Genomic Medicine in Central Nervous System Tumors

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There are two main applications of genomic medicine with respect to CNS tumors: awareness and prevention of hereditary and/or familial tumors, and personalized medicine for sporadic tumors in individuals. We need to understand the difference between these two medicinal approaches and the status of genomic medicine in this lecture note.

Firstly, this lecture will show the status of hereditary and familial tumors. The lecture will also explain what medicine has to offer for these tumors and the dangers of taking genetic tests blindly. Next, we will discuss personalized medicine. Recent advances in molecular biology have significantly impacted clinical practice. Molecular biological analysis methods are necessary for the classification of tumors, especially for central nervous system (CNS) tumors. The classification of a tumor indicates its prognosis and grade. The fact that this technology is being used suggests that the clues to treatment will depend on molecular biological properties. However, the treatment of CNS tumors has not progressed compared to changes in diagnostic technique. There are some issues that need to be overcome to develop new therapeutics for CNS tumors, such as the blood–brain barrier and the rarity of epidemiology for CNS tumors. Finally, we will discuss how we are working to overcome this challenge.

Key words: genome, genomic medicine, central nervous system tumors

Introduction

Genomic medicine has two important medical implications. One is personalized prevention for patients genetically predisposed to disease, and the other is personalized therapy based on genetic abnormalities of individual tumors. In terms of neoplasms, hereditary and familial tumors are diagnosed as patients genetically predisposed to tumors, while solitary tumors are covered by the latter, personalized therapy.

Hereditary and familial tumors

Hereditary diseases complicating central nervous system tumors are listed (Table 1), and often, the tumor driver genes and causative genes have been genetically identified.

One of the familial tumors is glioma. Five percent of patients suffering from glioma may have a first- or second-degree relative with a similar tumor. A recent study revealed that mutations in the POT1 member of the telomere shelterin complex have been associated with familial gliomas. Familial oligodendrogliomas have been associated with germline mutations in shelterin-complex genes1. Tumorigenesis can be caused by two mechanisms. One is an increasing rate of genetic mutations, as typified by Li-Fraumeni and Turcot’s syndromes, which make tumor control difficult. The other is the accumulation of small genetic abnormalities that lead to the failure of tumor control pathways to grow. The latter is characterized by neurofibromatosis and tuberous sclerosis2. Since the genetic abnormalities that cause these diseases cannot be repaired to date, the main role of medicine is the prevention and early detection...
of tumors.

To educate people about such medical care, some companies in Europe and the U.S. offer advice on whether or not to take a genetic test by simply answering a few simple questions on their websites. However, there are warnings against easy genetic testing, especially for minors who might be exposed to test results without having the experience or understanding to prepare for possible future diseases. Genetic societies in Japan have issued the following guidelines, which should be understood by medical professionals before testing.

Genetic testing may not be performed in the following cases:

・ If the patient requests a genetic test, but the physician in charge determines that the test is not appropriate.

Table 1: Familial tumors syndrome (Modified from reference 17)

| Gene               | Inheritance | CNS tumors                                                                 |
|--------------------|-------------|----------------------------------------------------------------------------|
| Neurofibromatosis type 1 | NF1        | 50% AD; 50% de novo 15~20% optic pathway glioma                           |
|                    |             | 4% low-grade glioma (Brainstem glioma)                                     |
|                    |             | 1% glioblastoma                                                            |
| Neurofibromatosis type 2 | NF2        | 50% AD; 50% de novo 50% intracranial meningioma                            |
|                    |             | 20% spinal meningioma                                                      |
|                    |             | 30% spinal ependymoma, glioma                                              |
| Schwannomatosis    | SMARCB1     | AD                                                                          |
|                    |             | Meningioma                                                                 |
| Li-Fraumeni        | TP53        | 80% AD; 20% de novo Wide range of brain tumors reported in 20~60%         |
|                    |             | Glioblastoma                                                               |
|                    |             | Medulloblastoma                                                            |
|                    |             | Choroid plexus carcinoma                                                   |
| Von Hippel-Lindau  | VHL         | 80% AD; 20% de novo 80% hemangioblastoma (cerebellum/spinal cord/retina)   |
| Turcot type 1 (brain tumor–polyposis syndrome 1, hereditary non–polyposis cancer syndrome (HNPC), constitutional mismatch repair cancer syndrome or deficiency, Lynch syndrome) | MMR genes | 3% glioblastoma (Hypermutated phenotype) |
|                    |             | AD                                                                          |
| Turcot type 2 (brain tumor–polyposis Syndrome 2, familial adenomatous polyposis (FAP), Gardner syndrome) | APC | 85% AD; 15% de novo Medulloblastoma (WNT-activated) |
| Gorlin syndrome (Nevoid basal cell carcinoma) | PTCH1, SUFU | 75% AD; 25% de novo 5% medulloblastoma (SHH-activated) Meningioma |
| Tuberous sclerosis complex | TSC1, TSC2 | 85% AD; 25%AD 10% subependymal giant Cell astrocytoma |
| Melanoma–astrocytoma (Familial atypical multiple mole Melanoma (FAMMM)) | CDKN2A, CDKN2B, P14/ARF | AD  Astrocytoma Pleomorphic xanthoastrocytoma Meningioma |
| Breast cancer (BRCA) | BRCA-1, BRCA-2 | AD  Astrocytoma Pleomorphic xanthoastrocytoma Meningioma |
| Cowden syndrome (multiple hamartoma syndrome) | PTEN | 50% AD; 50% de novo Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos syndrome) |
| DICER1 syndrome (pleuropulmonary Blastoma familial tumor and dysplasia syndrome) | DICER1 | AD  Pineoblastoma Pituitary blastoma |
| Multiple endocrine neoplasia type 1 (Werner syndrome) | MEN1 | AD  Pituitary adenoma Ependymoma |
not appropriate in light of ethical and social norms, or if the patient is unable to consent to the test because of his or her firm beliefs, the physician may refuse the test after a thorough explanation of the reasons.

- However, if the patient refuses the test because of his/her own beliefs, referral to another medical institution should be considered.
- For hereditary diseases that develop in later adulthood, and there is no established cure or prevention. In general, genetic testing should be avoided during childhood.
- From the standpoint of protecting future free will, genetic testing of minors is not recommended, unless the test results indicate that immediate treatment or preventive measures should be taken or there is an emergency, it should be withheld until the individual reaches adulthood.

**Sporadic Tumors**

Among the medical treatments currently known as genomic medicine, treatment for sporadic tumors account for two-thirds of the total. Recent developments in the field of molecular biology have increased the options for the medical treatment of developing tumors.

It is known that when a tumor develops, some genetic abnormality occurs. Due to the many genomic changes that occur in cancer cells, it is not possible to truly understand cancer cell development and maintenance. Therefore, we need to identify the mutations involved in their maintenance. Our efforts should focus on identifying the factors involved in maintenance.

Research on this has resulted in drugs that target specific molecular biological mutations and have replaced the cytotoxic, tumor-killing, and chemotherapeutic agents of the past. In other words, if a tumor has a specific genetic abnormality and is prone to growth and metastasis due to that genetic abnormality, then a drug that repairs that genetic abnormality alone can be administered to suppress growth and metastasis. The development of therapeutic drugs in this field has attracted a great deal of attention, and in recent years, it has come to account for the majority of research papers.

The hallmark of these drugs is that they are not organ-specific. For example, molecular biological mutations associated with the ALK gene cause a variety of tumors, such as neuroblastoma, non–small cell lung cancer, lymphoma, and inflammatory myofibroblastic tumor. These genetic abnormalities are being discovered every day, and it is now suggested that rather than considering tumor development by organ, it may be more directly relevant for treatment if tumors are considered on the basis of genetic abnormality.

There are many different types of genetic abnormalities, some with increasing numbers of mutations, others with one copy activated on oncogene, both copies inactivated in tumor suppressor gene, activated oncogene by gene fusion via translocation, abnormal genomic amplification, and homozygous deletion, leading to both copies of gene being deleted.

There are various approaches to repair genetic abnormalities, including targeting angiogenesis, targeting immunological mechanisms, and directly acting on genetic abnormalities.

**Central Nervous System Tumors and Cancer Panel Testing**

This recent trend in cancer genomic medicine also applies to tumors of the central nervous system. First of all, the evaluation of genetic mutations has become necessary for the diagnosis of brain tumors, and the 2016 revision of the WHO diagnostic criteria for brain tumors now includes molecular biological diagnosis in addition to the previously used histopathological diagnosis. Moreover, the molecular biological diagnoses are more prognostic. For example, the prognostic factors for high–grade glioma are age at diagnosis, residual tumor volume, pretreatment performance status, O-6-Methylguanine–DNA methyltransferase (MGMT) promoter methylation, and isocitrate dehydrogenase (IDH) mutation, which means that the only factor that can be controlled by the medical side is the residual tumor volume after surgery, which depends on the molecular biological properties of the tumor.

The development of molecular analysis and the segmentation of tumor types sometimes creates confusion in clinical practice, but they can also bring benefits. For example, gefitinib, which has been used for non–small cell lung cancer, is effective in some non–small cell lung cancers with EGFR gene abnormalities. Although the tumor classifica-
tion has been further subdivided, the effective administration of gefitinib has become possible. In other words, patients were not given ineffective drugs, and the medical and economic losses were reduced. A similar case can be seen in glioblastoma, where bevacizumab showed no clear improvement in prognosis for primary glioblastoma as a whole but did improve the prognosis for proneural-type glioblastoma for more than 4 months.

Therefore, it can be said that the nature of brain tumors, especially parenchymal tumors, is defined by genetic abnormalities. However, since the incidence of CNS tumors is extremely low and the organs are not suitable for systemic administration of drugs due to the existence of the brain-blood barrier, the development of molecularly targeted drugs is not an area that is actively pursued.

However, the prognosis of brain parenchymal tumors is poor. Patients who suffer from so-called WHO grade 3 tumors have only about 3 years of life, and grade 4 tumors have a prognosis of about 1 year, which is extremely poor compared to other cancers.

As mentioned above, some brain tumors have been shown to have abnormalities in multiple signaling pathways associated with abnormalities in tumor suppressor genes.

In brain tumor cells, abnormal growth signals are constantly being sent out. Subsequently, the abnormal cells produced by abnormal signals are managed. This means that the defense mechanisms for normal tissue are totally failing. Furthermore, epigenetic anomalies are considered in the maintenance of tumor cells. Fortunately, some brain parenchymal tumors have been found to have genetic abnormalities in common with tumors in other organs, and there is a possibility that molecularly targeted drugs developed for tumors in other organs can be used for these tumors.

The cancer genome panel test was developed as a means to identify such common genetic abnormalities and to select appropriately targeted drugs and has recently become available in Japan under health insurance.

This test can examine hundreds of genetic abnormalities that may be therapeutic target genes at a time and can be performed on excised specimens or blood. This information will be reported to the patient after consultation with an expert panel and the patient's physician, which will lead to the selection of appropriate medical care. In addition, the data is collected in the Center for Cancer Genomic and Advanced Therapeutics (C-CAT), which is a national project to collect cancer genome information in Japan and use it for future treatment.

Considering the purpose of this project, the work of surgeons is expected to change. Surgeons have previously focused on radical resection as their primary goal, but in the future, if there is a good drug, it may be enough to collect a specimen containing enough genetic material to tell us if we should use that drug.

There are a few problems with this test. First, it is very expensive, and second, it does not always find the right drug. Only 30% of the patients who underwent this test were able to receive any form of drug treatment. There is an absolute lack of therapeutic agents available. We need to identify the genetic abnormalities that occur in tumor cells that are directly related to growth, invasion, metastasis, etc., and drugs to correct these abnormalities.

Brain tumors are difficult to resect radically. On the other hand, tumor type is determined by molecular biological properties, and the prognosis is also analogous based on molecular biological properties. This is where cancer genome medicine can come into its own. However, in my experience, no patient with brain tumor patient has ever found a therapeutic drug from this test.

Therefore, the indications for the test should be carefully judged. At this point, it is thought that refractory tumors after the completion of standard treatment and rare tumors for which there is no effective treatment are the indications for the test.

For example, it should be an intractable brain tumor in children and also considered to be a brain tumor of the young adult generation.

Some pediatric brain tumors are known to express the same genetic abnormality as malignant tumors, such as sarcoma, at a frequency of a few percent. Fortunately, a drug has recently been developed to suppress this genetic abnormality in sarcomas. The use of this drug in pediatric brain tumors has been reported to inhibit tumor growth for several months.

The government has also prepared a system to
encourage the use of such drugs. For example, if a patient requests it, the government will allow the use of the relevant drug even if it is not covered by insurance, or the drug company may provide the drug for free. Society as a whole is becoming ready to promote this kind of medicine.

It is also necessary to promote the development of more such drugs in parallel.

Conclusion

We have summarized the recent developments in central nervous system tumors and genomic medicine. Currently, the most important is the development of therapies that follow these tests. Even if genetic abnormalities can be identified, there is an absolute lack of drugs and medical tools to correct them. I sincerely hope that all of you with young and flexible minds will propose new treatments in this field through your research.

Conflicts of interest

The author declares that there are no conflicts of interest.

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Table 2  Major Prognostic Biomarkers of brain tumors (modified from reference 17)

| Tumor Type                  | Median age at diagnosis (years) | 5 year Survival rate | 10 year prognostic biomarkers | Major favorable prognostic biomarkers | Major negative prognostic biomarkers |
|-----------------------------|--------------------------------|----------------------|-------------------------------|--------------------------------------|-------------------------------------|
| Pilocytic astrocytoma (WHO I) | 12                             | 94%                  | >90%                          | BRAF-KIAA1549 fusion                |                                     |
| Oligodendroglioma (WHO II)  | 43                             | 81%                  | 65%                           | IDH1/2-mutation 1p/19q codeletion    |                                     |
| Diffuse astrocytoma (WHO II) | 48                             | 50%                  | 40%                           | IDH1/2-mutation                     |                                     |
| Anaplastic Oligodendroglioma (WHO III) | 50                         | 57%                  | 43%                           | IDH1/2-mutation 1p/19q codeletion    |                                     |
| Anaplastic astrocytoma (WHO III) | 53                         | 30%                  | 20%                           | IDH1/2-mutation MGMT methylation    |                                     |
| Glioblastoma (WHO IV)       | 64                             | 5–5%                 | NA                            | IDH1/2-mutation MGMT methylation    | H3 K27M-mutation                     |
| Ependymoma (WHO I–III)      | 45                             | 83%                  | Close to 80%                  | RELA-fusion positive Gain chromosome arm 1q |
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