

# FG syndrome

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## Abstract

*FG syndrome, initially considered a rare, completely recessive X-linked disorder occurring only in males and constituting a unique disorder, is now increasingly documented as a common disorder that may also affect carriers with a wide range of manifestations which extensively overlap those of the G/BBB (Opitz) syndrome. Typical manifestations include relative shortness compared to headsize, congenital hypotonia with delayed motor and speech development, gastroesophageal reflux, constipation, mild spastic diplegia with delayed development of sensory integration, attention deficit disorder, self-absorption and fascinations with mechanical toys and objects. Gross malformations may include agenesis of corpus callosum, Chiari I malformation, congenital heart defects, intestinal atresias and limb defects.*

## Keywords

FG syndrome, Opitz-Kaveggia syndrome, multiple congenital anomalies, congenital hypotonia, megalencephaly, developmental/speech delay, autism, Asperger syndrome, pervasive developmental disorder, constipation, gastroesophageal reflux, delayed sensory integration, genital abnormalities.

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## Disease name and synonyms

- FG syndrome
- Opitz-Kaveggia syndrome, includes the neurofaciodigitorenal (NFDR) syndrome and probably some cases of the Neuhäuser megalocornea syndrome.
- Syndrome FGS1
- Megalocornea-Mental Retardation syndrome

## Excluded disorders

- For the moment the Opitz (G/BBB) syndromes are excluded.
- Opitz syndrome.

## Diagnostic criteria and definition

FG syndrome may affect boys and girls with a syndrome of relative shortness of stature with disproportionately large head, a characteristic combination of minor anomalies including high,

prominent forehead, cowlicks and abnormalities of hair whorls, apparent hypertelorism, relatively thin vermilion of the upper lip with prominence of the lower lip, hypotonic mouth breathing facial changes, minor ear anomalies, the appearance of relatively large corneae, broad thumbs and halluces, short perineal body, deep pilonidal dimple and diastasis recti. Malformations include (partial) agenesis of corpus callosum, Chiari I malformation, vertebral malformation, intestinal/anal atresia, limb malformations (poly-, oligo-, syndactyly), genitourinary abnormalities, cryptorchidism, herniae and congenital heart defects.

### Nosology

Primarily with the "Opitz" (G/BBB) syndromes which show extensive overlap with FG except that laryngeal cleft, pulmonary agenesis or hypoplasia and tetralogy of Fallot have been seen only in the G/BBB syndrome so far.

### Prevalence

The disease is possibly as common as 1:1,000 in the population of the Utah valley, but apparently common elsewhere in the US and in Italy.

### Clinical description

The first clinical features include prenatal oligohydramnios, ultrasonographic ventricular dilatation, reduced fetal movements, fetal distress with frequent delivery by caesarian section, neonatal respiratory distress syndrome, thrombocytopenia, transient jaundice, gastroesophageal reflux at times requiring fundoplication, constipation, frequent middle ear infections, delayed acquisition of speech and motor skills. Childhood is frequently dominated by severe behavior problems, in part in response to communication difficulties but to a larger part to delayed sensory integration with overreaction to sensory stimulation including touch, sound, light, crowds, emotional pressure, temperature variations, and oral aversion to food textures (with tendency to "bolt" food and risk of aspiration and asphyxiation); overreactions occur in the form of severe temper tantrums and withdrawal. Frequent fascinations with mechanical objects and toys, tendency to self-absorption. Frequently diagnosed as "autistic" or as having Asperger syndrome or "pervasive developmental disorder". Mental retardation is rare- most affected boys and girls function in the normal range. Seizures are rare, spastic diplegia more common.

### Management

Correct diagnosis is mandatory. Symptomatic treatment for reflux, constipation, seizures, hyperactivity and attention deficit is the rule. Psychological and pediatric neurological care; rarely orthopedic care for consequences of lower limb spasticity are required. Helmet for plagiocephaly; neurosurgical care for symptomatic Chiari malformation with syrinx and craniosynostosis; cardiac evaluation (most patent ductus, atrial septal and ventricular septal defects close spontaneously) are needed. Patients should be placed in a correct school setting and may need to learn sign language or to use assisted communication devices. Early introduction of educational computers is advised.

### Etiology

This syndrome is presumed to be due to mutations on the X-chromosome. *FGS1* is roughly mapped to Xq13, *FGS2* (on the basis of an X paracentric inversion) to Xq11 or Xq28, and *FGS3* to Xp22.3. Clinical overlap with the G/BBB syndromes suggests not only a pathogenetic but perhaps a causal relationship, since midin, a product of the X-linked G/BBB syndrome gene, is known to interact with that of the gene *MIDIA1* at Xq13, a candidate gene for the FG syndrome. Many/most carriers show more or less subtle signs of the FG syndrome including high forehead, cowlick(s)/widow's peak, broad thumbs/halluces, at times constipation, migraines, depression, anxiety. The fact that FG signs are frequently found in all of the sibs in segregating cases and in some of the fathers suggests a genetic abnormality (*i.e.* meiotic drive, segregation distortion) or gene/gene (*i.e.* FG/G/BBB) interaction.

### Diagnostic methods

Routine pediatric, neurological, gastroenterological, cardiologic, child psychological approaches, including MRI, EEG, echocardiography, and electromyography.

### Genetic counseling

Only after careful examination of parents and all sibs. Truly sporadic cases (*i.e.* presumed new mutations) are extremely rare; the FG syndrome is not as strikingly an iceberg mutation as the G/BBB syndrome with uncommon recurrence of cases as severe as that of the propositus. Rather, in the FG syndrome recurrence as severe as in propositus is common and may affect sibs, first cousins, nephews and other maternal relatives. It is hoped that molecular methods will soon help diagnosis, carrier detection, prenatal diagnosis and more reliable genetic counseling.

### Antenatal diagnosis

Prenatally frequently symptomatic on the basis of reduced fetal movements, oligohydramnios, asymmetric intrauterine growth retardation with increased biparietal diameter and dilated ventricles and abnormal fetal responses indicating fetal distress. No specific molecular diagnosis as yet.

### Unresolved questions

Causal or pathogenetic relationship with G/BBB syndromes, segregation ratio, paternal influence, gene mapping, cloning, sequencing and mutation analysis.

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