**Bilateral Frontoparietal Polymicrogyria**

**Alternative Names**
- BFPP
- Cerebellar Ataxia with Neuronal Migration Defect
- Polymicrogyria, Bilateral Perisylvian

**WHO International Classification of Diseases**
Congenital malformations, deformations and chromosomal abnormalities

**OMIM Number**
606854

**Mode of Inheritance**
Autosomal recessive

**Gene Map Locus**
16q13

**Description**
Polymicrogyria is a common malformation of cortical development that is grossly characterized by abnormal cortical lamination and an excessive number of small gyri. The syndrome is manifested by global developmental delay of at least moderate severity, epilepsy, dysconjugate gaze, and bilateral pyramidal and cerebellar signs. Polymicrogyria can be generalized or focal, unilateral or bilateral. Among the rare, bilateral symmetrical forms several syndromes, such as bilateral frontal, frontoparietal, perisylvian, and parasagittal parieto-occipital polymicrogyria have been recognized. Severity of polymicrogyria is dependant on the location and size of the affected area.

The etiology of polymicrogyria is heterogeneous. The topographic arrangement of the lesions, the frequency of bilateral symmetry, and historical data may suggest a transient intrauterine perfusion failure in many patients. However, abnormal hemodynamic data in the fetal cerebral arteries and infectious or toxic theories fail to explain completely the distribution of all polymicrogyric lesions.

**Molecular Genetics**
Both extrinsic and inherited factors can cause polymicrogyria. Bilateral frontoparietal polymicrogyria can be caused by splice site, frameshift, and missense mutations in the G Protein-Coupled Receptor 56 (GPR56) gene. The GPR56 gene, assigned to the region 16q12.2-q21 on chromosome 16, contains 14 exons covering 15 kb and has a 3-kb open reading frame. GPR56 signaling plays an essential role in regional development of human cerebral cortex.

**Epidemiology in the Arab World**

**Palestine**
Straussberg et al. (1996) described a Palestinian family in which the parents were first cousins and three of the siblings suffered from moderate mental retardation, pachygyria and strabismus. In 2002, Piao et al. described the clinical and genetic features of the autosomal recessive stereotyped form of polymicrogyria in two consanguineous families from Palestine. The first pedigree was originally reported by Straussberg et al. (1996) and was described as having pachygyria. However, improved magnetic-resonance imaging (MRI) clearly showed that the core disorder was polymicrogyria. Three of four children in the family were affected. They all had normal prenatal and perinatal history and normal head growth but showed gross developmental delay and moderate mental retardation. At ages 14, 9, and 7.5 years they could speak a few words and walk independently. All three developed medically refractory seizures. All three had esotropia, increased muscle tone, mild truncal ataxia, and finger dysmetria, without dysmorphic features or other congenital anomalies. They also had strabismus. The
second pedigree came from the same village as the first, although there was no known relationship between the two families. The proposita, a 13-year-old girl, was the first child of healthy Palestinian parents who were first cousins. The course and physical findings were similar to those in the affected members of the first pedigree. A younger son was also affected in the second pedigree.

Chang et al. (2003) reported 19 patients from 10 kindreds with apparent autosomal recessive bilateral frontoparietal polymicrogyria. Included were the 2 families reported previously by Piao et al. (2002). Clinical features included motor and cognitive developmental delay, esotropia, strabismus, pyramidal signs, and seizures. Brain MRI of all patients showed bilateral symmetric polymicrogyria, most often in a frontoparietal distribution, although in some patients it was diffuse. All patients also had enlarged ventricles, reduced white matter volume, patchy white matter signal changes, and hypoplasia of the cerebellum and brainstem. Chang et al. (2003) also described a family with six children born to Palestinian first cousin parents. They lived in a village 5 to 10km away from the one in which families of Piao et al. (2002) resided. Two children were clinically affected and had the characteristic MRI pattern of bilateral frontoparietal polymicrogyria. A younger sibling had suggestive clinical abnormalities. The older affected child, 11 years old, had mental retardation and motor delay. She had spasticity and exaggerated deep tendon reflexes on examination. Her head circumference (HC) was less than the second percentile. Her mother also had a small HC (50cm, less than the second percentile). The youngest possibly affected child, 4 months old at latest follow-up, had spasticity and exaggerated deep tendon reflexes on examination. MRI of the oldest child demonstrated polymicrogyria symmetrically extending from the frontal lobes back to the parietal-occipital sulcus. The ventricles were large and white matter volume was reduced. Large subcortical perivascular spaces were present. The superior vermis, cerebellar hemispheres, and ventral pons were small, as was the splenium of the corpus callosum. Chang et al. (2003) noted that several of the patients had previously been reported as having 'cobblestone lissencephaly'; a 'neuronal migration abnormality,' pachygryria, or 'lissencephaly with cerebellar hypoplasia,' but reinterpretation or repeats of the imaging showed that these patients had findings consistent with bilateral frontoparietal polymicrogyria. Chang et al. (2003) noted that the syndrome of bilateral frontoparietal polymicrogyria appears to be very common and may be frequently misdiagnosed.

**United Arab Emirates**

Guerrini et al. (2000) reviewed the clinical records, brain MRI, and EEG results of 13 patients, including one at least from UAE, with symmetric polymicrogyria of both frontal lobes back to the precentral sulcus: bilateral frontal polymicrogyria. The abnormal cortex extended from the frontal poles anteriorly to the precentral gyrus posteriorly and to the frontal operculum inferiorly and was relatively symmetric in all 13 patients. All patients presented with developmental delay and mild spastic quadriaparesis, but variably impaired language development (12/13), mental retardation (11/13), and epilepsy (5/13) also occurred. BFP was sporadic in 13 of 13 patients, but 2 of 13 had consanguineous parents.

Sztiriha and Nork (2000) reported two patients with bilateral frontoparietal polymicrogyria. The first case was a male born at term to unrelated parents of United Arab Emirates origin. The parents had nine healthy children. The second case was a male born at term to consanguineous parents of United Arab Emirates origin. The parents had two healthy sons and two healthy daughters. In both families there was no history of neurological disorders. The main clinical features of the two patients included severe developmental delay, mental retardation, spastic tetraplegia, and seizures. Magnetic resonance imaging revealed a bilateral thick cortex with irregular gyri and a festoonlike gray-white matter junction. Sztiriha and Nork (2000) suggested that bilateral frontoparietal polymicrogyria may represent a further form of the bilateral polymicrogyria syndromes in addition to perisylvian and parasagittal parieto-occipital polymicrogyria. Sztiriha and Nork (2002) reported a third case of bilateral symmetrical frontoparietal polymicrogyria in an 8-year-old-boy who was born at term to consanguineous parents of United Arab Emirates origin. The parents had eight children who were all healthy and there was no history of neurological disorder in the family. The patient had a congenital bilateral, symmetrical, frontoparietal cortical malformation with an MRI appearance of polymicrogyria, serious delay in mental and motor development and seizures with epileptiform electroencephalographic findings. This patient had similar clinical and radiological abnormalities to the cases of Sztiriha and Nork (2000). The aetiology of the sporadic polymicrogyria in the patient remained unknown. The localization was not consistent
with the distribution of any cerebral artery, and no evidence of any intrauterine infectious or toxic insult was evident.

Sztriha et al. (2004) reported two boys with chromosome 22q11 deletion syndrome and polymicrogyria. Both patients showed severe developmental delay with cardiovascular malformations and one of them had drug resistant epilepsy. Patient 1 was born to non-consanguineous parents by Cesarean section after a pregnancy complicated with gestational diabetes. The patient developed myoclonic and generalized tonic clonic seizures, which were refractory to several antiepileptic drugs. Brain MRI revealed polymicrogyria in the frontal, parietal, and temporal areas, unilaterally. Right functional hemispherectomy was performed because of intractable epilepsy. The clinical and radiological findings were suggestive of 22q11 deletion. Chromosomal analysis and fluorescent in situ hybridization (FISH) with a DNA probe specific for the DiGeorge syndrome were performed. It showed monosomic microdeletion at 22q11.2. None of the parents had the deletion. Patient 2 was born post-term to non-consanguineous parents. Brain MRI revealed bilateral polymicrogyria in the frontal, parietal, and temporal areas. Chromosomal analysis with FISH showed monosomic microdeletion at 22q11.2. None of the parents had the deletion. Both patients had serious delay of mental and motor development. They also had dysmorphic features and cardiovascular abnormalities. Histology revealed four-layered polymicrogyria.

References


Contributors
Ghazi O. Tadmouri: 14.5.2005