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PROGRESS IN MOLECULAR GENETIC RESEARCH ON LONG-TERM EPILEPSY-RELATED TUMORS

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Abstract: Long-term epilepsy-related tumors (long - term epilepsy associated tumor, LEAT) grows slowly, has a lower histological grade, and is accompanied by varying degrees of glial and neuronal differentiation. With the development of molecular genetics, LEAT Relevant genetic variants with diagnostic and/or prognostic significance are discovered. BRAF Gene mutation most common in ganglioglioma, BRAF V600E Mutation into the most common form of variation. Dysembryoplastic neuroepithelial tumors Common genetic alteration is FGFR 1 mutation. The most common genetic alteration in pilocytic astrocytoma is KIAA 1549 and BRAF Genetic fusion. almost all Angiocentric gliomas contain MYB - QKI Fusion. Polymorphic low-grade neuroepithelial tumors in children are often associated with BRAF V600E Mutation or FGFR 2/ FGFR 3 Fusion changes, and both changes often occur in mutually exclusive ways. Whole genome DNA Methylation analysis has become a powerful means of classifying primary brain tumors. Facilitates classification of tumors with unclear histological type.
Keywords: Long-term epilepsy-related tumors; Molecular genetics

1. MOLECULAR GENETIC CHANGES IN MIXED GLIAL NEURONAL TUMORS

Epilepsy, as a common neurological disease in children, seriously damages children's health and quality of life. There are many causes of epilepsy, including cortical developmental malformations, brain tumors, trauma, inflammation, etc. 201 0 Anniversary et al. [1] found that brain tumors accounted for a large proportion of the pathological manifestations of epileptogenic lesions in Chinese patients with continuous refractory epilepsy. 11.7% (51/435). and 2017 Blümcke et al [2] studied nearly 10,000 cases of epileptogenic focus resection specimens and found that brain tumors accounted for 23.6% of refractory epilepsy (2 244/9 523). long-term epilepsy associated tumor, LEAT) was first developed by Luyken et al [3] in 2003 It was proposed in 2008 that after analyzing the histological and clinical characteristics of patients with drug-resistant epilepsy associated with neuroepithelial tumors, it was concluded that the prognosis is better after surgical resection. LEAT It is common in young people, grows slowly, and has a low histological grade. It is mostly located in the cortex (more common in the temporal lobe). The tumor is often accompanied by focal cortical dysplasia (focal cortical dysplasia). cortical dysplasia, FCD) [4]. LEAT There are two main categories: mixed glial neuronal tumors and glial tumors. ganglioglioma GG) and dysembryoplastic neuroepithelial tumors (dysembryoplastic neuroepithelial tumor, DNT) are the two most common tumors of the former; pilocytic astrocytoma (pilocytic astrocytoma, PA), pleomorphic xanthoastrocytoma, angiocentric glioma (angiocentric gli omas, AG), diffuse astrocytoma (diffuse Astrocytoma) and oligodendroglioma are the most common tumor types in the latter [4]. Glial tumors are associated with early-onset drug-resistant epilepsy (mean age at onset <15 years) is closely related to PA and AG. The epilepsy-related tumors described above form a spectrum with varying degrees of glial and neuronal differentiation, and tumor subtypes are often not distinguishable by histological features. At the same time, simple histological diagnosis is difficult to reveal biological characteristics such as malignant potential. close 10 With the development of molecular genetics, LEAT Relevant, diagnostic and/or prognostic Genetic mutations are gradually being discovered. LEAT Isocitric acid removal generally does not exist Hydrogenase (isocitrate dehydrogenase, IDH) gene mutations and infections color body 1p/19q co-deletion occurs frequently Ras/Raf/mitogen-activated protein kinase (mitogen activated protein kinas e, MAPK) path pathway signaling pathway and phosphatidylinositol -3- kinase (phosphatidylinositol-3-kinase, PI3K)/protein exciting Enzyme B (protein kinase B, AKT)/mammalian target of rapamycin (mammalian target of rapamycin, mTOR) signaling pathway gene abnormalities [5]. In recent years, all base due to group DNA Methylation analysis becomes powerful tool for classifying primary brain tumors means [6].

1.1 GG Related Genetic Variants

GG To differentiate well, grow slowly Neuroepithelial tumors, most common in the temporal lobe, are more common in children. Histology can See abnormally developed neurons. These neurons have a morphology similar to ganglion- like cells, showing large multipolar cell bodies and vesicular nuclei (which may be binucleated). or multinucleated) and obvious nucleoli and Nisslsite. Immunohistochemistry table Reaching CD34, it can show background diffuse positive expression or plexiform/cluster-like positive expression. It can also show strong positivity in the cytoplasm, membrane and processes of single cells [4]. GG middle The proportion, type and distribution of proliferated glial cells are

different, and star- shaped cells can be seen. cells and oligodendrocyte components, etc. In addition, calcification and lymphocytes are common. infiltration.
Research shows that BRAF The gene mutates to GG The most common genes in changes, accounting for approximately 50% of this tumor [7-8], BRAF V600E mutates most often Variations seen. At the same time, other forms of variation include MACF 1- BRAF, AGK - BRAF and GNAI 1- BRAF fusion genes [7]. Other Outside, GG There can still be TSC 2 mutation, H3K27M mutation and P35 burst Change [9- 11]. 2013 Dahiya et al. [8] found that when GG Accompanied by increased tumor cell density, lack of oligodendrocyte components, inflammatory cell infiltration, and microvascular hyperplasia and BRAF When V 600E mutates, the degree of malignancy is greater. But BRAF V 600E mutation is closely related to oligodendrocyte components and tumor cells There is no correlation between degree and microvascular infiltration, but there is correlation with inflammatory cell infiltration. Tips in GG Lymphocyte infiltration can be seen as predictive of malignant behavior an indicator. It was recently reported that BRAF Phase III inhibitor vemurafenib (vemurafenib) to treat BRAF V600E mutated metastatic melanin Clinical trials of tumors can effectively improve patient survival rates and provide opportunities for future use BRAF target therapy BRAF V 600E mutation GG provided good Select [12].

1.2 DNT Related Genetic Variants

DNT It is a benign mixed glue Cytoplasmic neuronal tumors are more common in children and adolescents, and the sites of onset are mostly located in Temporal lobe, recurrence or malignant progression is rare. DNT under the microscope Contains mixed Synthetic glial neuronal components, tumors often appear as nodules in the temporal cortex Growth like oligodendrocyte-like cells (oligodendrocyte - like) can be seen cells, OLCs) are arranged in micro-columnar shapes around blood vessels, DNT characteristic knot It is composed of a myxoid matrix and neurons floating within it [13].
IDH 1 mutations, NF 1 mutations, and BRAF V 600E mutation in DNT were discovered one after another in DNT possible causes. and Rivera et al. [14] pointed out that DNT The most common types of genetic changes are FGFR 1 mutation change, account for approximately DNT of 58% (25/43), tyrosine kinase domain, TKD) heavy complex yes most often See of sudden Change kind type (50%). Qaddoumi [7] found that FGFR 1 mutations are more likely to occur in have Among low-grade neuroepithelial tumors characterized by OLCs, DNT middle achieve 82%. FGFR 1 Diversity of mutated forms, including TKD Heavy Complexity (24%), point mutations (multiple hot spots, multiple mutations) (6.7%), fusion (FGFR - TACC) (3%) etc. These variant types are found in other malignant It has been reported in tumors such as low-grade glioma, malignant melanoma, and glioblastoma. Blastoma. Studies have found that FGFR 1 Mutations can cause autophosphorylation ation, and simultaneously activates MAPK/ERK and PI 3K pathway, while FGFR 1 special heterosexual blockers PD 173074 and BGJ 398 as well as MEK 1 blockers PD 0325901 can block FGFR 1 autophosphorylation and The specific mechanism of activation of the MAPK/ERK pathway remains to be studied [15].

1.3 Progress in the Molecular Genetics of Mixed Glial Neuronal Tumors

Mixed glial neuronal tumors are morphologically diverse, often intersecting, transitioning, or coexisting histologically, and lack clear histopathological boundaries. It brings great difficulties to clinical pathological diagnosis. Qaddoumi Wait [7] vs. 91 Whole genome, whole exome and transcriptome sequencing (WGS, WES, RNA-seq) were performed on 71 patients with low-grade neuroepithelial tumors. Whole-genomic DNA analysis of tumor samples Methylation profiling revealed that most GG belong The molecular group of BRAF mutations, while DNT and oligodendrogliomas are Molecular panel of FGFR 1 mutations. 2018 Year, Stone [16] In order to study the presence of different types of entities in the mixed glial neuronal tumor spectrum, we collected 111 glial neuronal tumor cases and divided them into 3 group, that is GG, DNT and glial neuronal tumors not otherwise specified (glioneuronal tumours, non - specific histology, GNT NOS). Already DNA methylation array and Cluster analysis of RNA sequencing test results identified two different molecular groups of mixed glial neuronal tumors, but only some cases in the molecular groups matched the existing Histological classification. Further analysis revealed that each molecular group possesses Different pathogenic mutations and phenotypes: Chapter 1 Group for BRAF Mutation driven, obvious Shows astrocyte differentiation; Chapter 2 grouped as FGFR1 mutation drives, shows less Glial cell differentiation. Also pointed out CCND 1, CSPG 4 and PDG **-** FRA Immunohistochemical staining helps distinguish the two molecular groups. about GNT NOS The positioning and typing of genes have yet to be based on a large sample size. and epigenetic levels.

2. MOLECULAR GENETIC CHANGES IN GLIAL TUMORS

2.1 PA Related Genetic Variants

PA It is a kind of boundary that is relatively clear and slow. Cystic astrocytoma that grows and often occurs in children and young adults. Clinical manifestations include epilepsy, headache and visual impairment [17]. PA Having organizational bipolar type, so that the dense zone contains Rosenthal Fibers with many spindle cells and loose areas It

is characterized by the formation of polar cells with microcysts and granular bodies. part PA and GG The histological features overlap, and in this case, CD 34 and MAP -2 Enter line identification [18].
MAPK Abnormal activation of pathways PA occurrence plays an important role. PA The most common genetic alteration is KIAA 1549 and BRAF fusion of genes,See At More than 70% of cases, and most often happens in the cerebellum [19]. BRAF of N The terminal regulatory domain is KIAA 1549 albumen N terminal substitution, whereas BRAF C The terminal protein kinase domain is retained, so KIAA 1549- BRAF Fusion Egg Whiteware have exciting enzyme Active and resulting in MAPK The pathway is continuously activated. Recent studies have pointed out that I Neurofibromatosis type (NF 1) and PA of the optic nerve and chiasm Close relationship. Neurofibromin is NF 1 The expression product of a gene, the loss of which will result in Ras Increased activity and astrocyte proliferation [20]. also, Apart from MAPK/ERK Outside the signaling pathway, PI 3K/ AKT Activation may mediate an increase in cell proliferation activity and lead to histological anaplastic and invasive biological behaviors [21].

2.2 AG Related Genetic Variants

AG Slow-growing, mostly affecting children and young adults, first diagnosed by Lellouch - Tubiana etc. [22] and Wang [23] proposed that in 2007 included in the year WHO In the classification of central nervous system tumors, it is classified among other tumor types in neuroepithelial tumors [24]. 2016 The revised version classifies it as other glioma. The clinical manifestations are chronic intractable epilepsy and the histological feature is uniform bipolar short spindle cells arranged around blood vessels. Immunohistochemical staining GFAP, S- 100 and vimentin are positive, EMA is "spot" positive, and nerve Metamarkers (synaptophysin, Syn) and NeuN is negative [25]. Tatevossian [26] discovered the presence of MYB in astrocytomas while studying genetic mutations in low-grade gliomas. Amplification and high expression, and AG (1/2 Example) in MYB Localized deletions at the ends. Ramkissoon [27] found that in AG ChineseMYB Gene copy number changes or gene fusions are located at 6q23, which is consistent with previous studies of AG The molecular changes are similar. The data from Qaddoumi et al. [7] show that Almost all AG all contain MYB - QKI Fusion (13/15). This discovery is important for the treatment and diagnosis of the disease. Despite directly targeting MYB The development of small molecule inhibitors may be difficult, but can target compounds such as KIT or MYB - QKI for CDK 6 Transcriptional targets [28].

2.3 Polymorphic Low-Grade Neuroepithelial Tumors of Childhood (Polymor-Phous Low-Grade Neuroepithelial Tumor of the Young, PLNTY) Related Genetic Variants

PLNTY Low-grade neuroepithelial tumors are a new type of tumor that occur in children and young adults. Despite variable morphology, OLCs are present Composition, Infiltrative Growth Pattern and CD34 of powerful Positive sex surface reach. PLNTY often companion have BRAF V600E Mutation or FGFR 2/ FGFR 3 Fusion changes, and the two changes often occur in mutually exclusive ways. Histology is homogeneous OLCs, The nuclei are round, the perinuclear halo is obvious, or there are changes in nuclear size, mostly oval or spindle-shaped nuclei, nuclear membrane wrinkles and nuclear furrow formation, etc. Occasionally, false inclusions can be seen in the nucleus. Sometimes tumor cells are distributed along the blood vessels and a pseudorose-shaped structure can be seen. Calcification was visible, perivascular lymphocytic infiltration was found only in a few cases (1/10), and mitotic figures were rare. Immunohistochemistry GFAP, CD34 and OLIG2 expression, BRAFV600E in Weak expression in 3 cases, NeuN and IDH1 (R132H) negative, no EMA Point or circular expression of, Ki 67 insufficient 1%. OLCs The morphology and perivascular pseudorosette structure make PLNTY Differential diagnosis needs to be made with oligodendroglioma and ependymoma [4]. and PLNTY characteristic DNA Methylation tip PLNTY and GG, PA and with MAPK DNT characterized by pathway activation Closely related, providing a direction for the histogenesis of this tumor [29].

3. OUTLOOK

As molecular genetics LEAT Applications in categories, as related It provides the basis for the diagnosis, differential diagnosis and targeted treatment of tumors. BRAF Gene mutations and FGFR 1 Prognostic judgment brought about by genetic mutations and corresponding treatment options remain to be further studied. Such as vemurafen Vemurafenib is effective in the treatment of metastatic malignant melanoma and is Can it be applied to GG It is not known yet, but it may provide guidance for future clinical treatments. new ideas. DNA Epigenetic changes such as methylation are gradually being It plays an important role in understanding the histogenesis and differentiation status of tumors. It also provides new means and methods for accurate tumor classification.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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