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Genetic malformations of the human frontal lobe

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Interest in genetic malformations of the frontal lobe has grown from the recognition that certain brain malformations have a predilection for the frontal lobes or are more severe in the anterior brain. These malformations can be deleterious, as the frontal lobes in humans are particularly large in comparison with those of other species and play an important role in cognitive developmental functions.

Types of Frontal Malformations

A subset of brain malformations is confined to the frontal lobes, or to two or more lobes including the frontal lobes; another group of malformations shows an anteroposterior (a > p) gradient of severity, such as the continuum agyria–pachyria/band heterotopia as well as several cobblestone and cobblestone-like encephalopathies. Our objective here is to provide a brief overview of genetically determined human frontal malformations.

Malformations involving the frontal lobes alone or in combination with other lobes

Polymicrogyria

Polymicrogyria can range from mild forms localized to a single gyrus, to one or more lobes, or be diffuse, and is classified according to its lobar topography. It is a heterogenous condition, clinically and etiologically; extensive investigations may help to refine the diagnosis and to improve genetic counseling (Jansen & Andermann, 2005). Among the various patterns, several involve the frontal lobes bilaterally or unilaterally to various degrees.

Bilateral frontal polymicrogyria. In an observation of 13 unrelated children, the polymicrogyria extended symmetrically, from the frontal pole to the precentral gyrus, and to the frontal operculum inferiorly. Several patients showed associated abnormalities in the white matter, including reduced volume and multiple small foci of T2 hyperintensity. In two families, the parents were first cousins, suggesting possible autosomal recessive (AR) inheritance in some cases (Guerrini et al., 2000).

Bilateral frontoparietal polymicrogyria (BFPP), GPR56 mutations, and BFPP type 2 (BFPP2). The main clinical features of typical BFPP include: global developmental delay; bilateral pyramidal and cerebellar signs; and seizures, mostly generalized, in 94% of patients (Chang et al., 2003; Piao et al., 2005). In four patients, a Lennox-Gastaut syndrome was reported (Parrini et al., 2008). Patients with BFPP2 may not have epilepsy and lack the pyramidal and cerebellar signs. BFPP is consistently associated with anomalies in the white matter and brainstem as well as cerebellar hypoplasia, whereas BFPP2 is not. BFPP seems to be genetically homogeneous, since all families reported to date show an AR pattern and association with mutations in the *GPR56* gene. Patients with BFPP2, on the other hand, do not have a mutation in the *GPR56* gene (Piao et al., 2005).

The GPR56 protein is an adhesion G protein–coupled receptor. Studies of the biochemical properties of the wild-type and mutant protein have shown that this protein undergoes two major modifications: a G protein-coupled receptor (GPCR) proteolytic site (GPS)-mediated proteolytic cleavage and *N*-linked glycosylation. Loss-of-function mutations in these two modification sites lead to impairment of cell-trafficking and cell surface expression (Jin et al., 2007). Loss of *GPR56* in knockout mice leads to overmigration of neurons through a defective basal membrane into the pial layer, forming a cobblestone-like brain malformation (Li et al., 2008), suggesting that BFPP might be a cobblestone-like brain malformation.

Bilateral perisylvian polymicrogyria. In these patients, the polymicrogyria involves the frontal, parietal, and/or temporal opercula, and can be further classified into holosylvian polymicrogyria in which the entire perisylvian

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cortex is affected, and posterior polymicrogyria in which only the posterior perisylvian cortex is involved (Barkovich et al., 1999).

Unilateral polymicrogyria—a distinct entity?

Unilateral polymicrogyria is usually right-sided and affects mainly the anterior brain areas, extending to the frontal/perisylvian or frontoparietal cortex, and is often associated with ipsilateral hemispheric atrophy or hypoplasia (Caraballo et al., 2000; Hayakawa et al., 2002; Chang et al., 2006; Kuchukhidze et al., 2007). In one of the families, the mode of transmission suggests autosomal dominant (AD) or X-linked inheritance, whereas in three other families, each with two affected siblings, the inheritance is AD with decreased penetrance or AR. In two additional families, the parents were first cousins, suggesting AR inheritance.

Aicardi syndrome

Aicardi syndrome (AS) is a rare neurodevelopmental disorder characterized by: pathognomonic congenital chorioretinal lacunae; infantile spasms; a complex brain malformation including total or partial agenesis of the corpus callosum, cortical dysgenesis such as polymicrogyria and periventricular heterotopia, and intracranial cysts; and often occurrence of costovertebral defects (Aicardi, 2005). AS is X-linked dominant, since it occurs only in individuals with two X chromosomes; indeed, the syndrome has been reported only in girls and exceptionally in two boys with XXY karyotype (Aicardi, 2005). In a series of 23 girls with AS, magnetic resonance imaging (MRI) findings showed consistent presence of polymicrogyria that was predominantly frontal in 21 subjects (91%) (Hopkins et al., 2008).

Goldberg-Shprintzen syndrome (GOSHS) and KIAA1279 *mutations*

GOSHS (microcephaly, mental retardation, facial dysmorphism, iris coloboma, and Hirschsprung's disease) can be associated with bilateral generalized polymicrogyria and loss of parenchymal volume that is prominent in the frontoparietal regions. A novel locus has been identified on 10q21.3–q22.1 with mutations in the *KIAA1279* gene. The multitissue KIAA1279 mRNA is ubiquitously expressed in the adult central nervous system (CNS), and its protein is a member of the tetratricopeptide repeats (TPRs) protein family, whose structural motifs are involved in mediation of protein–protein interactions (Brooks et al., 2005; Ohnuma et al., 1997).

Difficulty of distinguishing pachygyria from polymicrogyria

Polymicrogyria and pachygyria may be difficult to distinguish on MRI because the cortical thickness can appear to be increased and the gyri can appear broad and smooth in polymicrogyria as they are in pachygyria. However the characteristic of polymicrogyria is the irregularity of the cortex (well visualized on high-definition T_1 slices), associated with complete distortion of the organization of the sulci and gyri in the affected region. In contrast, pachygyria shows a thickened cortex, always symmetric, with normally positioned but reduced number of sulci (C Raybaud 2009, personal communication).

Malformations showing an anterior to posterior (a>p) gradient of severity

These mainly include various types of lissencephaly (LIS), recently reclassified (Jissendi-Tchofo et al., 2009), most of which are genetically defined.

The agyria–pachygyria/band heterotopia continuum

LIS and subcortical band heterotopia (SBH) are caused by deficient neuronal migration. Several genes have been identified as crucial in migration, and specific patterns of LIS, with or without other brain or somatic malformations, have been associated with each of these genes.

Both the *LIS1* gene (OMIM 601545) at 17p13.3 and the *DCX* gene (OMIM 300121) at Xq22.3, encoding for microtubule associated proteins, can cause classical LIS and/or SBH, inherited as autosomal dominant or X-linked dominant forms, respectively. A continuum from absent gyri (agyria) or reduced gyration (pachygyria) to SBH may occur, and is further classified into six grades (Dobyns & Truwit, 1995); the *DCX*-related LIS and SBH are more severe in the anterior brain (a > p gradient), whereas the *LIS1*-related LIS and SBH are more severe posteriorly (p > a gradient) (Dobyns et al., 1999).

LIS and SBH associated with *LIS1* gene mutations occur equally in both genders and are usually sporadic, whereas LIS and SBH associated with *DCX* mutations can be observed in several members of the same family, LIS occurring primarily in hemizygous males and SBH primarily in heterozygous females (Pinard et al., 1994; Andermann & Andermann, 1996; Dobyns et al., 1996; D'Agostino et al., 2002; Guerrini et al., 2003; Guerrini & Parrini, 2009).

DCX mutations: genotype–phenotype correlations

Patients with LIS, primarily males, typically have global developmental delay, infantile-onset seizures, and severe mental retardation. Patients with SBH, primarily females, may be asymptomatic or show variable degrees of cognitive disabilities and epilepsy.

Severe expression of *DCX* mutations causes a>p LIS in males and a>p SBH in females. These tend to be sporadic because the patients do not reproduce. Milder phenotypes allow reproduction and, therefore, tend to be familial (Gleeson et al., 1999). A milder expression of *DCX* mutations causes a>p pachygyria in males and milder SBH in females. The mildest expression of *DCX* mutations causes

isolated SBH in boys and mild reduction in volume of the frontal lobes in females (Guerrini et al., 2003).

The severity of the phenotype is correlated with the functional consequences of the mutation, depending on the presence of protein truncation mutations versus single amino acid substitutions, the localization of the mutation in critical functional domains of the DCX protein, the amount of X-inactivation, and possible somatic or germline mosaicism (Gleeson et al., 1999, 2000; Matsumoto et al., 2001).

In contrast to the protein truncation mutations (either nonsense or frameshift) that appear to occur throughout the predicted DCX protein and are more often associated with a severe phenotype, single amino acid substitutions (mainly missense mutations) are identified more frequently in inherited SBH and appear to cluster in two critical regions for the DCX protein, representing two evolutionarily conserved domains: the tandem repeats N-DC (R1) and C-DC (R2) (Sapir et al., 2000; Taylor et al., 2000), both essential for correct tubulin interaction.

DCX mutations may be observed in mothers or maternal relatives of male patients with isolated SBH. These women may have mild mental retardation with or without epilepsy, or be asymptomatic, and they may have normal brain MRIs. This mild or normal phenotype has been associated with mutations with mild functional consequences or favorable X-inactivation skewing (D'Agostino et al., 2002; Guerrini et al., 2003; Guerrini & Parrini, 2009). Therefore, *DCX* mutations may cause nonsyndromic mental retardation.

Recently, genotype–phenotype correlations were studied in 33 males with agyria–pachygyria/SBH and a hemizygous *DCX* mutation. Nineteen were missense mutations, most of which were clustered in the two evolutionarily conserved domains of doublecortin: N-DC and C-DC. The missense mutations in the C-DC domain tended to lead to less severe LIS, for example, anterior pachygyria (grade 4b), and SBH with anterior pachygyria (grade 5); SBH alone (grade 6) was associated with somatic mosaicism in the *DCX* gene (Leger et al., 2008).

Other subtypes of LIS

Termed variant LIS in the 2009 classification (Jissendi-Tchofo et al., 2009), these subtypes encompass X-linked LIS with abnormal genitalia (XLAG) due to mutations in the *ARX* gene, LIS with cerebellar hypoplasia due to *RELN* mutations, and LIS due to *VLDLR* mutations; all three show an a>p gradient as well.

Cobblestone and cobblestone-like cortical malformations

Among the group of cobblestone lissencephalies, characterized by congenital muscular dystrophies with CNS involvement, and comprising Fukuyama congenital muscular dystrophy (FCMD), Walker-Warburg syndrome, and muscle-eye-brain disease, FCMD is notable for an unlayered frontal polymicrogyria, in addition to cobblestone dysplasia (Jissendi-Tchofo et al., 2009). Some of the cobblestone-like cortical malformations, including congenital glycosylation type 2 (CDG type 2) and the tubulinopathy TUBB2B show an a>p gradient of severity (Van Maldergem et al., 2008; Jaglin et al., 2009).

Conclusions

The frontal lobes, encompassing one-third of the hemispheric volume in humans, have been shown to harbor an increasing number of malformations. Several of these malformations can now be identified or diagnosed during life, allowing a more accurate genetic counseling.

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Disclosure

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