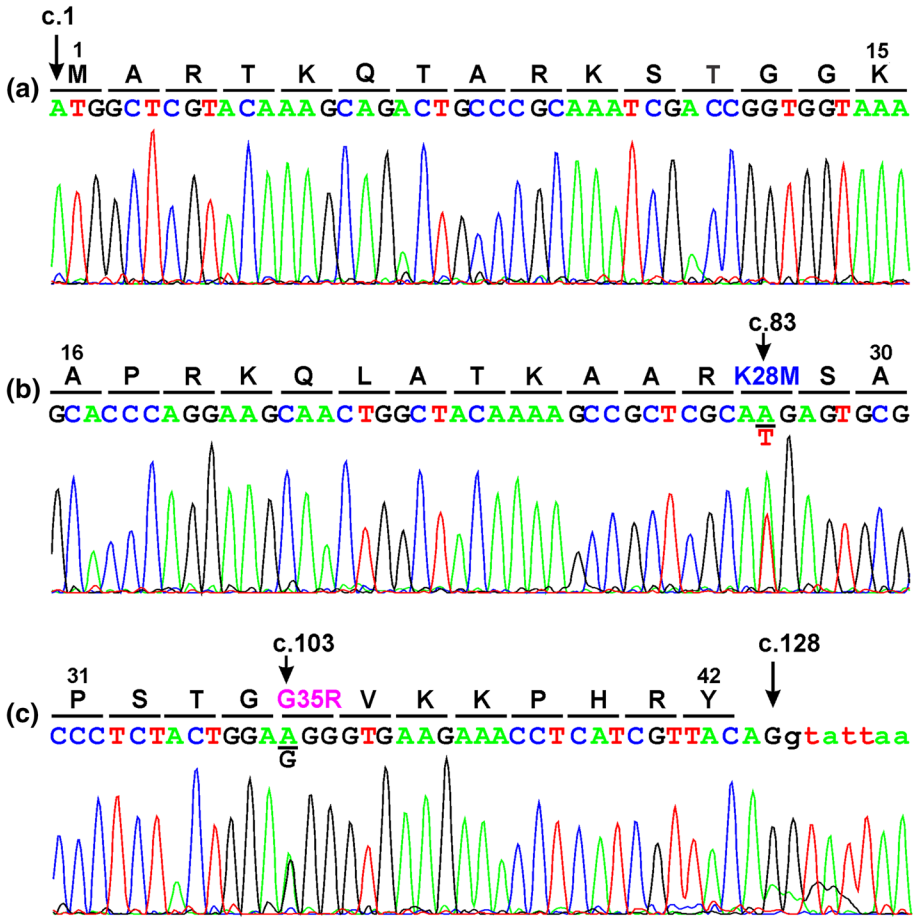

Fig. 1 Illustration of *H3F3A* mutations. The figure represents the chromatogram, coding DNA and amino acid sequence of *H3F3A* with selected mutations. Whereas there are no mutations within the first 15 amino acids (**a**), the sequence of an exemplarily case of H3.3K27M-mutant diffuse midline glioma (**b**) highlights that the exchange of the amino acid lysine (K) into methionine (M) takes place at position 28, and therefore corresponds to a K28M mutation. The sequence of another case with H3.3G34R mutation is depicted in (**c**), showing that position G35 rather than G34 is altered and thus represents a G35R mutation

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