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BRAIN OVERGROWTH IN DISORDERS OF RTK-PI3K-AKT SIGNALING: A MOSAIC OF MALFORMATIONS

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Abstract

Disorders of brain overgrowth are significant causes of intractable epilepsy, intellectual disability, autism, and other complex neurological problems. The pathology of these disorders is sometimes striking and characteristic, as in hemimegalencephaly, but can also be subtle, as in autism. Recent genetic studies have shown that many diverse forms of brain overgrowth are caused by *de novo* mutations that increase activity in the receptor tyrosine kinase (RTK)–phosphatidylinositol-3-kinase (PI3K)–AKT signaling pathway, a key mediator of signaling by growth factors in the developing brain, such as fibroblast growth factors. In cases where mutations arise in postzygotic embryos, brain regions exhibit mosaic pathology that reflects the distribution of mutant cells, ranging from focal cortical dysplasia to lobar or hemispheric overgrowth. In turn, the histopathology of these disorders is also remarkably varied. The common underlying mechanisms of RTK-PI3K-AKT overactivation suggest new possibilities for drugs that inhibit this pathway.

Keywords

megalocephaly; thanatophoric dysplasia; Apert syndrome; balloon cells; dysplastic neurons; heterotopia; polymicrogyria; pachygyria; tuberous sclerosis

Introduction

Brain overgrowth disorders are a diverse lot that may occur in isolation, or in more than 100 different megalencephaly syndromes.¹ Broadly defined, brain overgrowth disorders encompass not only developmental megalencephaly (brain weight 2 standard deviations above mean), but also some forms of focal or mild overgrowth that may not meet strict criteria for overall megalencephaly, such as tuberous sclerosis and autism. Excluded from this classification are metabolic forms of megalencephaly (such as storage diseases), and

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disorders with macrocephaly (increased head size) but not increased brain mass (such as hydrocephalus).

This review will focus on the pathology of brain overgrowth disorders in which receptor tyrosine kinase (RTK)–phosphatidylinositol-3-kinase (PI3K)–AKT and downstream pathways are overactivated. This group includes some forms of autism, focal cortical dysplasias (FCDs), hemimegalencephaly (HMEG), dysplastic megalencephaly (DMEG), tuberous sclerosis, thanatophoric dysplasia, Apert syndrome, and various other rare disorders. In particular, this review will attempt to elucidate how characteristic pathologies in brain overgrowth disorders arise from specific mutations, patterns of gene expression, clonal cell migration pathways, and developmental stages.

Historical perspective: phenotypes and genotypes in isolation

The striking pathology of some brain overgrowth disorders led to their early recognition and descriptions as early as the first half of the 19th century, while some rarer or subtler malformations were only recognized in the late 20th century. The first systematic descriptions of brain “hypertrophy,” including HMEG, are usually attributed to Sims, who reported in 1835 that “the brain is sometimes affected partially by hypertrophy, either of one hemisphere, one lobe, or of the corpora striata or thalami.”² Cortical tubers were also recognized in the 19th century, and were linked to seizure genesis by Bourneville in 1880.³ Epileptogenic FCDs distinct from tubers were first described by Taylor and colleagues in 1971.⁴ In the same year, excessive gyration and size of the temporal lobe was linked to thanatophoric dysplasia.^{5,6} In Apert syndrome, megalencephaly and gyral anomalies were not recognized until 1990.⁷ Autism, although it is a very heterogeneous disorder, was found to exhibit transiently increased brain size (during early childhood) in a substantial proportion of cases in 2001.⁸ Despite similarities among several of these entities, their diverse phenotypes would mask their relatedness until genetic and biochemical analyses revealed that all involve overactivation of RTK-PI3K-AKT signaling in the developing brain.

Genes linked to human diseases have been identified at a breakneck pace during the past 25 years, including genes for brain overgrowth syndromes related to RTK-PI3K-AKT signaling (Table 1). The first disorder in this group to be linked to an identified gene was tuberous sclerosis, linked to *TSC2* in 1993.⁹ By that time, it had become clear that tuberous sclerosis was caused by mutations in two separate genes, the second of which, *TSC1*, was identified in 1997.¹⁰ The early progress identifying genes for tuberous sclerosis was possible because tuberous sclerosis is relatively common in the population, exhibits specific identifiable phenotypes in several organs (not only the brain), and is sometimes inherited. The genes for thanatophoric dysplasia (*FGFR3*) and Apert syndrome (*FGFR2*) were likewise identified in the mid-1990s,^{11,12} as both of these disorders exhibit striking somatic phenotypes (severe dwarfism in thanatophoric dysplasia, severe craniosynostosis in Apert syndrome) and are relatively common. Interestingly, the *FGFR3* and *FGFR2* mutations in thanatophoric dysplasia and Apert syndrome (respectively) were found to cause increased receptor activation (i.e., gain-of-function). Indeed, the *FGFR3* and *FGFR2* genes both appear highly susceptible to gain-of-function point mutations. Autism, as a heterogeneous entity, has hundreds of contributing genes, but *PTEN* was among the first to be associated with

increased brain size in autism, in 2001.¹³ Also, autism has been associated with tuberous sclerosis since the 1980s,¹⁴ thus implicating *TSC1* and *TSC2* in autism pathogenesis.

Genetic analysis of HMEG, DMEG, and FCDs would take longer, but progress on these disorders in the present decade has been pivotal. A major breakthrough came in 2011 with the identification of mosaic activating *AKT1* mutations in Proteus syndrome, a rare disorder in which many organs, including brain, display variable, patchy overgrowth, dysplasia, and tumors.¹⁵ Significantly, Proteus syndrome is one of several syndromes associated with HMEG in some cases,¹⁶ and the recognition of Proteus syndrome as a mosaic overgrowth disorder provided an immediate explanation for the asymmetric brain overgrowth characteristic of HMEG. Since *AKT1* is widely expressed in many tissues during development, including brain, the patchy distribution of overgrowth lesions in Proteus syndrome is thought to reflect the distribution of clonal cells that acquired a *de novo* *AKT1* activating mutation during early postzygotic development. Thus, *AKT1* was the first gene causally linked to HMEG, in syndromic form.

In 2012, three groups published reports showing that HMEG and DMEG are caused by *de novo* mutations in *PIK3CA*, *PIK3R2*, *AKT3*, and *MTOR*.^{17–19} Moreover, DMEG affecting the entire brain was associated with *de novo* germline mutations, while HMEG was linked to *de novo* postzygotic mutations causing somatic mosaicism in the brain. Together, these papers solidified the conclusion that overactivation of RTK-PI3K-AKT signaling and downstream pathways are crucial to many disorders of brain overgrowth. Subsequently, DMEG was linked also to *CCND2* mutations in a pathway downstream of RTK-PI3K-AKT signaling,²⁰ and FCD type IIa was linked to a somatic mutation in *PIK3CA*.²¹ A previously reported *PTEN* somatic mutation in FCD type IIb was likely also pathogenic.²²

The new gene linkages to HMEG, DMEG and FCD type II demonstrated conclusively that overactive RTK-PI3K-AKT signaling causes a spectrum of brain overgrowth disorders. Moreover, the phenotypes can now be reinterpreted in view of the underlying genetic mechanisms. But first, a brief overview of the RTK-PI3K-AKT signaling pathway provides context.

Putting it all together: RTK-PI3K-AKT overactivation and brain overgrowth

Early clues from genetic studies of tuberous sclerosis and Cowden syndrome suggested that overactive PI3K-AKT signaling might be central to developmental overgrowth disorders.²³ Studied extensively for its role in cancer,²⁴ RTK-PI3K-AKT signaling (Fig. 1) is a key mediator of cell proliferation and growth in many biological systems.²⁵ RTKs are activated by growth factors that, in the developing brain, include insulin-like growth factor 2 (IGF2), fibroblast growth factor 2 (FGF2), and others.^{26–30} All four FGF receptors, and the IGF I receptor (IGF1R), are RTKs that activate PI3K-AKT.^{28,30} Not surprisingly, IGF1R and FGFRs also activate other signaling pathways, notably mitogen-activated protein kinase (MAPK) signaling mediated by the Ras-Raf-MEK-ERK cascade,³¹ so RTK-PI3K-AKT signaling is not purely linear. Indeed, divergent and convergent signaling occurs at all levels of the RTK-PI3K-AKT pathway, influencing the different phenotypes generated by specific gene mutations.

Ligand-stimulated RTKs in turn activate PI3K, a lipid kinase that phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP₂) to phosphatidylinositol-3,4,5-trisphosphate (PIP₃), a potent second messenger. Pten, a negative modulator of RTK-PI3K-AKT signaling, converts PIP₃ back to PIP₂. PIP₃ binds and activates AKT (also known as protein kinase B), a protein kinase with more than 100 substrate proteins.²⁵ Accordingly, AKT activation has pleiotropic effects that are often context-specific. In brain development, as in cancer, AKT activation generally leads to increased proliferation, decreased apoptosis, and increased cell growth, although the specific effects differ among neural progenitors, neurons, and glia. Some processes, such as proliferation and cell growth, have been related to specific pathways downstream of AKT, some of the most important of which are shown in Figure 1.

Perhaps the best-known pathway downstream of AKT is mTOR (for mammalian target of rapamycin), a pathway that promotes cell growth. Actually, the mTOR protein is part of two different complexes, mTORC1 and mTORC2, and it is the mTORC1 complex that connects AKT signaling to cell growth. The pathway from AKT to mTOR is controlled by hamartin (TSC1) and tuberlin (TSC2), which are negative regulators of mTOR signaling. Thus, the mTOR pathway is highly activated in tuberous sclerosis, representing a major branch downstream of RTK-PI3K-AKT signaling. Other major branches include the GSK3 (glycogen synthase kinase 3) pathway, which promotes cell proliferation via Myc and Cyclin-D (CCND) activation; and the FoxO (forkhead box O) pathway, which promotes apoptosis and is negatively regulated by AKT. Interestingly, DMEG and HMEG have been associated with genes all along this pathway, indicating that genetic heterogeneity probably explains much of the gross and histopathologic heterogeneity in these disorders.

Brain pathology and genetic mechanisms: connecting the dots

Brain overgrowth disorders linked to RTK-PI3K-AKT signaling exhibit a great diversity of pathologies, some of which are quite subtle. Nevertheless, sufficient data are now available to begin correlating clinical manifestations and structural pathologies with the genetic bases of these disorders.

Disorders linked to overactive RTKs (Fig. 2)

The neuropathological features of thanatophoric dysplasia (*FGFR3* activating mutations) and Apert syndrome (*FGFR2* activating mutations) have been described.^{7,32} In both disorders (but only a subset of Apert syndrome cases), increased gyrification of the cerebral cortex and increased brain size are the principal manifestations. Also, humans with decreased or increased IGF signaling display micrencephaly or brain overgrowth, respectively, although the detailed neuropathology of IGF- and IGF1R-related disorders in humans is unknown.^{33,34} Histologically, the cerebral cortex in thanatophoric dysplasia and Apert syndrome displays a relatively normal appearance without cytomegaly, dysplastic cytology, or major disturbances of laminar architecture. An exception to this rule is the hippocampus, which is markedly hyperconvoluted in thanatophoric dysplasia.³² Thus, *FGFR3* and *FGFR2* overactivation seem to cause overgrowth mainly by developmental hyperplasia, with little or no hypertrophy or abnormal differentiation of brain cells. This

phenotypic pattern may occur because FGFRs and IGF1R are expressed mainly in neural progenitor cells, and are largely downregulated in most postmitotic neurons and glia (although IGF signaling also has important effects on oligodendroglia). Also, intracellular feedback loops may limit some RTK-PI3K-AKT signaling driven by overactivation of RTKs. Interestingly, thanatophoric dysplasia shows excessive growth of predominantly the occipitotemporal regions, where the *FGFR3* gene is highly expressed in neural progenitors during development.³²

Disorders linked to overactive PI3K or AKT (Fig. 3)

Activating mutations of *PIK3CA* or *PIK3R2* (encoding PI3K subunits), or of *AKT1* or *AKT3* (encoding different AKT isoforms), cause severe overgrowth (HMEG or DMEG) with marked laminar disorganization and variable cytologic dysplasia. The cortex in HMEG and DMEG displays a variety of pathologies that differ among cases, including periventricular heterotopia, leptomeningeal heterotopia, polymicrogyria, pachygyria, and focal aggregates of small undifferentiated cells.^{18,35,36} Some cases of DMEG and HMEG also show cytologic atypia, especially cytomegalic neurons and balloon cells, although the latter are seen in only a minority of HMEG cases.³⁶ Mosaic *PIK3CA* mutation has also been linked to one case of FCD type IIa,²¹ a disorder with many features of HMEG and DMEG but more limited extent. Indeed, these three disorders (FCD type II, HMEG, and DMEG) appear to form a spectrum differing mainly in the extent of cortex containing mutant cells, due to mosaicism. (An alternative possibility, that FCD type IIb is caused by HPV16 infection during brain development, has also been proposed.³⁷)

In the developing cerebral cortex, radial migration of new excitatory pyramidal neurons from the progenitor-rich ventricular and subventricular zones to the cortical plate restricts mutant cells to geographic patches of cortex that vary in size, shape and contiguity. Small lesions, as seen in FCD type II, display funnel-like morphology, narrow at the ventricular surface and broad at the cortical surface. (Mosaicism in FCD type II may also extend to areas outside cerebral cortex, as unilateral overgrowth of a brainstem inferior olivary nucleus was also described in the original paper on FCD type II by Taylor et al.⁴) More expansive lesions may involve entire lobes ("lobar FCD"), a hemisphere (HMEG), or combinations thereof ("HMEG plus"). In this schema, DMEG is essentially equivalent to bilateral HMEG. In contrast to pyramidal neurons, nonpyramidal interneurons migrate tangentially in the cortex and might be expected to cause more dispersed cortical abnormalities, but no cases of selective interneuron overgrowth have been reported.

Overall, activating mutations of PI3K and AKT genes appear to cause profound disturbances of cellular proliferation, differentiation, and growth, reflecting the central role of these enzymes in development, and the widespread expression of the cognate genes in progenitors, neurons, and glia. Indeed, it has been speculated that some PI3K and AKT mutations are found only in mosaic form because they are lethal as germline mutations.³⁸ Interestingly, *AKT3* is expressed mainly in the brain, and *AKT3* mutations affect brain predominantly. In contrast, *AKT1*, *PIK3CA*, and *PIK3R2* mutations cause overgrowth of many different somatic tissues.

Disorders linked to overactive pathways downstream of AKT (Fig. 4)

The most important signaling pathways downstream of RTK-PI3K-AKT signaling in brain overgrowth disorders appear to be the GSK3 and mTOR pathways (Fig. 1). On the GSK3 pathway, *CCND2* (cyclin-D2) mutations cause a megalencephaly syndrome that presumably involves mainly excess proliferation, since this is the primary function of most cyclins, but no histological studies of *CCND2*-linked DMEG are available.²⁰ In contrast, *TSC1* and *TSC2* mutations cause tuberous sclerosis, in which abnormal cortical lamination, aberrant neuronal and glial differentiation, cytomegaly, and cytologic dysplasia are prominent features. These phenotypes are consistent with the interpretation that mTOR signaling (downstream of *TSC1/2*) functions primarily to promote cell growth, with less effect on proliferation. While tubers are focal lesions, it is important to distinguish that *TSC1* and *TSC2* mutations cause loss, not gain of function as occurs with *FGFR2*, *FGFR3*, *PIK3CA*, *AKT1*, and *AKT3* mutations described above. Thus, tubers are thought to arise from “second hit” mutations. Interestingly, mosaic *MTOR* mutation has been linked to HMEG,¹⁷ although it is unclear as yet how closely this form of HMEG might resemble tuberous sclerosis at the histological level. It would be interesting to compare the histopathologic features of *CCND2*- and *MTOR*-linked forms of HMEG, to evaluate how mutations in different pathways downstream of RTK-PI3K-AKT signaling affect proliferation, differentiation, and cell growth.

Disorders of heterogeneous or uncertain genetic composition

Autism and FCD type I fall into this category. Autism has been linked to mutations in *PTEN* and *TSC1/2*, which occupy upstream and downstream positions on the RTK-PI3K-AKT pathway (Fig. 1). It is conceivable that mild overactivation of RTK-PI3K-AKT signaling by mutation of any genes on this pathway (e.g., *AKT3*) could contribute to the autistic phenotype. Given the tremendous genetic and phenotypic heterogeneity of autism, it is important to remember that overactive RTK-PI3K-AKT signaling and brain overgrowth are factors in only a fraction of autism cases.

FCD type I (characterized by dyslamination without neuronal cytomegaly) has not yet been linked to any somatic mutations, but mosaicism seems to be the most likely underlying mechanism. The lack of neuronal cytomegaly may indicate that mTOR signaling is increased little or not at all in FCD type I, in contrast to tuberous sclerosis.

Conclusions and future directions

Research leading to the identification of RTK-PI3K-AKT signaling pathway mutations in brain overgrowth disorders has produced breakthroughs on several fronts. First, it is now clear that *de novo* mutations and genetic mosaicism cause several types of epileptogenic cortical malformations, as well as autism and intellectual disability. Second, a variety of diverse and sometimes bizarre brain malformations can now be classified and understood together as variations on the theme of RTK-PI3K-AKT overactivation, with pathologic manifestations that reflect specific mutations and, in cases with mosaicism, the unique distribution of mutant cells in each case.^{39,40} Third, the centrality of RTK-PI3K-AKT in

brain overgrowth disorders suggests that small molecules that interfere with this pathway might be effective in combating neurological and psychiatric symptoms, as well as disease progression. Indeed, advances have already been made in using rapamycin-like drugs that inhibit mTOR, such as everolimus, to slow the growth of subependymal giant cell astrocytomas in tuberous sclerosis.⁴¹ If inhibitors of RTK-PI3K-AKT signaling can be applied successfully to other epileptogenic malformations, such as HMEG, DMEG, and FCDs, a major advance could be achieved in reducing the costs and morbidity of these disorders. Epilepsy in HMEG, DMEG, and FCDs is frequently resistant to current medications, and in such cases, surgical lobectomy or hemispherectomy is the only option. New drug treatments would be especially beneficial in these cases.

One major area where further effort will be needed is the genetic analysis of FCDs. These are very heterogeneous disorders that can be difficult to classify, although recently updated classifications are helping.⁴² Since only two cases of FCD type II have been linked to postzygotic mutations so far,^{21,22} it seems likely that further studies will identify not only more genes, but also perhaps significant genotype-phenotype correlations. FCD type I remains to be linked to any genes.

Together, the improved clinical recognition of brain overgrowth syndromes linked to overactive RTK-PI3K-AKT signaling, targeted genetic testing, and new therapeutic approaches may be enough to reduce the burden of epilepsy and other neurologic and psychiatric problems caused by this group of disorders.

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Figure 1.

The RTK-PI3K-AKT signaling pathway. Growth factors bind RTKs such as FGFRs and IGF1R, leading to activation of PI3K, then AKT, then multiple divergent downstream pathways. RTKs can also activate the parallel Ras-Raf-MEK-ERK cascade, illustrated for comparison.

Figure 2.

Thanatophoric dysplasia and Apert syndrome. **(A)** Thanatophoric dysplasia at 20 gestational weeks, showing lateral view of hemispheres with smooth lateral surface and aberrantly convoluted inferior and medial surfaces. The vascular meninges (m) were partially removed. **(B)** Sagittal slice of brain from another case of thanatophoric dysplasia at 20 gestational weeks, showing abnormal deep sulci and ventricular recesses in the temporo-occipital regions. **(C)** Apert syndrome, 20 gestational weeks: the left hemisphere medial surface showed aberrant convolution of fetal occipito-temporal cortex. **(D)** Apert syndrome, 13 years old: the brain showed megalencephaly (brain weight 1741 g) and abnormal gyral configuration.

Figure 3.

HMEG and DMEG. (A–E) HMEG in a premature infant born at 34 gestational weeks who lived for less than one day. (A) The left hemisphere was larger, as evident especially in the occipital region (arrow), presumably reflecting selective allocation of mutant cells with overactive RTK-PI3K-AKT signaling. (B) The cortex was variably thickened. (C) The left cerebellar hemisphere was larger. (D) The dentate gyrus was dysplastic. (E) Leptomeningeal glioneuronal heterotopia. (F–I) DMEG in a child born at 37 gestational weeks who lived for 11 weeks. (F, G) Both hemispheres were large (brain weight 905 g, expected 506 ± 67 g) and exhibited abnormal gyral patterns. (H) The cortical gray was dysplastic, and the white matter appeared prematurely myelinated. (I) Histologic section through lateral temporal cortex, stained immunohistochemically for microtubule-associated protein 2 (MAP2), revealed pachygyria with dyslamination of the cortical gray, and numerous small periventricular heterotopia (arrows). Scale bar: (B), 2 mm.

Figure 4.

Tuberous sclerosis. (A) Surface view of cortical tuber (black arrows), with meninges stripped to reveal pale, expanded, gliotic cortex. (B) Brain slice reveals a hamartomatous subependymal nodule (black arrow) and multiple cortical tubers (white arrows). (C) Focal accumulation of small immature cells (microdysgenesis) in tuber. (D, E) Large, dysplastic neurons in tuber. (F) Balloon-like, pale eosinophilic cells. Scale bars: (B), 2 cm; (C), 50 μm for (C) and 25 μm for (D–F).

Table 1

Brain Overgrowth Syndromes: Phenotypes and Genotypes

Disorder	Gross Cortical Phenotype	Original Pathology Mutated Descriptions	Gene(s) Mutated (*mosaic)	Original Gene Reports	Proteins
HMEG	Asymmetric hemispheric hyperplasia	2	<i>PIK3CA</i> *, <i>AKT1</i> *, <i>AKT3</i> *, <i>MTOR</i> *, <i>PTEN</i> *	15, 17–19	PI3K, AKT1, AKT3, mTOR, Pten
FCD (type II)	Subtle gyral thickening	4	<i>PIK3CA</i> *, <i>PTEN</i> *	21,22	PI3K, Pten
DMEG	Global hyperplasia with gyral abnormalities	2?	<i>PIK3CA</i> , <i>PIK3R2</i> , <i>AKT3</i> , <i>CCND2</i>	19,20	PI3K, AKT3, Cyclin-D2
Autism	Mild overgrowth	8	<i>PTEN</i> , <i>TSC1</i> , <i>TSC2</i>	9,10,13	Pten, Hamartin, Tuberin
TSC	Tubers	Bourneville (1880) ³	<i>TSC1</i> , <i>TSC2</i>	9,10	Hamartin, Tuberin
Thanatophoric dysplasia	Excess temporal convolution	5,6	<i>FGFR3</i>	11	FGF Receptor 3
Apert syndrome	Excess convolution	7	<i>FGFR2</i>	12	FGF Receptor 2