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A Review of Donnai-Barrow and Facio-oculo-acoustico-renal (DB/FOAR) Syndrome: Clinical Features and Differential Diagnosis

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Abstract

Mutations in the gene *LRP2* have recently been identified as the cause of Donnai-Barrow and Facio-oculo-acoustico-renal (DB/FOAR) syndrome. More than two dozen cases, the first reported more than 30 years ago by Holmes, have been published. Summarizing available information, we highlight the cardinal features of the disorder found in ≥90% of published cases. These features include: agenesis of the corpus callosum, developmental delay, enlarged anterior fontanelle, high myopia, hypertelorism, proteinuria, and sensorineural hearing loss. Congenital diaphragmatic hernia and omphalocele are reported in only half of the patients. There is no evidence for genotype-phenotype correlation, though the sample size is too small to preclude this with certainty. Although several conditions to consider in the differential diagnosis are highlighted, the diagnosis of DB/FOAR syndrome should not be difficult to establish as its constellation of findings is strikingly characteristic.

Keywords

Donnai-Barrow (DB) syndrome; facio-oculo-acoustico-renal (FOAR); syndrome; *LRP2*; megalin; congenital diaphragmatic hernia; agenesis of corpus callosum

INTRODUCTION

More than two dozen patients with a remarkably distinct phenotype have been described in the medical literature since the initial report of two affected siblings by Holmes and Schepens (1972). Their index patient, an almost 3-year-old girl, showed hypertelorism, down-slanting palpebral fissures, macrocephaly, a broad forehead, and an enlarged anterior fontanelle. She also had numerous ophthalmological abnormalities (including high myopia, posterior subcapsular lens opacity, iris stromal hypoplasia, and choroidal atrophy), sensorineural hearing loss, and proteinuria. No other anomalies were noted and intelligence testing was normal at 8 years of age. The proband's younger brother was similarly affected, and in addition had an umbilical hernia requiring surgery, microcornea, and developmental delay. They suggested this constituted a "new syndrome of multiple anomalies: the mode of inheritance of which is possibly autosomal recessive".

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Following this paper, several other highly accomplished geneticists reported additional affected individuals, thereby confirming the existence of this disorder and its likely autosomal recessive pattern of inheritance (Chassaing et al., 2003; Devriendt et al., 1998; Donnai and Barrow, 1993; Gripp et al., 1997). All of these patients, affected with the condition variously named facio-oculo-acoustico-renal (FOAR) syndrome or Donnai-Barrow syndrome (DBS), shared several features in common. Initially these were thought to be distinct entities as proteinuria was prominently found in FOAR but not in DBS, whereas agenesis of the corpus callosum was commonly reported in DBS but not in FOAR. However, by the late 1970s, several authors recognized that similarities far out-weighed apparent differences and suggested the conditions were allelic. Recent identification of mutations in the gene low-density lipoprotein receptor-related protein 2 (*LRP2*; chromosome 2q24-q31), encoding the protein megalin, confirms this to be true (Kantarci et al., 2007). Knowledge of megalin's function, with an important role in both endocytosis of numerous ligands and in signaling pathways, provides a rational explanation for the diverse and seemingly unrelated pattern of malformations found in affected individuals. This article will present a critical review of all published cases with what now is recognized as a single entity, DB/FOAR syndrome, and provide clues to the diagnosis and the differential diagnosis.

METHODS

A literature review was performed searching for cases previously published with the diagnoses of Donnai-Barrow syndrome, facio-oculo-acoustico-renal (FOAR) syndrome, diaphragmatic hernia-hypertelorism-myopia-deafness syndrome, or diaphragmatic hernia-exomphaloshypertelorism syndrome. Clinical and diagnostic information based on prenatal imaging and/or postnatal study was collected from each published report. All patients, or at least one member of an affected sibling pair, had normal routine karyotypes unless otherwise stated. Patients reported in Kantarci et al. (2007, 2008) were recruited into the study *Gene Mutations and Rescue in Human Diaphragmatic Hernia*, which is approved annually by the Massachusetts General Hospital Institutional Review Board. Gel electrophoresis on a sample of urine to screen for low molecular weight proteinuria and gene sequencing to detect *LRP2* mutations were performed on a subset of patients. The methodologies used for gel electrophoresis, DNA extraction, and gene sequencing were as previously described (Kantarci et al., 2007, 2008).

RESULTS

A total of 27 affected individuals with DB/FOAR syndrome features, emanating from 15 families, have been published (Table 1) (Avunduk et al., 2000;Chassaing et al., 2003;Devriendt et al., 1998;Donnai and Barrow, 1993;Gripp et al., 1997;Holmes and Schepens, 1972;Kantarci et al., 2007;Kantarci et al., 2008;Patel et al., 2007;Schowalter et al., 1997). Seven kindreds have a single affected individual, six have two affected siblings, and two have three or more affected siblings. Consanguinity is suspected or reported in five parents of affected offspring. Ten cases were deceased at the time of their publication because of pregnancy termination (n = 6), neonatal death secondary to complications of congenital malformations (n = 3), or status epilepticus (n = 1).

Common Features

Information was not available for all features in every case, because of the high number of nonsurvivors. The most frequently reported congenital malformations were as follows: hypertelorism (26/26 = 100%); large anterior fontanelle (19/20 = 95%); agenesis of the corpus callosum, either partial or complete (17/18 = 94%); congenital diaphragmatic hernia (15/27 = 56%); and omphalocele/umbilical hernia (15/27 = 56%). Other malformations were noted less

frequently, such as macrocephaly (n = 9), coloboma (n = 7), congenital heart disease (n = 2), and rib/vertebral anomalies (n = 1); an estimate of these latter features is not possible as all cases, especially the deceased cases, which may not have been as thoroughly examined for these features.

In addition to the craniofacial features mentioned previously, photographs of patients with DB/FOAR syndrome, which have been either published or personally reviewed, revealed subtle, noncoarse but characteristic facies. Most often, affected individuals showed down-slanting palpebral fissures, a flat bridge of the nose with a triangular tip, and a tall broad forehead. In a few patients, prominent globes or proptosis were noted.

Functional deficits could be assessed only in the long-term survivors (Table 1). Sensorineural hearing loss, high myopia, proteinuria, and developmental delay were almost universal, the first three occurring in 100% of those examined, whereas developmental delay was reported in 87%. No formal study of intelligence was provided on any patient, so information on the typical pattern or range of impairment is not available.

Intrafamilial Variability

The features that demonstrated the most intrafamilial variability were congenital diaphragmatic hernia and omphalocele/umbilical hernia. Among affected children belonging to the eight multiplex kindreds, siblings were discordant for congenital diaphragmatic hernia in five kindred and discordant for omphalocele/umbilical hernia in four. Sibling discordance for coloboma was documented in two kindreds, but considerable missing information precludes determining whether or not this is a highly variable feature.

Genotype-Phenotype

DNA from 16 patients with DB/FOAR syndrome, belonging to eight kindreds, was available and an *LRP2* mutation was identified in all (Table 1). Affected children of consanguineous unions were homozygous mutation carriers as would be expected owing to homozygosity by descent. Affected offspring of nonconsanguineous unions were heterozygous for a variety of missense, splice-site, and non-sense mutations scattered throughout the gene, except for the most recently published patient who was homozygous for an intragenic deletion resulting from paternal chromosome 2 uniparental disomy. There was no evidence of genotype-phenotype correlations, either in terms of the type or the location of the mutation. However, none of the four patients clinically diagnosed with features more suggestive of the FOAR phenotype demonstrated agenesis of the corpus callosum (Devriendt et al., 1998;Holmes and Schepens, 1972;Schowalter et al., 1997). The single patient with FOAR who was available for genotyping (Devriendt et al., 1998) was a compound heterozygote, carrying a missense and a splice-site mutation, but this mutation combination was observed in one other kindred (Donnai and Barrow, 1993;Kantarci et al., 2007) in whom all three affected children had agenesis of the corpus callosum.

Urine Studies

Results from urine studies were available for 12 patients, and proteinuria was documented in all. In nine cases from whom urine was available for further study, a characteristic pattern of low molecular weight proteinuria, containing excess spillage of vitamin D and retinol-binding proteins, was demonstrated (Kantarci et al., 2007). Mutations in *LRP2* were identified in all patients with the characteristic pattern of proteinuria.

An Additional Patient Where the Diagnosis of DB/FOAR Syndrome Was Suggested

Ferrero et al. (2006) suggested the diagnosis of DB/FOAR syndrome in a 9-month-old patient, who was subsequently found to have an unbalanced chromosome rearrangement t(9;16)(q34.3;q24.3). This child had an anterior congenital diaphragmatic hernia, agenesis of the corpus callosum, large anterior fontanelle, small umbilical hernia, hypertelorism, high myopia, developmental delay, and possible but not confirmed hearing loss. Although these malformations overlap with DB/FOAR syndrome, the authors also noted features less suggestive of this diagnosis including microcephaly, noncharacteristic facial features, and up-slanting palpebral fissures.

DISCUSSION

A highly distinct constellation of findings first reported by Holmes and Schepens (1972) has withstood the test of time. Furthermore, the recent identification of the genetic basis of this disorder may afford insights in causation of its component malformations (Kantarci et al., 2007).

Donnai-Barrow syndrome and FOAR syndrome, herein referred to as DB/FOAR syndrome, is a unique malformation complex. Based on this review of published cases the core features of this syndrome consist of:

1. Congenital anomalies found in ≥90%: hypertelorism; partial or complete agenesis of the corpus callosum; enlarged anterior fontanelle; characteristic facial features;
2. Functional anomalies found in ≥90%: proteinuria; high myopia, sensorineural hearing loss; developmental delay; and
3. Anomalies found in ~50%: congenital diaphragmatic hernia and omphalocele/umbilical hernia; additional features such as coloboma and macrocephaly also appear to occur in ~50% of cases, but the numbers are too small to state this with certainty.

Based on data tabulated from the currently small number of cases, the combined presence of the features listed in items 1 and 2 appear highly suggestive of the diagnosis of DB/FOAR syndrome, as no other syndrome matches this constellation. Several conditions have partial overlap with DB/FOAR syndrome and may be considered in the differential diagnosis as discussed below. However, the full spectrum of DB/FOAR syndrome may become broader over time because of several factors, including availability of *LRP2* mutation analysis, increased number of cases with a confirmed diagnosis, and decreased bias in publishing only the cases that are most severely affected.

Craniofrontonasal syndrome (CFNS, OMIM 304110) is an X-linked condition caused by mutations in the gene *EFNB1*. Overlapping features include hypertelorism, downslanting palpebral fissures, frontal bossing, umbilical hernia, agenesis of the corpus callosum, and congenital diaphragmatic hernia. Features that distinguish CFNS from DB/FOAR syndrome include coarser facial features, craniosynostosis, bifid nasal tip, thick and wiry hair, and a variety of limb anomalies including brachydactyly, syndactyly, and longitudinally grooved nails. Females with CFNS are more severely affected than males.

Chudley McCullough (OMIM 604213) and Acrocallosal (OMIM 200990) syndromes are each autosomal recessive disorders with agenesis of the corpus callosum, macrocephaly, and developmental delay. Patients also demonstrate sensorineural hearing loss, or hypertelorism and polydactyly, respectively. However, neither condition includes the additional functional deficits of myopia and proteinuria, nor do they include omphalocele/umbilical hernia and/or diaphragmatic hernia.

Generating the differential diagnosis surrounding the presence of a congenital diaphragmatic hernia, Fryns (OMIM 229850) and Pallister-Killian (OMIM 601803) syndromes should be considered as they show partial overlap with DB/FOAR syndrome. However, the characteristic constellation of structural and functional deficits is not recapitulated in either of these disorders.

The presence of low molecular weight proteinuria is not restricted to DB/FOAR syndrome but more typically occurs along with other renal tubular abnormalities as in Dent disease 1 (OMIM 30009), which is caused by mutations in a chloride channel gene. Two related disorders with proteinuria are Dent disease 2 (OMIM 300555) and Lowe syndrome (OMIM 300535) due to mutations in the gene *OCRL1*. Although Lowe syndrome patients can have multi-system anomalies involving the ocular, dental, and central nervous systems, the specific anomalies in these organ systems differ from those found in DB/FOAR syndrome.

Mutations in the gene *LRP2* are responsible for DB/FOAR syndrome. An *LRP2* targeted gene deletion mouse was initially generated and characterized in 1996 (Willnow et al., 1996). Homozygous null pups showed craniofacial anomalies (including microophthalmia, shortened nose, agenesis of the corpus callosum, and dysplasia of the olfactory bulbs), and low molecular weight proteinuria. The vast majority of *LRP2* null mice died of “respiratory insufficiency” in the perinatal period. Remarkably, the pattern of anomalies in both mice and humans is consistent with the distribution of expression of *LRP2* during development, though the knock out mouse phenotype does not completely recapitulate the human phenotype (in that the mice demonstrate microophthalmia, a finding not observed in DB/FOAR patients).

The gene *LRP2* encodes megalin, a large single-spanning transmembrane glycoprotein that serves as a multiligand endocytotic receptor. Megalin is highly expressed on the apical surface of absorptive epithelia in the developing brain and spinal cord, optic cup, otic placode, and developing renal system (Assemat et al., 2005; Wicher and Aldskogius, 2008). In the mature kidney, megalin is intensely expressed in the renal proximal tubule and its lack of normal expression in patients with DB/FOAR syndrome and in megalin knockout mice accounts for the low molecular weight proteinuria (Christensen and Birn, 2002). Megalin is also expressed in thyrocytes, lung buds, and reproductive tract (as reviewed in Fisher and Howie, 2006). Megalin performs reuptake of numerous ligands including retinol binding protein, vitamin D binding protein, and a variety of lipoproteins (Christensen and Birn, 2002), and it is possible that more await discovery. Failure to re-uptake one or more of these compounds, particularly at a critical time in development and/or possibly in a tissue-specific manner, might contribute to the structural and functional abnormalities that typify DB/FOAR syndrome. A direct signaling role for megalin has also been postulated for a few of its ligands.

Although the widespread distribution of megalin during development accounts for much of the DB/FOAR phenotype, the mechanisms responsible for the fact that omphalocele/umbilical hernia and congenital diaphragmatic hernia each are found in only 50% of patients remain unclear. Their variable presence raise the possibility that “two-hits” are required for their appearance, the first being functional insufficiency of megalin and the second being a modifier gene or genes and/or an environmental cue. For example, failure to reuptake vitamin A in the preurine resulting in subphysiologic concentrations has gained traction as a plausible hypothesis, in light of several lines of evidence suggesting an important role for the retinoic acid pathway in normal diaphragm development (Kling and Schnitzer, 2007).

The occurrence of brain and craniofacial abnormalities, both cardinal features in DB/FOAR syndrome patients and in megalin knockout mice, underscores the importance of megalin in the developing nervous system. During murine development, megalin is expressed in the apical surface of the neuroepithelium at E9.5 (Willnow et al., 1996), where it may directly mediate endocytosis of molecules from the amniotic fluid before neural tube closure (Fisher and Howie,

2006). Deficient or dysfunctional megalin may also perturb endogenous signaling, particularly the Shh/*BMP4* and retinoic acid pathways (McCarthy and Argraves, 2003). Though the full role of megalin in Shh/*BMP4* signaling is not elucidated, available evidence from megalin knockout mice demonstrates defective Shh/*BMP4* signaling and impaired patterning of the ventral telencephalon in the developing central nervous system (Spoelgen et al., 2005).

The discovery that *LRP2* mutations are responsible for the DB/FOAR syndrome unifies two entities once considered distinct, and also draws attention to an important developmental pathway during embryogenesis. This finding also raises the question whether more subtle changes in *LRP2* function can cause or contribute to isolated malformation components of DB/FOAR syndrome, such as agenesis of the corpus callosum or congenital diaphragmatic hernia.

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Table 1

Phenotypes of Patients Diagnosed with DB/FOAR Syndrome

Patient	Sex	Age at last examination	CDH	Omphalocele/ umbilical hernia	Hypertelorism	High myopia	Coloboma	ACC	Large AF	OFC > 95th percentile	HL	Dev Del	Proteinuria	Miscellaneous	*LRP2* Mutant alleles (pat/mat)	Consanguinity[a]
Holmes Patient 1 (Holmes and Schepens, 1972)	F	2¾ years	−	−	+	+	−		+	+	+	−	+			−
Holmes Patient 2 (sib of Patient1) (Holmes and Schepens, 1972)	M	7 years	−	+	+	+	+			+	+	+	+	Microcornea, L cataract, ureteral reflux, B inguinal hernia		
Donnai Patient 1 (Donnai and Barrow, 1993; Kantarci and others, 2007)	M	19 years	+	+	+	+	+	+	+	−	+	+	+	Prominent eyes, L retinal detachment, seizures	IVS44+1G>A / c.10195C>T (p.R3399X)	−
Donnai Patient 2 (sib of Patient 1) (Donnai and Barrow, 1993; Kantarci and others, 2007)	F	21-week fetus	+	+	+			+	+		+	+	N/A		IVS44+1G>A / c.10195C>T (p.R3399X)	
Donnai Patient 3 (sib of Patient 1 and 2) (Donnai and Barrow, 1993) (Gripp and others, 1997; Kantarci and others, 2007)	F	17-week fetus	+	+	+			+	+	+			N/A	DORV, VSD	IVS44+1G>A / c.10195C>T (p.R3399X)	
Donnai Pt 3 (Donnai and Barrow, 1993)	F	Died at 6.5 years	+	+	+	+	−	+	+	+	+	+	N/A	Onset seizures just prior to death		−
Donnai Patient 4 (sib of Patient3) (Donnai and Barrow, 1993)	M	19-week fetus	+	−	+								N/A			
Donnai Patient in proof (Donnai and Barrow, 1993; Kantarci and others, 2007)	F	16 years	+	−	+	+	−	+	+		+	+	+	VSD, PDA, retinal pigmentary changes, seizures	c.8516_8519delTTTA / c.8516_8519delTTTA (p.V2839VfsX67)	+
Gripp Patient 1 (Gripp and others, 1997)	M	NND	+	+	+		+		+	+			N/A			+

Patient	Sex	Age at last examination	CDH	Omphalocele/ umbilical hernia	Hypertelorism	High myopia	Coloboma	ACC	Large AF	OFC > 95th percentile	HL	Dev Del	Proteinuria	Miscellaneous	*LRP2* Mutant alleles (pat/mat)	Consanguinity[a]
Gripp Patient in proof (Gripp and others, 1997)	F	NND	+	−	+			+	+	+			N/A	Bicornuate uterus		−
Schowalter (Schowalter and others, 1997)	M	11 years	−	−	+	+	+			+	+	−	+	R posterior subcapsular cataract		−
Devriendt (Devriendt and others, 1998; Kantarci and others, 2007)	M	12 years	+	−	+	+	−	−	+	+	+	+	+	Proptosis, Serum retinol = 238 ug/L (300–650)	IVS11+2T>G / c.1093C>T (p.R365X)	−
Avunduk (Avunduk and others, 2000)	M	9 months	−	+	+	+	+	+			+		N/A	Proptosis		+
Chassaing Patient 1 (Chassaing and others, 2003; Kantarci and others, 2007)	M	22 weeks fetus	−	−	+			+	+	−			N/A	Prominent eyes, arachnoid cyst	c.9484_9485delGT/ IVS18-1G>A (p.V3162LfsX2)	−
Chassaing Patient 2 (sib of Pt1) (Chassaing and others, 2003; Kantarci and others, 2007)	M	25 weeks fetus	+	−	+			+	+	−			N/A		c.9484_9485delGT/ IVS18-1G>A (p.V3162LfsX2)	
Chassaing Pt 3 (Chassaing and others, 2003; Kantarci and others, 2007)	F	26 weeks fetus	+	−				+		−			N/A		c.13139insC / IVS7-2A>G (p.P4380PfsX12)	−
Chassaing Patient 4 (sib of Patient3) (Chassaing and others, 2003; Kantarci and others, 2007)	F	6 years	−	+	+	+	−	+	−	−	+	+	+	Retinal dystrophy, serum retinol = 210 ug/L (300–650)	c.13139insC / IVS7-2A>G (p.P4380PfsX12)	
Patel Patient 1 (Patel and others, 2007)	M	4 years	+	+	+	+	−	+	+		+		N/A	Enlarged globes, diffuse R posterior subcapsular opacity, R retinal detachment, retinal pigmentary changes		−
Patel Patient 2 (sib of Patient1) (Patel and others, 2007)	F	2 years	−	+	+	+	−	+					N/A	Enlarged globes		
Kantarci Kindred 1: Patient IV-4 (Kantarci and others, 2007)	F	NND	+	−	+				+				N/A	Large prominent eyes		+

Patient	Sex	Age at last examination	CDH	Omphalocele/ umbilical hernia	Hypertelorism	High myopia	Coloboma	ACC	Large AF	OFC > 95th percentile	HL	Dev Del	Proteinuria	Miscellaneous	*LRP2* Mutant alleles (pat/mat)	Consanguinity[a]
Kantarci Kindred 1: Patient IV-5(sib of IV-4) (Kantarci and others, 2007)	F	6 years	−	−	+	+	+	+	+		+	+	N/A	Macrocephaly, large prominent eyes, retinal dystrophy	c.7564T>C/ c.7564T>C (p.Y2522H)	
Kantarci Kindred 1: Patient IV-6 (sib of IV-4 and 5) (Kantarci and others, 2007)	F	3 years	+	+	+	+	−	+	+		+	+	N/A	Megalocornea, retinal dystrophy, scoliosis, rib and vertebral anomalies	c.7564T>C/ c.7564T>C (p.Y2522H)	
Kantarci Kindred 1: Patient IV-2 (cousin of IV-4,5,6) (Kantarci and others, 2007)	M	12 years	−	+	+	+	−		+		+	+	+		c.7564T>C/ c.7564T>C (p.Y2522H)	
Kantarci Kindred 1: Patient IV-3 (sib of IV-2) (Kantarci and others, 2007)	M	6 years	−	+	+	+	−		+		+	+	+	Albinism	c.7564T>C/ c.7564T>C (p.Y2522H)	
Kantarci Kindred 6: Patient 1 (Kantarci and others, 2007)	F	5 months	+	+	+			+	+		+		+		c.9358_ 9359delAG / c.9358_ 9359delAG (p.S3120WfsX26)	+
Kantarci Kindred 6: Patient 2 (sib of Patient1) (Kantarci and others, 2007)	F	7 years	−	−	+	+					+	+	+	Heart murmur, mild interdigital webbing	c.9358_ 9359delAG / c.9358_9359delAG (p.S3120WfsX26)	−
Kantarci (Kantarci and others, 2008)	M	9 years	−	+	+	+	+	+	+	+	+	+	+	R cataract, L lenticonus, rod and cone retinal dysfunction	Paternal UPD c.11469_ 11472delTTTG / c.11469_ c.11469_ 11472delTTTG (p.Cys3823Tr-pfsX159)	−
Total			15/27	15/27	26/26	17/17	7/17	17/18	19/20	9/14	18/18	13/15	12/12			5/15[a]

[a] Presence or absence of consanguinity is shown for the index case of each family.

+, Feature present; −, feature absent; ACC, agenesis of corpus callosum; AF, anterior fontanelle; CDH, congenital diaphragmatic hernia; CLP, cleft lip + palate; DB/FOAR, Donnai-Barrow and Facio-oculo-acoustico-renal; DORV, double outlet right ventricle; F, female; FTT, failure to thrive; HL, hearing loss; L, left; M, male; N/A, sample not available; NND, neonatal death; OFC, occipofrontal circumference (measured in centimeters); PDA, patient ductus arteriosus; R, right; SS, short stature; Unk, unknown; UPD, uniparental disomy; VSD, ventriculoseptal defect.