ORIGINAL ARTICLE

Fraser syndrome and cryptophthalmos: review of the diagnostic criteria and evidence for phenotypic modules in complex malformation syndromes

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Fraser syndrome is characterised by cryptophthalmos, cutaneous syndactyly, malformations of the larynx and genitourinary tract, craniofacial dysmorphism, orofacial clefting, mental retardation, and musculoskeletal anomalies. The inheritance is autosomal recessive. No diagnostic cytogenetic abnormalities have been documented in affected patients, and no molecular genetic studies have been reported. We have reviewed 117 cases diagnosed as Fraser syndrome or cryptophthalmos published since the comprehensive review of Thomas *et al* in 1986 in order to validate the published diagnostic criteria and to delineate the phenotype associated with this syndrome.

Our series showed more females (57/117) than males and consanguinity was present in 29/119 (24.8%). Eighty-eight patients satisfied the diagnostic criteria for Fraser syndrome (75%). Cryptophthalmos was present in 103/117 (88%), syndactyly in 72/117 (61.5%), and ambiguous genitalia in 20/117 (17.1%). Ear malformations were recorded in 69/117 (59%), and renal agenesis in 53/117 (45.3%). Use of the published diagnostic criteria excluded several patients with cryptophthalmos and one or more physical feature(s) consistent with Fraser syndrome. The frequency of additional anomalies in our series was also higher than previously reported (for example, imperforate anus or anal stenosis were found in 34/117 (29%) compared with 2/124 (2%) in the series of Thomas *et al* (1986) and choanal stenosis or atresia was present in 7/117 (6%) compared to 0/124. These findings emphasise the clinical variability associated with Fraser syndrome and support genetic heterogeneity of the syndrome. We also noted patterns of anomalies (for example, bicornuate uterus with imperforate anus or anal stenosis and renal malformations) that are found in other syndromes and associations without cryptophthalmos, suggesting that common modifier genes may explain some of the phenotypic variation in Fraser syndrome.

Cryptophthalmos (CO) was first noted by Pliny the Elder who described a family of three children born with a membrane over the eye. In more modern times, the first report of CO with additional malformations was attributed to Zehender (1872). These authors reported a female infant who had "classical" manifestations of Fraser syndrome including CO, syndactyly, abnormal genitalia, hypertelorism, a broad, depressed nasal bridge, a tongue of hair extending from the temple to the brow, umbilical hernia, anal stenosis, and diastasis of the symphysis pubis. Fraser syndrome (FS) was recognised as a clinical entity and named after George Fraser, who described two sibships with physical findings of CO, syndactyly, genital anomalies, laryngeal stenosis, ear malformations, and renal abnormalities.[1]

There are more than 200 published case reports of patients with CO and FS and several comprehensive reviews have previously been published.[2–5] Diagnostic criteria for distinguishing between isolated CO or CO with other malformations and FS were provided by Thomas *et al*[2] following a study of 124 cases of CO (table 1). Two major criteria and one minor criterion or one major and at least four minor criteria were required for the diagnosis of Fraser syndrome.[2] The inheritance pattern is autosomal recessive on the basis of parental consanguinity (estimated to be as high as 15%)[2] and multiple affected sibs born to the same parents. There have been no reports of diagnostic cytogenetic aberrations or biochemical markers and no molecular genetic studies have been published for CO or FS.

Since the detailed review of Thomas *et al*,[2] no large study has re-examined phenotypic findings in FS or the utility of the published diagnostic criteria. We have ascertained 117 cases of CO and Fraser syndrome published since the review of Thomas *et al*.[2] We have not included the seven cases reported by them, but have included several patients reported in 1985 or 1986 not mentioned in the same paper. Our aim was to characterise further the phenotype associated with FS and CO.

MATERIALS AND METHODS

Eighty-eight cases of FS satisfying the published diagnostic criteria were ascertained using the search terms "Fraser syndrome" or "cryptophthalmos" on the OMIM database (www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?db=OMIM) and PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi).[3–5 7–54]

Table 1 Diagnostic criteria for Fraser syndrome

Major criteria
Cryptophthalmos
Syndactyly
Abnormal genitalia
Sib with Fraser syndrome
Minor criteria
Congenital malformation of nose
Congenital malformation of ears
Congenital malformation of larynx
Cleft lip +/– palate
Skeletal defects
Umbilical hernia
Renal agenesis
Mental retardation

Table 2 Complications during pregnancy

Complication	Frequency	Reference
Oligohydramnios or anhydramnios	20 (17.1%)	4, 17, 16, 19, 21 (two cases), 29, 31, 32, 36 (three cases), 40, 41, 44 (two cases), 47, 50 (two cases), 53
Antepartum haemorrhage	3 (2.6%)	3, 4, 51
Vaginal bleeding	3 (2.6%)	14, 42, 53
Fetal hydrops/nuchal oedema	9 (7.7%)	4 (two cases), 19, 31, 36 (two cases), 41, 44 (two cases)
Fetal ascites	9 (7.7%)	4, 29, 32, 31, 36, 44 (two cases), 47, 53
Intrauterine growth retardation	3 (2.6%)	4, 26, 40
Hypoplasia/single umbilical artery	5 (4.3%)	3, 16, 19, 26
Malnutrition in pregnancy		58
High AFP		4
Polyhydramnios		16, 26
Fetal bradycardia		3, 26
Cystic adenomatoid malformation		47

Table 3 Type of CO

Type of CO*	Frequency	Reference
Unilateral CO	32 (27.4%)	3 (two cases), 4 (four cases), 5, 8, 14, 17, 19, 21, 23, 28 (two cases), 31, 35, 37, 39 (two cases), 41, 44, 52, 60, 61, 62 (four cases), 65, 66 (two cases)
Bilateral CO	62 (53%)	3, 4 (six cases), 7, 10, 11 (two cases), 12, 13, 15 (two cases), 16 (two cases), 18, 19 (three cases), 20–22, 24, 25, 26 (two cases), 27, 28 (two cases), 30, 32, 36 (three cases), 38, 39 (two cases), 40, 42–44, 47, 48, 49, 50, 51, 52 (two cases), 56, 57, 58 (three cases), 59, 60, 63, 64, 67–69
Absent	14 (12%)	4, 9, 16, 33, 34, 41, 45 (three cases), 50, 53, 55, 62 (two cases)
Unstated	9 (7.7%)	16, 29, 32, 45 (four cases), 46, 54

Twenty-nine cases of CO or eyelid colobomas did not satisfy the diagnostic criteria for FS and were obtained using the same methods.[39 52 55–69] We did not include the cases reported in Philip *et al*[70] and King *et al*[71] as insufficient clinical details were provided. We also noted that the details of the four cases reported by Vanlieferinghen *et al*[72] were the same as described in Francannet *et al*[19] and we have only included these cases once as Francannet *et al*.[19] The patients reported by Pe'er and BenEzra[73] and Pe'er *et al*[11] are also the same and the clinical details in the latter paper were used. Similarly, the patient reported by Chattopadhyay *et al*[74] appears to be the same as the patient in Jagtap *et al*[37] and has been included once as Jagtap *et al*.[37] We included the cases of Feldman *et al*,[55] Ohtsuka *et al*,[56] and Wiznitzer *et al*[7] as these cases were published in close chronology to and omitted from the review of Thomas *et al*.[2]

For each case, the following information was collated when available: parental ages, consanguinity, family history, sex of proband, karyotype, and details of pregnancy including length of gestation, weight, and other measurements at the time of birth. We recorded eye malformations, airway malformations, digital abnormalities, renal malformations, genital abnormalities, cardiac malformations, gastrointestinal malformations, cerebral malformations, orofacial clefting, skeletal defects, abnormalities of the thymus, developmental status, and other phenotypic findings.

RESULTS

Data from the 117 cases are shown in tables 2-18. There were 57 females (48.7%), 54 males (46.2%), and six (5.1%) in whom the sex was not able to be determined. Eighty-eight patients (75.2%) satisfied the published diagnostic criteria for FS, whereas 29/117 (24.8%) did not (see Materials and methods for listing of individual cases). Consanguinity was present in 29 cases (24.8%, data not shown) and the most common consanguineous union was first cousins.[7 11 13 19 25 29 42 50 55] Of those born to non-consanguineous parents, one child was from gypsy parents[33] and one child was born to parents from the same village.[9] Forty-eight patients (41%) had a significant family history of a relative with CO or physical findings suggestive of FS (data not shown). The oldest subjects were alive in the fourth decade of life.[58]

The average paternal age (rounded to the nearest whole year) was 27 years of age and the average maternal age (rounded to the nearest whole year) was 24 years of age (data not shown). Thirty-six patients were reported to have a normal female karyotype and 21 patients had a normal male karyotype (data not shown). Two patients had an inversion of chromosome 9 that was considered to be unrelated to their physical findings ((46,XX,inv(9)(p11q21) and 46,XY,inv(9)(p11q21)).[21]

Pregnancy

Oligohydramnios was the most frequent complication during pregnancy (17.1%, table 2). The majority of babies in whom gestational age was stated were born at term (data not shown).

CO and ocular malformations

CO was present in 103/117 (88%) of cases and was bilateral in 62 cases (53%) and unilateral in 32 cases (27.4%, table 3). The type of CO was often not provided but complete CO appeared to be the most common form (data not shown). CO was commonly associated with a tongue of hair extending across the lateral face (40/117, 34.2%, table 4), absent eyebrows or eyelashes (34/117, 29.1%), and coloboma of the eyelid (21/117, 17.9%). Other abnormalities included microphthalmia (25/117, 21.4%), anophthalmia (7/117, 6.0%), and corneal opacification (12/117, 10.3%).

Digital anomalies

Syndactyly was the most common digital abnormality (72/117, 61.5%, table 5). Syndactyly of the hands and feet was present in half of the cases with syndactyly. Brachydactyly, nail hypoplasia, and abnormal palmar creases were present in less than 10% of patients.

Table 4 CO and other ocular malformations

CO/ocular malformation	Frequency	Reference
Tongue of hair	40 (34.2%)	3 (two cases), 8, 9, 11 (two cases), 16 (two cases) 19–22, 32, 33, 37, 38, 42, 51, 52 (three cases), 56–58 (three cases), 60–62 (six cases), 63, 66 (two cases), 67–69
Absent eyelashes/eyebrows or alopecia of eyebrows	34 (29.1%)	3, 4, 10, 11 (two cases), 14, 18–20, 16 (two cases), 21, 25, 32, 37, 39, 42, 45, 48, 49, 60, 51, 52 (two cases), 58 (three cases), 61, 63, 66 (two cases), 67–69
Coloboma of eyelid	21 (17.9%)	3, 14, 21, 23, 27, 30, 42, 43, 49, 52 (two cases), 56, 58, 60, 62 (four cases), 64, 66, 68
Groove in frontal bone/furrow to forehead/temporal depression	10 (8.5%)	3, 8, 16, 19, 27, 59, 60, 63, 64, 68
Microphthalmia	25 (21.4%)	55–58, 3, 12, 4 (three cases), 17–19 (two cases), 20, 21, 63, 36 (two cases), 41–43, 66 (two cases), 52, 69
Anophthalmia	7 (6.0%)	3, 4, 34, 45 (three cases), 62
Corneal opacification/corneal clouding/sclerocornea	12 (10.3%)	4, 16, 27, 33, 37, 43, 49, 58, 60, 62, 64, 67
Microcornea/absence of the cornea/corneal epithelial defect	3 (2.6%)	16, 41, 58
Abnormal anterior chamber/absence of the anterior structures	6 (5.1%)	11 (two cases), 18, 41, 52, 67, 69
Hypoplasia of the optic nerve/atrophy of optic nerve	6 (5.1%)	4 (two cases), 11, 24, 25, 52
Symblepharon/oculopalpebral synechiae	17 (14.5%)	4, 5, 8, 16, 30, 37, 39, 43, 47, 49, 60 (two cases), 61, 62, 64, 65, 68
Orbital or corneal dermoid		5, 27
Skin tag over left eye		37
Coloboma unstated		38
Ocular coloboma		5, 21, 41
Cataracts		41

Table 5 Syndactyly and other digital malformations

Digital abnormality	Frequency	Reference
Syndactyly - hands and feet (includes all limbs)	37 (31.6%)	4 (six cases), 7, 9, 11 (two cases), 12, 15 (two cases), 16 (three cases), 17–19 (four cases), 21, 22, 24, 29, 35–37, 41, 42, 44 (two cases), 47, 51, 53, 54
Syndactyly - hands only	9 (7.7%)	4, 8, 14, 21, 33, 34, 36 (two cases), 40
Syndactyly - feet only	4 (3.4%)	4, 38, 50 (two cases)
Bilateral syndactyly	4 (3.4%)	3, 27, 31, 39
Syndactyly unstated	18 (15.4%)	4, 5, 20, 28 (two cases), 41, 43, 45 (seven cases), 46, 47, 49, 50
Brachydactyly of first digit (includes short phalanges and metacarpals)	8 (6.8%)	14, 16 (two cases), 34, 38, 40, 50, 69
Hypoplastic, dysplastic or poorly developed nails	4 (3.4%)	11, 16, 39, 51
Single or abnormal palmar creases	10 (8.5%)	4 (two cases), 14–16, 36, 41 (two cases), 50, 51
Proximal thumbs		3, 50
Polydactyly		34, 35
Clinodactyly of the fifth digits		16, 33
Camptodactyly		50
Hyperextension of digits		26

Genital malformations

Ambiguous genitalia were found in 20/117 (17.1%, table 6). In females, clitoromegaly was the commonest genital abnormality (21/57, 36.8%). Bicornuate uterus, uterine hypoplasia, vaginal agenesis, and synechiae or hypoplasia of the labia were present in more than 8% of females. In males, cryptorchidism (17/54, 31.5%), micropenis, phimosis, chordee, hypospadias, and scrotal hypoplasia were noted.

Nasal malformations

Nasal anomalies were common with 24 having a broad nose or nasal bridge (20.5%, table 7), 13 with a depressed or flat nasal bridge (11.1%), and 18 with a bifid nose or a midline nasal groove (15.4%). Coloboma of the nares or notched nares were present in 13/117 (11.1%).

Malformations of the ears

Malformed and/or low set ears,(63/117, 53.8%, table 8), microtia (19/117, 16.2%), and atresia or stenosis of the external auditory meatus (21/117, 17.9%) were recorded.

Malformations of the airway and lungs

Laryngeal stenosis or atresia was reported in 36/117 (30.8%, table 9). Choanal stenosis or atresia (7/117, 6%) and subglottic stenosis (10/117, 8.5%) were also described.

Orofacial clefting

Clefting of the lip, palate, uvula, or upper gum or a combination of clefts were noted in 13/117 (11.1%, table 10). A high arched palate was found in 14/117 (12%).

Musculoskeletal anomalies

Absence or hypoplasia of the orbital or skull bones (12/117, 10.2%) and defects in skull ossification (8/117, 6.8%) were among the most frequent musculoskeletal anomalies (table 11). Talipes (10/117, 8.5%) and abnormalities involving the pubic symphysis (9/117, 7.7%) were relatively common.

Gastrointestinal malformations

The commonest malformation was imperforate anus (15/117, 12.8%, table 12), but anal atresia and anal stenosis were mentioned in 9/117 (7.7%) and 8/117 (6.8%) cases, respectively. Thirteen patients had a low set umbilicus (11.1%).

Renal malformations

Bilateral renal agenesis with or without agenesis of the ureters was present in 27 of patients (23.1%, table 13) and unilateral renal agenesis with or without ureteral agenesis in 26 cases (22.2%). The bladder was small or absent in 20 (17.1%) and cystic dysplasia of the kidneys was reported in 14 patients (12%).

Table 6 Malformations of female and male genitalia

Genitourinary malformation	Frequency	Reference
Ambiguous genitalia	20 (17.1%)	4 (two cases), 19 (two cases), 21, 24, 28, 32 (two cases), 33, 36, 39, 45 (five cases), 51, 53, 55
Female abnormalities		
Clitoromegaly/prominent clitoris	21 (36.8%)	4 (two cases), 9, 10, 11, 14, 16 (two cases), 18, 24, 28, 38, 41 (two cases), 45 (three cases), 49–51, 54
Bicornuate uterus	5 (8.8%)	4 (two cases), 16, 36, 50
Absent, small, or hypoplastic uterus	5 (8.8%)	16, 34, 42, 45, 53
Vaginal agenesis, atresia, aplasia and imperforate vagina	7 (12.3%)	9, 16, 24, 32, 36, 37, 41
Synechiae, adhesions or fusion of the labia	5 (8.8%)	4 (two cases), 11, 32, 45
Hypoplasia or absence of the labia (majora or minora)	5 (8.8%)	9, 14, 19, 49, 51
Rectovaginal fistula or perineal fistula	5 (8.8%)	9, 20, 16 (two cases), 28
Persistent cloaca	2 (3.5%)	24, 45
Male abnormalities		
Cryptorchidism, unilateral or bilateral	17 (31.5%)	3 (two cases), 4 (two cases), 11, 16, 17, 21, 22, 26, 28, 32, 36, 43, 44 (two cases), 45
Micropenis	8 (14.8%)	3, 4 (three cases), 21, 30, 44 (two cases)
Phimosis	4 (3.4%)	11, 21, 36, 45
Chordee	3 (5.5%)	30, 44
Hypospadias	5 (9.3%)	4 (two cases), 22, 27, 43
Hypoplastic scrotum and or atypical scrotal raphe	5 (9.3%)	16, 22, 25, 44 (two cases)
Unspecified abnormalities	2 (1.7%)	20, 37
Streak gonads/absent internal organs		4 (two cases)
Malformed Fallopian tubes		4
Hypoplastic ovaries/ovarian cyst		16, 26, 45
Large or hypertrophic labia majora		40
Hypoplastic external genitalia		16 (two cases)
Small, hypoplastic clitoris		36, 37
180 degree malrotation of penis		23
Macropenis		16
Left ovarian gonadoblastoma in situ		57

Table 7 Nasal malformations

Nasal malformation	Frequency	References
Broad nose and/or nasal bridge	24 (20.5%)	11, 16 (two cases), 23, 28 (two cases), 30, 32 (two cases), 37–39, 44, 49, 50 (two cases), 51, 52 (three cases), 54, 59, 68, 69
Depressed or flat nasal bridge	13 (11.1%)	10, 22, 30, 38, 39, 44, 50, 52 (three cases), 54, 55, 68, 69
Bifid nose, midline groove, or dimple to nasal tip	18 (15.4%)	8, 9, 13, 16, 19, 25, 30, 33, 37, 42, 43, 51, 52 (three cases), 62 (two cases), 68
Coloboma of nares/notched nares	13 (11.1%)	3, 8, 9, 11, 15, 16, 22, 23, 27, 28, 42, 51, 52
Small, short, and/or flat nose	16 (13.7%)	4 (five cases), 10, 11, 19 (three case), 16 (three cases), 38, 50, 51
Nasal hypoplasia/small nostrils/hypoplasia of nasal root or bridge	15 (12.8%)	14, 16 (two cases), 18, 28 (two cases), 32, 36, 39, 45 (five cases), 49, 52
Non-specific abnormalites of nasal shape*	9 (7.7%)	14 (two cases), 19, 32 (two cases), 31, 35, 44, 48
Single nostril/absence of nasal septum		3, 55
Atresia of the nose		45
Widely set or widely flared nostrils		24, 28
Deviated nasal septum, asymmetrical alae		37, 69

*Abnormal nose, hooked nose, beaked nose, gryphoid nose, splayed nose, downturned nasal tip.

Cerebral malformations

Hydrocephalus was recorded four times[3 4 31 55] and polymicrogyria or abnormal brain gyri were seen in three cases.[4] Two patients had encephaloceles.[39 65] Other single findings were mild cerebellar hypoplasia,[16] holoprosencephaly with hydromelia of the spinal cord,[3] periventricular leucomalacia,[12] diffuse gliosis of the brain,[41] and low brain weight.[26]

Cardiac malformations

Cardiac malformations included hypertrophy of the left ventricle,[33] hypertrophic heart,[16] a variant of Ebstein anomaly,[36] coarctation of the aorta,[4] an atrial septal defect,[37] an interventricular communication,[15] and a truncus arteriosus and a ventricular septal defect.[4] One patient had complex heart disease with dysplasia of the pulmonary and aortic valves and endocardial fibrosis.[50] A patent foramen ovale and patent ductus arteriosus were present in three cases[26 40 44] and one patient had a patent ductus arteriosus and dilated coronary sinus.[26] Dextrocardia[3] and transposition of the great vessels[55] were also noted.

Thymic abnormalities

Absence or hypoplasia of the thymus[3 36] and two thymuses[26] were described.

Developmental delay/psychomotor retardation

Information regarding intellectual development was provided in few cases. Developmental delay was present in five patients[25 37 49 52 61] and delayed motor development was found in two.[3 13] Speech delay was specified in one subject.[14] Development was normal in 13 cases.[3 58 60 62 65–67 69] Hypotonia was reported twice.[13 25]

Dysmorphological findings

There was no recognisable facial phenotype (table 14). Twenty-five (21.4%) subjects had hypertelorism or pseudohypertelorism, 11/117 (9.4%) had micrognathia, 8/117 (6.8%) had microstomia, and 8/117 (6.8%) had a short neck.

Fetal and postnatal growth

In babies born at or after 33 weeks of gestation, the majority had normal growth parameters (data not shown). Nine out of

Table 8 Malformations of the ear

Ear malformation	Frequency (%)	References
Malformed and/or low set ears, can be with posterior rotation	63 (53.8%)	3 (two cases), 4 (nine cases), 7–12, 14, 15 (two cases), 17–19 (four cases), 20, 16 (three cases), 21, 23, 24, 26 (two cases), 28 (two cases), 31, 32 (two cases), 33, 36 (three cases), 37, 39, 41 (two cases), 42, 44 (two cases), 46–49, 51, 52 (three cases), 56, 63, 64, 68
Fusion of the ear helix to scalp	3 (2.6%)	9, 13, 25
Microtia	19 (16.2%)	4, 9–12, 18, 25, 26 (two cases), 27, 28 (two cases), 36–38, 41, 44, 52, 64
Atresia/stenosis of the external auditory canals	21 (17.9%)	3 (two cases), 4, 8–11, 14, 16 (two cases), 21, 28 (four cases), 37, 40, 41, 44, 45, 47
Deafness/abnormal BAERs	7 (6.0%)	9, 10, 14, 28 (three cases), 37
Abnormal ossicles		13, 14
Small or absent tympanic membranes		10, 4
Anomalous ears		35
Two accessory tragi		56
Unilateral cholesteatoma		28

Table 9 Malformations of the airway and lungs

Airway malformation	Frequency	Reference
Choanal stenosis/atresia	7 (6.0%)	4, 13, 20, 24, 28 (two cases), 41
Laryngeal stenosis or atresia, narrow laryngeal vestibule	36 (30.8%)	3 (two cases), 4 (eight cases), 9, 11, 12, 14, 16 (three cases), 17, 19, 21, 36 (three cases), 38–41 (two cases), 44 (two cases), 45, 47–49, 53, 54
Stenosis at or below glottis (subglottic stenosis)	10 (8.5%)	4 (two cases), 8, 26, 28 (four cases), 29, 35
Hypoplastic epiglottis	2 (1.7%)	37, 47
Tracheal atresia/abnormality	3 (2.6%)	35, 43, 53
Enlarged, hypertrophic, or hyperechoic lungs	10 (8.5%)	4, 19, 21, 29, 36 (two cases), 44 (two cases), 47, 53
Hypoplasia of the lungs	13 (11.1%)	4 (five cases), 7, 11, 16 (two cases), 32, 39, 50 (two cases)
Abnormal lung lobation	5 (4.3%)	7, 21, 40, 44 (two cases)
Abnormal diaphragm/placement*	5 (4.3%)	21, 43, 44 (two cases), 53
Hoarse voice		35
Laryngeal stridor		8, 14
Unable to intubate		4, 16, 35
Absent pillar left tonsil		37
Fusion of arytenoids		3, 8, 14

*Downward/caudal displacement of the diaphragm, flat hemidiaphragm, and abnormalities of the diaphragm.

Table 10 Orofacial clefting

Dysmorphology	Frequency	Reference
Cleft lip	2 (1.7%)	41, 65
Cleft hard or soft palate	4 (3.4%)	4, 26 (two cases), 45
Cleft lip and palate	4 (3.4%)	4, 5, 16, 45
Bifid or bipartite uvula	2 (1.7%)	16*, 41
High arched palate	14 (12%)	3, 4, 9, 11, 14, 19, 22, 27, 37, 39, 41, 50, 56, 67
Lateral facial cleft	3 (2.6%)	5, 7, 45
Cleft of upper gum		38
Midline furrow of lower lip with sublabial groove and notch at tip of tongue*		16

50 (18%) had a growth parameter below the 3rd centile (data not shown). Fraser syndrome is compatible with normal postnatal growth but both microcephaly[37] and macrocephaly[62] have been recorded and one patient had a final height of 128 cm (<3rd centile, 50th centile for age 8-9 years), whereas another case had growth hormone deficiency.[25]

Survival

The age at reporting or age of death are shown in table 15. In those who died in the first week of life, the commonest causes of death were laryngeal stenosis/atresia or respiratory insufficiency,[4 16 26 32] obstructive uropathy or bilateral renal agenesis, [4 7 16 21 31 34 41] or a combination of laryngeal and renal malformations.[12 40 46] Pulmonary agenesis and bilateral renal agenesis were seen in one infant.[11] Patients who were alive at 10 years of age or older had fewer major malformations (data not shown) and only one of the 10 satisfied the diagnostic criteria for Fraser syndrome. Interestingly, there was a strong phenotypic similarity and concordance of the degree of severity of the disease in families for both severely affected[4 19 21 32 36 44 50] and mildly affected[62 66] sibs. However, intrafamilial variation was seen in the family described by Hancheng,[58] in which two sibs survived to the fourth decade of life and one died at 2 months of age.

DISCUSSION

We have compiled the phenotypic features of 117 patients with CO and FS (figs 1 and 2) reported since the review of Thomas *et al*[2] in 1986 and compared the incidences of phenotypic findings with previous reviews (table 16).[2 3] Our aim was to review the phenotypic manifestations associated with CO

Table 11 Musculoskeletal abnormalities

Musculoskeletal abnormality	Frequency	Reference
Absence or hypoplasia of orbital or skull bones	12 (10.2%)	3, 5, 36, 37, 42, 45, 48, 52, 57, 61, 65, 69
Defects in skull ossification (parietal and occipital bones)	8 (6.8%)	4, 10, 11, 17, 16 (two cases), 18, 43
Wide sutures or fontanelles	5 (4.3%)	4 (three cases), 11, 16
Abnormalities of chest shape*	6 (5.1%)	4 (two cases), 16, 17, 21, 56
Abnormal symphysis pubis†	9 (7.7%)	3, 4 (three cases), 9, 16 (two cases), 24, 54
Talipes unspecified or talipes equinovarus	10 (8.5%)	4, 12, 16 (two cases), 19 (two cases), 28, 34, 50, 51
Contractures of large joints	5 (4.3%)	4, 11, 34, 50 (two cases)
Craniosynostosis		4
Parietofrontal depression		15
Abnormal thoracic spine		16
Thoracic kyphoscoliosis		16, 61
Lumbar lordosis		61
Sacral dimple		50
Deficient right clavicle		16
Hypoplastic or absent 12th ribs		16, 56
Supernumerary ribs		16
Talipes valgus		39
Talipes calcaneovalgus		11
Rockerbottom feet		4 (two cases)
Tibial bowing		4
Bowing of the limb bones		58
Bilateral genu recurvatum		39
Micromelia of all limbs		4

*Barrel shaped thorax, bell shaped thorax, narrow chest, pectus excavatum, funnel chest.
†Wide or separated symphysis pubis, diaphysis of pubic bones, small or absent pubis, cleft of pubic bones.

Table 12 Gastrointestinal malformations

GIT malformation	Frequency (%)	Reference
Anal atresia	9 (7.7%)	9, 13, 4 (three cases), 16 (two cases), 31, 51
Rectal atresia	2 (1.7%)	3, 24
Anal stenosis	8 (6.8%)	3, 8, 16, 28 (two cases), 62 (three cases)
Imperforate anus	15 (12.8%)	3, 4, 11, 20, 22, 25, 36 (two cases), 41, 45 (four cases), 51, 53
Anteriorly placed or displaced anus	7 (6.0%)	14, 16, 23, 45, 62 (three cases)
Umbilical hernia	7 (6.0%)	9, 11, 14, 16, 18, 33, 45
Low set umbilicus	13 (11.1%)	4, 11, 14, 16 (two cases), 20, 22, 24, 31, 45 (two cases), 47, 54
Malrotation of intestine/bowel or incomplete rotation	6 (5.1%)	4, 12, 16, 18, 20, 24
Fistula		28
Perianal fistula		9, 22
Intestinal fistula		45
Large or protuberant abdomen		36, 47
Lower abdominal wall defect		54
Deep set umbilical cord		34
Hypoplasia of the stomach		4, 34
Hiatus hernia		28
Duodenal stenosis		44
Hepatomegaly		11, 53
Abnormal lobulation of the liver		16
Non-fixation of the intestine		44 (two cases)
Mesenteric abnormalities with simple arterial pattern		4 (two cases)
Absent appendix		16, 21
Meckel diverticulum		17
Ectopic adrenal tissue		26
Ectopic pancreatic tissue		40

and FS and to examine the efficacy of the published diagnostic criteria.[2] The frequency of malformations in this patient group does not differ significantly from the frequencies reported by Gattuso *et al*.[3] However, they are lower than those reported by Thomas *et al*[2] owing to selectivity of the latter paper in including only patients in whom the presence or absence of a feature had been documented. The incidence of published malformations could also be skewed because of the preferential inclusion of rare features and complications or severely affected patients in medical publications in a well described syndrome.

Our data show an increased incidence of consanguinity (24.8%) compared to the incidence of 15% published by Thomas *et al*,[2] consistent with autosomal recessive inheritance. The prevalence of FS has previously been estimated to be approximately 11 cases in 100 000 live births.[45]

CO is considered to be the single most important diagnostic malformation in FS. Complete CO is usually bilateral and can be associated with absence or poor development of the eyebrows, eyelashes, gland structures and conjunctival sac, microphthalmia, symblepharon, and abnormalities of the anterior chamber of the eye.[8 75] In incomplete or atypical CO, rudimentary lid structures with small, lateral conjunctival sacs are present with small palpebral fissures, microphthalmia, and symblepharon.[8 75] CO should be differentiated from microblepharon (vertical shortening of the eyelids)[76] and mesodermal corneal metaplasia.[77 78]

Abortive CO or congenital symblepharon and ablepharon are descriptive terms used to describe an upper eyelid without

Table 13 Renal malformations

Renal malformations	Frequency	Reference
Unilateral renal agenesis	22 (18.8%)	3, 9, 14, 18–21, 24, 28 (three cases), 35, 38, 41, 43, 45 (four cases), 51, 52, 54
Unilateral renal agenesis with agenesis of ureter	4 (3.4%)	32 (two cases), 44, 45
Bilateral renal agenesis	6 (5.1%)	12, 15, 16, 19, 39, 44
Bilateral renal agenesis with agenesis of ureters	21 (17.9%)	4 (seven cases), 7, 11, 16 (two cases), 19, 21, 29, 31, 34, 36, 40–42, 53
Cystic dysplasia of kidneys or renal cysts	14 (12%)	4 (four cases), 9, 17, 19, 32, 36, 44–46, 50 (two cases)
Unilateral or bilateral renal hypoplasia or small kidneys	14 (12%)	3, 4 (three cases), 8, 9, 17, 27, 29, 32 (two cases), 49, 50 (two cases)
Absent, hypoplastic, or small bladder with or without urethra	20 (17%)	4 (four cases), 7, 11, 16 (two cases), 19, 21, 36 (two cases), 39, 40, 42, 44 (two cases), 45, 50, 53
Agenesis of entire urinary apparatus		29
Solitary pelvic kidney*		20, 24
Bilateral renal artery agenesis		41
Enlarged kidneys		50
Duplex left kidney system/two left ureters		3, 26
Hydronephrosis		4, 36
Renal dysplasia		45 (two cases), 49
Hypertrophied or thick bladder		4, 17
Bladder pseudexstrophy		54
Anterior urethral atresia with deformed urinary bladder, bilateral hydronephrosis, and dilated ureters and umbilical discharge of urine		46

*Included in unilateral renal agenesis.

Table 14 Dysmorphology findings

Dysmorphology	Frequency	Reference
Potter facies	3 (2.6%)	19, 34, 44
Facial asymmetry	6 (5.1%)	3, 13, 15 (two cases), 36, 69
Abnormalities of skull shape*	5 (4.3%)	4, 16 (two cases), 40, 56
Sloping forehead	4 (3.4%)	17, 50 (two cases), 51
Prominent, protuberant, and/or broad forehead	5 (4.3%)	4, 14, 16 (two cases), 51
Low posterior hairline	3 (2.6%)	12, 33, 37
Hypertelorism or pseudohypertelorism	25 (21.4%)	9, 14, 16 (two cases), 18, 21, 28 (two cases), 33, 37, 38, 40, 45 (two cases), 49, 50 (two cases), 51, 56, 62 (six cases)
Frenula or thick frenula, tongue tie, short frenula	5 (4.3%)	8, 3, 4, 28, 56
Microstomia	8 (6.8%)	16, 19 (three cases), 37, 40, 43, 51
Micrognathia	11 (9.4%)	4 (two cases), 16, 26 (two cases), 44 (two cases), 45, 50 (two cases), 51
Short neck with redundant skin and/or extra skin	8 (6.8%)	3, 7, 16 (two cases), 33, 50 (two cases), 51
Widely spaced nipples	5 (4.3%)	3, 38, 52 (two cases)
Haemangioma	4 (3.4%)	3, 8, 11, 48
Non-specific dysmorphism		27, 29
Hirsutism		19
Upward slanting palpebral fissures		37, 50
Upsweeping eyebrows		16
Epicanthic folds		45
Blepharophimosis		37, 45
Telecanthus		23, 49
Long philtrum		21, 50
Short philtrum		16, 32
Thin vermilion border to the lips, dowrnturned lips		26 (two cases)
Thick lips		69
Fibrous band of buccal mucosa		69
Relative macrostomia and macroglossia		50
Hypoplastic nipples		45
Oculocutaneous albinism		68
Vitiligo		61

*High, narrow skull, scaphocephaly, dolichocephaly, brachycephaly, flat occiput.

a well defined margin that is adherent to the cornea, often with a small globe and keratinisation of the cornea.[8] Symblepharon and ablepharon have been considered by some authors to be an abortive form of CO[8 79] and by others to constitute a separate pathological entity.[80] The degree of CO and the range of ocular abnormalities in FS was very variable (tables 3 and 4) and many patients had complete CO in one eye with incomplete or abortive CO affecting the other eye (data not shown).

We found patients who had symblepharon and ablepharon and phenotypic features consistent with FS, suggesting that symblepharon is part of the ocular manifestations of FS. The ocular abnormalities in FS were almost all confined to the anterior chamber of the eye with the exception of six patients who had hypoplasia or atrophy of the optic nerve (table 4).

In our series, 14 (12%) patients did not have CO.[4 9 16 33 34 41 45 50 53 55 62] Most of these patients had other ocular abnormalities consistent with FS (for example, corneal clouding,[4] sclerocornea,[33] microphthalmia,[55] anophthalmia,[34 62] microcornea,[41] and a lateral tongue of hair,[62] and 78.6% satisfied the diagnostic criteria for FS (data not shown). However, in the absence of CO, anterior chamber abnormalities could conceivably be confused with other malformation syndromes (for example, Walker-Warburg syndrome or Peters' plus

Table 15 Survival of affected subjects

Survival	Frequency	Reference
Alive up to 4 weeks	5	23, 39, 46, 52, 59
Alive up to 1 year	16	3 (two cases), 8, 11, 14, 20, 22, 23, 30, 39, 52 (two cases), 57, 63, 64, 67
1-10 years	16	5, 9, 13, 25, 28 (four cases), 33, 35, 39, 43, 48, 54, 66, 69
10-20 years	8	37, 60 (two cases), 61, 62, 65, 66, 68
Older than 20 years	2	58 (two cases)
Age unstated, alive	18	10, 18, 24, 38, 41, 45 (six cases), 49, 60, 62 (five cases)
Stillborn or spontaneous abortion	8	4 (two cases), 15, 19, 26, 42, 50, 51
Termination of pregnancy	15	4, 15–17, 19, 21, 29, 36 (two cases), 44 (two cases), 47, 50, 53, 55
Died, age uncertain	1	39
Died in first week of life	24	4 (eight cases), 7, 11, 12, 16 (two cases), 19 (two cases), 21, 26, 31, 32 (two cases), 34, 40, 41, 46
Died in first year of life	4	3, 27, 56, 58

Table 16 Comparison of frequencies of phenotypic features in CO and FS

Physical finding	Ref 2 (n=124)	Ref 3 (n=63)	Our series (n=117)
CO	85%	93%	88%
Unilateral		25%	24.8%
Bilateral		57%	47.9%
Unstated		10%	
Extended hair growth		34%	34.2%
Facial asymmetry		10%	5.1%
Ear abnormalities	84%	44%	59%
Atresia/stenosis eam		15%	17.9%
Nasal abnormalities	85%	37%	
Cleft lip and palate	11%	7%	11.1%
Renal abnormalities		37%	
Renal agenesis	84%	37%	45.3%
Bladder abn		10%	17%
Cystic dysplasia		3%	12%
Abnormal genitalia	80%	49%	
Indeterminate sex		6%	5.1%
Abnormalities in females		54%	
Clitoral hypertrophy		39%	36.8%
Bicornuate uterus		14%	8.8%
Vaginal atresia		14%	12.3%
Cystic ovaries		11%	
Rudimentary uterus		4%	8.8%
Abnormalities in males		41%	
Cryptorchidism		24%	31.5%
Micropenis		21%	14.8%
Hypospadias		3%	9.3%
Syndactyly	79%	54%	61.5%
Laryngeal atresia	83%	21%	30.8%
Lung hypoplasia		7%	11.1%
Anal stenosis/atresia		6%	16.2%
Talipes		6%	10.2%
Congenital heart disease		6%	12%
Umbilical hernia	28%	12%	6%
Umbilicus displaced		6%	11.1%

syndrome). The presence of microphthalmia or anophthalmia without CO in a sporadic case constitutes a further diagnostic dilemma. For example, a male reported by Glanz *et al*[81] as having Lenz microphthalmia because of short palpebral fissures could be considered to satisfy the diagnostic criteria for FS with syndactyly, cryptorchidism and hypospadias, renal hypoplasia, and a cleft palate.

The diagnosis of FS must therefore be made with caution in patients who do not have CO or a family member with CO, even if other ocular abnormalities consistent with FS are present. For example, in the patient reported by Martinez-Frias *et al*[33] who had sclerocornea, syndactyly, ambiguous genitalia, a furrowed nasal tip, low set, posteriorly rotated ears, and an umbilical hernia, the authors did not consider that the diagnosis of FS was correct although this patient did fulfil the diagnostic criteria. Without CO, FS can be overdiagnosed because of the relatively high frequency of digital and genital abnormalities in multiple congenital anomaly syndromes.

In the patients with CO who did not satisfy the diagnostic criteria for FS, only one had CO without any other phenotypic findings and with an unremarkable family history.[60] Autosomal recessive inheritance in isolated CO should still be considered and three affected patients with CO as the sole physical finding were born to consanguineous parents.[39] A common anomaly found in addition to CO without FS was a tongue of hair extending from the scalp to the lateral eyebrow (table 4).[58] We consider that this finding makes an underlying diagnosis of FS with the implication of autosomal recessive inheritance more likely and would consider it as having at least equal importance to a minor diagnostic feature.

The incidence of syndactyly in this patient cohort was 61.5% (table 5), less than the frequency of 79% reported by Thomas *et al*.[2] However, the syndactyly in many patients was distinctive because of the involvement of both upper and lower limbs (table 5) and the extensive nature of the cutaneous webbing, which frequently included all digits (data not shown). A range of external and internal malformations of the genitalia were described, fully justifying the inclusion of these abnormalities as major diagnostic criteria.[2]

The minor criteria of malformations of the ears and nose can be non-specific and more weighting should be given to these features if they are included in the distinctive anomalies found in FS, such as coloboma of the nares or notched nares (table 7). Orofacial clefting (table 10) and mental retardation were infrequent and these criteria were rarely helpful in establishing the diagnosis. No mention has been made of gastrointestinal tract malformations in the diagnostic criteria and we would recommend consideration of malformations such as anal atresia, rectal atresia, anal stenosis, and imperforate anus as minor criteria owing to the occurrence of these features in more than 25% of affected subjects (table 12). A low set umbilicus may be more frequent and hence more diagnostically useful than an umbilical hernia (table 12). Renal agenesis has previously been considered to be an important diagnostic feature in FS and we would agree that this abnormality is pertinent to the diagnosis.[82–84]

The FS phenotype is complex and pleiotropic and therefore has significant overlap with other malformation syndromes. We were interested to determine if there were distinct patterns of physical features within the FS phenotype. Recently, more complex modes of inheritance involving modifier genes or three altered alleles have been described for a different autosomal recessive condition, Bardet-Biedl syndrome (BBS).[85 86] We therefore speculated that the more complex modes of inheritance identified in BBS could also be described for other pleiotropic syndromes and that, in some cases, the phenotypic consequences of the different genes or pathways may be identifiable within a syndromal phenotype.

Table 17 Malformations found in addition to vaginal agenesis in FS females

Author	Vaginal malformations	Gastrointestinal malformations	Renal malformations	Cardiac malformations	Other
9	Vaginal atresia	Anal atresia	L renal agenesis		Deafness
16	Vaginal atresia	Anal stenosis	R renal dystopia		Bicornuate uterus
24	Vaginal atresia	Rectal atresia	Pelvic kidney		Choanal atresia
32	Vaginal atresia		Renal cysts		
36	Vaginal atresia	Imperforate anus		Ebstein anomaly	Bicornuate uterus
50	Vaginal atresia		Sib with renal cysts	Atrial septal defect	Deafness
41	Vaginal atresia		Bilateral renal agenesis		Bicornuate uterus/choanal atresia

Table 18 Relative incidence of phentyopic features in FS

Phenotypic feature	Incidence in FS	Incidence in patients with VA	Significance
Vaginal agenesis	7/57 (12.3%)	–	
Anal stenosis	34/117 (29%)	4/7 (57%)	p=0.14
Renal cystic dysplasia	14/117 (12%)	2/7 (28.6%)	p=0.55
Cardiac malformations	14/117 (12%)	2/7 (28.6%)	p=0.55
Deafness	7/117 (6%)	2/7 (28.6%)	p=0.55
Choanal atresia	7/117 (6%)	2/7 (28.6%)	p=0.55
Bicornuate uterus	5/57 (8.8%)	3/7 (42.9%)	p=0.121

No phenotype-genotype correlation has as yet been consistently described for BBS patients. However, syndactyly, imperforate anus, Hirschsprung disease, cardiac defects, and female upper genitourinary tract malformations have previously been found with increased frequency in BBS patients with hydrometrocolpos owing to vaginal agenesis compared to unselected BBS patients (data not shown). In this patient cohort, we found seven females who fulfilled the diagnostic criteria for FS and who had vaginal agenesis or vaginal atresia. It was surprising to find that all of these patients also had at least one other finding consistent with the above pattern such as anal abnormalities, renal malformations including renal agenesis or renal cysts, and bicornuate uterus (table 17). In addition, cardiac abnormalities were identified in two patients[41 50] and one patient did not have CO.[16] The finding is more striking if one considers the relative rarity of some of these findings in FS (table 18). This phenotypic subset has some similarity to the MURCS association (Muellerian duct aplasia, renal aplasia, and cervical dysplasia) and the Rokitansky malformation sequence of vaginal atresia and uterine hypoplasia or a bicornuate uterus and renal agenesis.[87 88] Interestingly, corneal anaesthesia and punctate epithelial opacities have been described in the MURCS association[89] and a child with bilateral microtia and hypoplasia of the external ear canals, a cleft palate, hypoplastic thumbs, renal agenesis, pulmonary agenesis, and genital hypoplasia has been considered to have physical features consistent with MURCS association and Nager acrofacial dysostosis.[90]

Similarly, we found that laryngeal stenosis was present in 35/117 of patients with FS (29.9%) and stenosis of the external auditory meatus in 21/117 of FS patients (17.9%). Both of these malformations were present in 11 patients (52.4%, tables 12 and 13). This association is significant with a p value of 0.046. Although hypertelorism, hypopspadias, and laryngeal malformations are found in both Opitz syndrome and FS, there did not appear to be any association of these features in this patient group (data not shown).

Modifier genes are important determinants of phenotypic variation and have been shown to be clinically important in diverse conditions, including sensorineural deafness,[90] cystic fibrosis,[91] hypertrophic cardiomyopathy,[92] early onset glaucoma,[93] and keratin filament disorders.[94] Modifier genes can also have tissue specific effects.[95] The significance of modifier genes in the generation of the variability of the FS phenotype is unknown but is not supported by the strong familial concordance in phenotype in many reported cases (see above).

We therefore suggest that subsets of physical anomalies or phenotypic modules can be conserved across different syndromes and that they may prove to be a useful means for the delineation of specific abnormalities within a syndrome and for the determination of relevant molecular screening tests. The pathogenesis of phenotypic modules could include disruption to a morphogenetic field or a developmental field,[96] mutation specific effects, or malfunction of temporally distinct genes. Consideration of the physical findings in a syndrome as a series of interacting phenotypic modules may also be a useful method for determining phenotype-genotype correlations in the future.

CONCLUSION

We have reviewed 117 patients diagnosed with FS and CO since the publication of the diagnostic criteria for FS by Thomas *et al*.[2] The diagnosis should be made with caution in probands and families without CO, although in the presence of typical findings, CO is not essential for the diagnosis. The physical features of orofacial clefting, umbilical hernia, and mental retardation were less useful in making the diagnosis, whereas gastrointestinal tract malformations may be helpful.

We also found that patients with vaginal agenesis and FS had a pattern of additional malformations previously described in MURCS association and BBS. This suggests that there is conservation of a subset of phenotypic features between different syndromes and that unusual mechanisms of inheritance such as modifier genes or triallelic inheritance may be present in malformation syndromes other than BBS.

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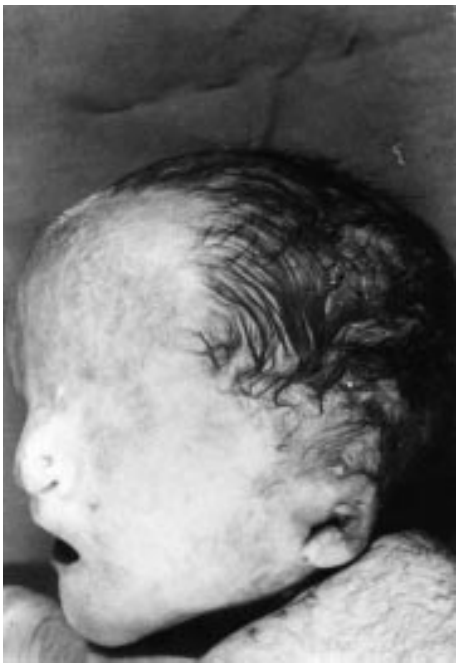

Figure 1 Profile of a baby with Fraser syndrome showing complete cryptophthalmos.

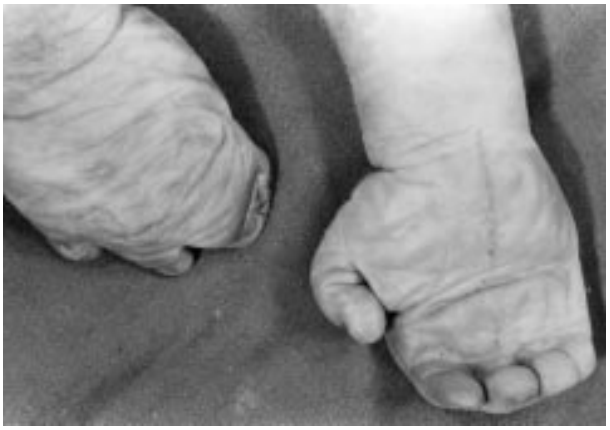

Figure 2 Hands of baby with Fraser syndrome showing extensive soft tissue syndactyly. Both photographs are reproduced with the kind permission of Dr Samir S Amr, MD, FCAP, Pathology Services Division, Dhahran Health Center, Saudi Aramco and the *Saudi Medical Journal* (previously published as figures in reference 42, *Saudi Med J* 1996;**17**:251–5).

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