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Clinical and Genetic Epidemiology of Bardet–Biedl Syndrome in Newfoundland: A 22-Year Prospective, Population-Based, Cohort Study

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Abstract

Bardet–Biedl syndrome (BBS) and Laurence–Moon syndrome (LMS) have a similar phenotype, which includes retinal dystrophy, obesity, and hypogenitalism. They are differentiated by the presence of spasticity and the absence of polydactyly in LMS. The aims of this study were to describe the epidemiology of BBS and LMS, further define the phenotype, and examine genotype–phenotype correlation. The study involved 46 patients (26 males, 20 females) from 26 families, with a median age of 44 years (range 1–68 years). Assessments were performed in 1986, 1993, and 2001 and included neurological assessments, anthropometric measurements, and clinical photographs to assess dysmorphic features. The phenotype was highly variable within and between families. Impaired co-ordination and ataxia occurred in 86% (18/21). Thirty percent (14/46) met criteria for psychiatric illness; other medical problems included cholecystectomy in 37% (17/46) and asthma in 28% (13/46). Dysmorphic features included brachycephaly, large ears, and short, narrow palpebral fissures. There was no apparent correlation of clinical or dysmorphic features with genotype. Two patients were diagnosed clinically as LMS but both had mutations in a BBS gene. The features in this population do not support the notion that BBS and LMS are distinct. The lack of a genotype–phenotype correlation implies that BBS proteins interact and are necessary for the development of many organs.

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Keywords

Bardet–Biedl syndrome; Laurence-Moon-Biedl syndrome; genotype–phenotype correlation

INTRODUCTION

In 1866, Laurence and Moon described four affected siblings with retinal dystrophy, obesity, and mental retardation. Three of them (males) also had small external genitalia and an abnormal gait [Laurence and Moon, 1866]. Bardet and Biedl reported a similar phenotype in individuals, who also had polydactyly [Bardet, 1920; Biedl, 1922]. The overlapping features of these cases suggested that the two disorders represented variable expression of a single condition [Solis-Cohen and Weiss, 1925; Klein and Amman, 1969] although this is controversial [Schachat and Maumenee, 1982; Lancet, 1988]. The finding of neurological manifestations in Bardet–Biedl syndrome (BBS) patients has prompted hypotheses that Laurence–Moon syndrome (LMS) and BBS are allelic [Beales et al., 1999].

BBS is more common than LMS, with a prevalence of 1 in 125,000–160,000 in Europe [Klein and Amman, 1969; Beales et al., 1997] and 1 in 65,000 in an Arab population [Farag and Teebi, 1988]. The cardinal features of BBS are retinal dystrophy, obesity, dystrophic extremities, renal structural abnormalities, and male hypogenitalism [Green et al., 1989]. There is considerable inter- and intra-familial variation in the phenotype [Beales et al., 1997; Riise et al., 1997].

BBS is genetically heterogeneous, with at least eight disease loci. Six BBS genes have been identified: *BBS1* [Mykytyn et al., 2002]; *BBS2* [Nishimura et al., 2001]; *BBS4* [Mykytyn et al., 2001]; *MKKS/BBS6* [Katsanis et al., 2000; Slavotinek et al., 2000a]; *BBS7* [Badano et al., 2003a]; and *BBS8 (TTC8)* [Ansley et al., 2003]. A further two loci have been mapped: *BBS3*, to 3p12 [Sheffield et al., 1994] and *BBS5*, to 2q31 [Young et al., 1999a]. Although BBS has been regarded as an autosomal recessive disorder, oligogenic inheritance has been reported in some cases [Katsanis, 2004]. The genetic basis of LMS is not known.

Few studies have compared the BBS phenotype with genotype, and these have noted only minor phenotypic differences [Carmi et al., 1995; Beales et al., 1997; Riise et al., 2002; Slavotinek et al., 2002]. This report describes a prospective, population-based study, with comprehensive ascertainment, and follow-up for 22 years. The objectives of the current study were: (a) to determine if BBS and LMS are a single disorder; (b) to describe the epidemiology of BBS; (c) to extend the phenotype; and (d) to determine if there are genotype–phenotype correlations in BBS.

MATERIALS AND METHODS

Patients

Patients have been ascertained since 1979 via several different routes, as previously described [Green et al., 1989], and subsequently through the provincial genetics program. Patients were enrolled if they had retinal dystrophy and any other feature suggestive of BBS or LMS, and further assessed, either by chart review or clinical examination. Two patients

from one family of Newfoundland parentage living in Ontario referred themselves. The current cohort consisted of 46 patients (26 males, 20 females) from 26 families, with an age range of 1.5–67.9 years (median 44 years). Consanguinity was documented in 27% (7/26) families, and suspected in another 15% (4/26).

Methods

Protocol-driven assessments were performed in 1986 [Harnett et al., 1988; Green et al., 1989], 1993 [O'Dea et al., 1996], and 2001. Earlier assessments included ophthalmological examination, measures of glucose tolerance, pituitary, renal function and renal imaging, using methodology described previously [Harnett et al., 1988; Green et al., 1989]. In the 2001 assessment, medical charts were reviewed for all 46 patients. Ten patients had died by 2001.

Fifty-six percent (26/46) patients had a clinical examination, performed by the same clinician (S.J.M.), including anthropometric measurements of head, face, ears, hands, feet, and genitalia. Twelve patients were also examined by another clinical geneticist (B.A.F.). Blood urea, creatinine, liver enzymes, random glucose, and glycosylated hemoglobin were measured. Urinalysis, microscopic analysis and culture were performed.

Quantitative dysmorphic features were compared with normal values [Hall et al., 1995]. Photographs for 19/26 patients were reviewed by three clinical geneticists (S.J.M., B.A.F., J.C.S.D.), who were not blinded to the diagnosis, to score qualitative facial dysmorphic features. Seven patients were also examined by a neurologist (M.S.). Nineteen patients (18 adults, one child aged 13 years) had a speech assessment in 2001, including an Edinburgh Articulation Test [Anthony et al., 1971]. Speech abnormalities and deficits in oral coordination have been reported previously in BBS [Beales et al., 1999], so diadochokinetic tests were used to measure the ability to make rapid alternating speech movements. The times to repeat syllables were recorded and compared with normal values [Shipley and McAfee, 1998].

Psychiatric diagnoses using standard DSM-IV criteria [Diagnostic and Stastistical Manual of Mental Disorders, 1997] were confirmed by a psychiatrist (A.B.), from medical chart review for 14 patients. Intelligence quotients (IQ) were measured using the Weschler Adult Intelligence Scale (WAIS) verbal subtests for verbal IQ (VIQ) and the Haptic Intelligence Scale, designed for those with severe visual impairment, for performance IQ (PIQ), except for one child who had adequate visual acuity for the Wescler Intelligence Scale for Children (WISC).

Seventy percent (32/46) patients had a renal ultrasound scan, performed in 2001 for 14 patients, reported by the same radiologist (BCC) in 78% (25/32) of cases.

For 21/26 families, DNA was extracted from venous lymphocytes. Linkage to *BBS1, BBS2, BBS3, BBS4*, or *BBS5* was assessed using microsatellite markers [Young et al., 1998, 1999a,b; Woods et al., 1999]. Association with *MKKS/BBS6* was determined as previously described [Katsanis et al., 2000]. Linkage to *BBS7* or *BBS8* was examined by haplotype analysis [Ansley et al., 2003; Badano et al., 2003a]. All affected individuals for whom DNA

was available were screened for the presence of the *BBS1* mutation, M390R, the *BBS2* mutation, Y24X, and the *MKKS/BBS6* mutations, A242S, D143fsX157, F94fsX103, and L277P [Fan et al., 2004].

Ethical approval was given by the Human Investigation Committee of Memorial University of Newfoundland and the Research Ethics Board of Simon Fraser University. Informed consent to participate was obtained from patients.

Definitions

BBS—At least four cardinal features (retinal dystrophy, obesity, renal abnormalities, male hypogenitalism, dystrophic extremities) or three cardinal manifestations in a sibling of an affected person with four cardinal features [Green et al., 1989].

LMS—Retinal dystrophy, obesity, spasticity, and at least one of hypogenitalism or mental retardation, in the absence of polydactyly.

Registered blind—Visual acuity <20/200 or visual field <20 degrees in the better eye, due to retinal dystrophy.

Obesity—Body mass index, BMI >27 kg/m^2 [Nelson et al., 1994].

Hypertension—Sitting systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg or taking antihypertensive medication [Harnett et al., 1988].

Moderate chronic renal failure—Estimated creatinine clearance <60 ml/min using the formula of Cockcroft and Gault [Cockroft and Gault, 1976], or serum creatinine >150 μmol/L in adults, or >100 μmol/L in children <2 years.

Mild chronic renal failure—Estimated creatinine clearance 60–90 ml/min, or serum creatinine 121–150 μmol/L.

Diabetes mellitus—Taking hypoglycemic therapy (diet/oral medication/insulin) for type 2 diabetes mellitus or fulfilling the diagnostic criteria of the 1998 clinical practice guidelines for the management of diabetes in Canada [Meltzer et al., 1998].

Age of onset—The age of onset of hypertension, diabetes mellitus, or renal failure was considered to be the age at which the clinical end-point was first recorded in the medical chart.

Analysis

The Kaplan–Meier survival analysis and log rank test were used to compare the age of onset of blindness, diabetes, hypertension, and renal failure between genotype groups. A “genotype group” refers to all patients who have mutations identified in both alleles at the same BBS locus, regardless of the nature of the mutation, or who show linkage to the same BBS locus (for *BBS3* and *BBS5*). Differences between continuous variables were evaluated using Student’s *t*-test for two groups, and ANOVA with Bonferroni adjustment for multiple

comparisons for more than two groups. A result was regarded as statistically significant if the *P* value was below 0.05. The denominator used in the calculation of prevalence for clinical endpoints varied, depending on the number of patients available for testing.

RESULTS

Genetic Epidemiology of BBS in Newfoundland

The current prevalence of BBS in Newfoundland is approximately 1 in 18,000. Thirty-one percent (46/150; 95% confidence interval: 23.6%–38.4%) of siblings in the 26 families were affected (Fig. 1).

Table I shows the mutations in BBS genes identified in the cohort. Only one case (NF-B12) has been found in which an affected person has mutations in more than one BBS gene. Two patients from one family were excluded from all eight BBS loci, implying that their disorder is associated with an as yet unidentified BBS locus.

Diagnosis of BBS Versus LMS

Of the forty-six patients initially diagnosed with BBS, two met the diagnostic criteria for LMS. Both had retinal dystrophy, spasticity, ataxia, hypogenitalism, mild mental retardation, and no polydactyly. One was from a large consanguineous pedigree (NF-B9, Fig. 1), which showed linkage to *BBS5*, the four other affected individuals did not have polydactyly, 3/4 were examined and did not have spasticity. The other LMS patient, from family NF-B5 (Fig. 1), had F94fsX103/L277P mutations in the *MKKS/BBS6* gene.

Clinical Manifestations

Blindness—Ninety-one percent (42/46) of patients were registered blind, with a median age to registration of 18 years (range 9–36 years). The age to register blind was similar across all genotype groups (Fig. 2).

Dystrophy of extremities—Brachydactyly was present in the feet of all patients (36/36), and in the hands in 86% (31/36). Syndactyly (mostly 2/3 toe) occurred in 95% (35/37). Postaxial polydactyly was present in 63% (29/46) of cases. Figure 3a shows the extremities affected in those with polydactyly by genotype group.

Obesity—BMI were available for 96% (44/46) of the patients (Fig. 3b). All were obese at some time, except a child who diedat 18 months. Morbid obesity(BMI greater than 40 kg/m^2) was present in 25% (11/44) of individuals. There was no significant difference in BMI with gender or genotype group.

Diabetes mellitus—Type 2 diabetes mellitus occurred in 48% (22/46) of patients and impaired glucose tolerance was diagnosed in a further four. The median age of onset of diabetes mellitus was 43 years and there was no significant difference among genotype groups (Fig. 2).

Hypertension—Hypertension occurred in 67% (31/46) with a median age to onset of 34 years. It was associated with all genotype groups except BBS2 and there was no significant difference in age of onset among these groups (Fig. 2).

Renal abnormalities—All 32 patients who had a renal ultrasound had an abnormality detected. Fetal lobulation was present in 84% (26/31), calyceal blunting, clubbing or diverticula in 78% (25/32), and cysts in 72% (23/32). Moderate chronic renal failure occurred in 20% (9/44) with a median age at onset of 57.6 years. Four patients progressed to end stage renal disease. A further seven had mild chronic renal failure. Renal impairment occurred in all genotype groups except BBS2.

Genital and reproductive abnormalities—These are shown in Table II. Patients with urethral strictures presented at 27 and 29 years. Two patients with vaginal atresia presented as a neonate and age 12 years.

Neurological, speech, and psychiatric abnormalities—Ataxia and impaired co-ordination were present in 86% (18/21) of patients. Twenty-one percent (5/24) had spasticity, involving all limbs in 4/5 patients and only lower limbs in one. Paucity of facial movements were observed in 75% (15/20) of patients representing all genotype groups. Thirty percent (6/20) had difficulty smiling, and 40% (8/20) had asymmetrical movement. These defects appeared to be due to impaired co-ordination or apraxia, rather than weakness. Eye movement range was limited in 81% (17/21) of patients, particularly upward gaze, with limitation in all directions in eight cases. This was not corrected by oculocephalic maneuvres, implying that the level of the defect is at or below the midbrain.

Syllable repetition times for patients were markedly prolonged (Fig. 4), with means of 14.1, 13.1, 12.9, and 14.4 sec compared with normal mean values of 3.3, 3.3, 3.7, and 5.7 sec for 20 repetitions of “puh,” “tuh,” “kuh,” and ten repetitions of “puhtuhkuh,” respectively (P <0.0001). This was seen in all genotype groups tested (BBS1, BBS3, BBS5, BBS6, and unknown).

Thirty percent (14/46) of patients met criteria for psychiatric illness during their lifetime. Anxiety disorders occurred in 20% (9/46), most (6/9) presented with recurrent psychosomatic symptoms at ages 20–40 years. Mood disorders occurred in 9% (4/46), three with major depression and one with bipolar disorder. All except one required in-patient treatment. One child with mutations in the *MKKS/BBS6* gene had autistic spectrum disorder, and required special education.

Twenty of the 22 VIQ scores and 12/14 PIQ scores were reported previously [Green et al., 1989]. The mean VIQ was 75 (range 53–102, N =24), and PIQ was 83 (range 44–105, N =14). An IQ less than 70 was recorded in 33% (8/24) of cases for VIQ and 21% (3/14) for PIQ. Patients linked to the *BBS3* locus had a significantly higher mean VIQ than those with mutation in *MKKS/BBS6*, or unassigned to a specific BBS locus (P =0.038 and P =0.015, respectively). There was no significant difference in PIQ among genotype groups.

Craniofacial dysmorphology—Table III shows the prevalence of craniofacial dysmorphic features, which were present in all genotype groups and are illustrated in Figures 5 and 6.

Additional medical disorders—Table IV shows medical disorders that occurred in at least two BBS patients, other than the major manifestations, which are summarized in Figure 2. There is no evidence of clustering for any of these clinical features with genotype group.

Gall stone disease—Cholecystectomy for cholelithiasis was performed in 55% (11/20) of females and 23% (6/26) of males. By 30 years of age, 25% of patients had a cholecystectomy. There was a trend towards an earlier age at cholecystectomy for females compared with males in the cohort (P=0.08).

Colonic disorders—Patients included one child with mutations in the *MKKS/BBS6* gene who had Hirschsprung disease, one patient with chronic constipation and four patients with irritable bowel syndrome (ages at onset 29–39 years).

Asthma—All 13 patients used inhalers or nebulisers regularly, and 8/13 (62%) required hospital admissions. One patient with chronic asthma died of cor pulmonale.

Congenital heart disease—These cases involved one ventricular septal defect and one case of aortic valve stenosis. Another patient had complex anomalies, including aortic stenosis and coarctation of the aorta. The latter two patients required cardiac surgery.

Other miscellaneous disorders—Four patients with epilepsy had childhood onset, mostly generalized tonic-clonic seizures. The adult onset disease involved absence seizures. Of six patients (two males, four females) with thyroid disease, three had hyperthyroidism, and three hypothyroidism. Myocardial infarctions (MI) occurred at the following ages: 40, 45, 48, 60, and 68 years (one unknown); all except one had diabetes mellitus, five had hypertension.

Death—The median survival of the cohort was 63 years. Twelve patients died between the ages of 1.5 and 68 years, with a median age of 46 years. Causes and ages of death were as follows: MI in three (40, 48, and 68 years), cerebrovascular disease in one (63 years), end stage renal disease in two (19 and 27 years), renal carcinoma in one (63 years), and septicemia due to urinary tract infection in one (62 years). One patient died following surgery for Hirschsprung disease (1.5 years). One patient with end-stage renal disease died after colonic resection for a gastro-intestinal hemorrhage of unknown etiology (45 years). Other deaths were due to pulmonary embolus in a patient with morbid obesity (32 years), and aspiration pneumonia following a seizure due to a meningioma (52 years).

DISCUSSION

Extension of the Phenotype

The association of abnormalities in almost every organ in this cohort of BBS patients is consistent with the widespread expression pattern demonstrated for each of the six BBS

genes identified thus far [Slavotinek et al., 2000a; Mykytyn et al., 2001; Nishimura etal., 2001; Mykytyn etal., 2002;Ansley etal., 2003; Badano et al., 2003a]. Dysmorphic extremities, particularly brachydactyly, are well recognized in BBS [Green et al., 1989], however, the skeletal dystrophy may be more widespread [Rudling et al., 1996; Beales et al., 1999] and were present in 11% and 4%, respectively in this cohort. Hirsch-sprung disease, anal stenosis, and atresia have been reported previously in association with BBS [Biedl, 1922; Slavotinek and Beisecker, 2000b]. The prevalence of colonic disorders in this cohort support the hypothesis that abnormalities of the developing hindgut are common in BBS. The high prevalence of asthma in this cohort confirms the findings of other reports [Beales et al., 1997, 1999]. The prevalence of cholecystectomy found in this cohort is higher than would be expected for the BMI of the patients [Stampfer et al., 1992], suggesting an underlying metabolic or structural abnormality predisposing to gall stones. An increased frequency of hypothyroidism and chronic serous otitis media has been reported previously in a large BBS cohort [Beales et al., 1999]. Both may cause significant morbidity and be difficult to detect in a timely manner due to co-morbidity in BBS, necessitating a high index of suspicion for clinicians.

Craniofacial Dysmorphology

There is a paucity of reports on the facial features of BBS. Two independent groups previously described a long philtrum, thin upper lip, small mouth, and premature male balding [Beales et al., 1999; Lorda-Sanchez et al., 2001]. The results from this study are consistent with these reports and indicate that characteristic findings in BBS patients include brachycephaly, macrocephaly, large ears, short and narrow palpebral fissures, bitemporal narrowing, a long shallow philtrum, thin upper lip, small downturned mouth, and male frontal balding. Increased awareness of the facial dysmorphology may facilitate the early diagnosis of BBS.

Neurological and Psychiatric Manifestations

The neurological abnormalities suggest a central defect causing impaired co-ordination, which appears to affect the brainstem with variable involvement of the cerebellar, oculomotor, and pyramidal tracts. The paucity of facial muscle movement results in a characteristic expressionless facies, which may give an impression of mental retardation, previously regarded as a cardinal feature of the syndrome [Schachat and Maumenee, 1982]. However formal IQ testing shows the majority do not have mental retardation, although in most cases IQ is in the low normal range [Green et al., 1989]. Behavioral disturbances considered to be characteristic of childhood BBS include anxiety, depression, somatisation, autistic, and obsessive traits [Barnett et al., 2002]. In the current study, adult patients also frequently presented with somatisation, anxiety, and mood disorders. Psychiatric disease may be underdiagnosed in patients with BBS. This may be partly due to associated speech defects, learning difficulties, neurological features (such as expressionless facies), and behavioral traits. Awareness of this neurobehavioral phenotype will facilitate early detection and appropriate treatment of psychiatric illness in BBS patients.

Phenotype–Genotype Analysis

BBS is a pleiotropic disorder, with wide variability of expression. The discovery that *BBS8* encodes a protein that localizes to the basal body of cilia implicated ciliary dysfunction in the pathogenesis of BBS [Ansley et al., 2003]. Ciliary abnormalities occur in a wide range of disorders, some of which resemble phenotypes seen in BBS, including retinal degeneration [Hong et al., 2001] and renal cystic disease [Nauli et al., 2003]. Skeletal patterning and growth may also involve a ciliary mechanosensory mechanism [Jensen et al., 2004].

In this study, the data reveal no significant difference between genotype group in the frequency and age to onset of the major clinical endpoints. The finding of no apparent genotype–phenotype correlation supports the hypothesis that all BBS genes are involved in the same cell process, involving ciliary function [Ansley et al., 2003; Katsanis, 2004], which is critical for the terminal maturation of many organs.

Bardet–Biedl and Laurence–Moon Syndrome

We have attempted to identify all cases of BBS and LMS in the Newfoundland population through comprehensive ascertainment. Two patients met the diagnostic criteria for LMS, but both had molecular genetic results diagnostic of BBS, implying that the underlying molecular basis for BBS and LMS is the same. BBS and LMS are differentiated by the presence of spasticity and/or ataxia and the absence of polydactyly in LMS [Schachat and Maumenee, 1982; Riise et al., 1997]. However, neurological features are prevalent in BBS [Beales et al., 1999], including ataxia and spasticity, which were present in 86% and 21% of this cohort, respectively. Furthermore, polydactyly was absent in 27% of this cohort, confirming other studies of large cohorts of BBS patients [Riise, 1998; Beales et al., 1999]. The original report of LMS [Laurence and Moon, 1866] showed wide intra-familial variability in phenotype [Hutchinson, 1882, 1900]. Schachat and Maumenee reviewed 17 LMS cases [Schachat and Maumenee, 1982], but three had polydactyly and two had an affected sibling with polydactyly. Neurological manifestations also showed wide intra-familial variability. The widely varying phenotypic expression within families of reported LMS patients, the prevalence of neurological features in BBS, the absence of polydactyly in 20%–30% of BBS patients, the finding of patients with clinical diagnoses of LMS who have molecular genetic changes of BBS, all imply that LMS and BBS may be variable manifestations of the same disorder.

High Prevalence of BBS in Newfoundland

The prevalence of 1 in 18,000 for BBS in Newfoundland is considerably higher than in most other populations. There is a particularly high prevalence of families with mutations in the *MKKS/BBS6* gene, and at least nine different BBS mutations. Founder effects, consanguinity, and large sibship size likely increased the prevalence of BBS in Newfoundland, and it is possible there was a heterozygous advantage, for example, an enhanced ability to store fat [Davidson et al., 2003].

One case of possible triallelism was identified (NF-B14). The affected person is homozygous for a stop mutation in *BBS2* (Y24X) and heterozygous for a missense mutation

in the *MKKS/BBS6* gene (A242S). This non-conservative change has been associated previously with the phenotypically-related McKusick–Kaufman syndrome: in the old order Amish, this variant segregates with the disorder in *cis* with a second missense variant, H84Y [Stone et al., 2000]. The serine has not been found in 90 ethnically matched control chromosomes [Katsanis et al., 2001] and has been shown to mislocalize the BBS6 protein in HeLa cells (N. Katsanis, unpublished observations). Thirty-one percent of siblings at risk in the Newfoundland BBS families are affected, which is higher than the 12.5% that would be expected if triallelism were the major mode of inheritance.

Concluding Comments

BBS and LMS should be considered the same disorder. The high prevalence in the Newfoundland population is associated with multiple loci, multiple mutations in the *MKKS/BBS6* gene, and an occurrence of triallelism. BBS can affect almost every organ system, and has a wide variability of expression. In addition to the cardinal manifestations, characteristic craniofacial dysmorphic features and a wide range of other medical disorders occur, including neuropsychiatric abnormalities, colonic disorders, gall stone disease, and asthma. The apparent lack of a phenotype–genotype correlation implies that BBS proteins interact and are all necessary for normal ciliary functioning, critical in the development of many organs.

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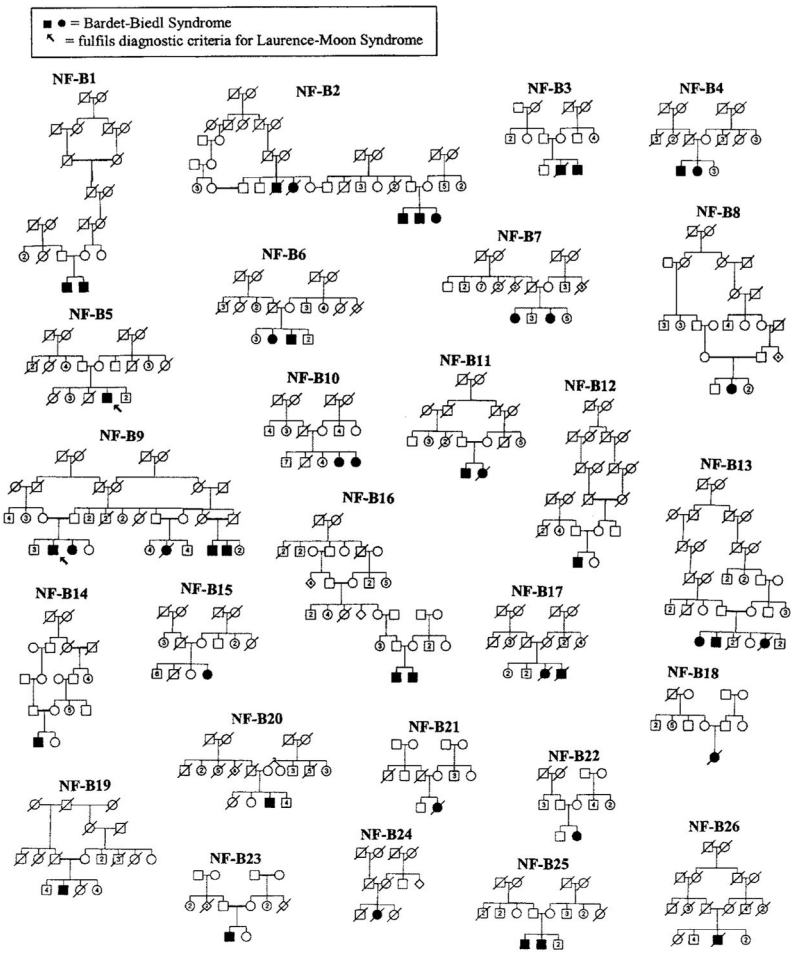

Fig. 1.
Pedigrees of Newfoundland Bardet–Biedl syndrome patients.

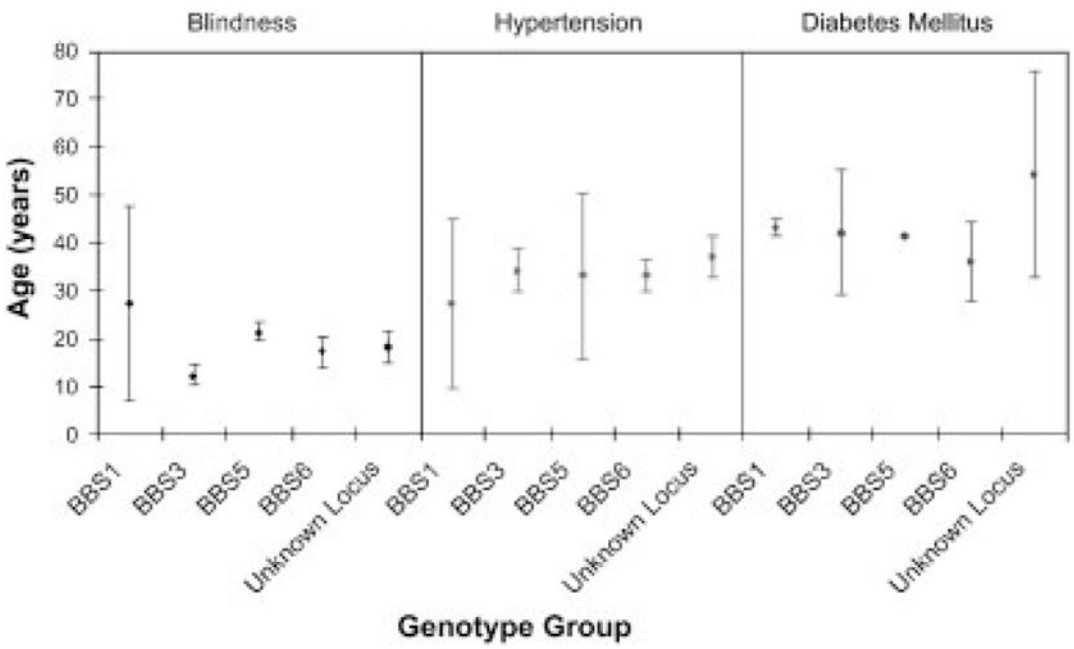

Fig. 2.

Median age in years (and 95% confidence intervals) to onset of major clinical endpoints in BBS by genotype group.

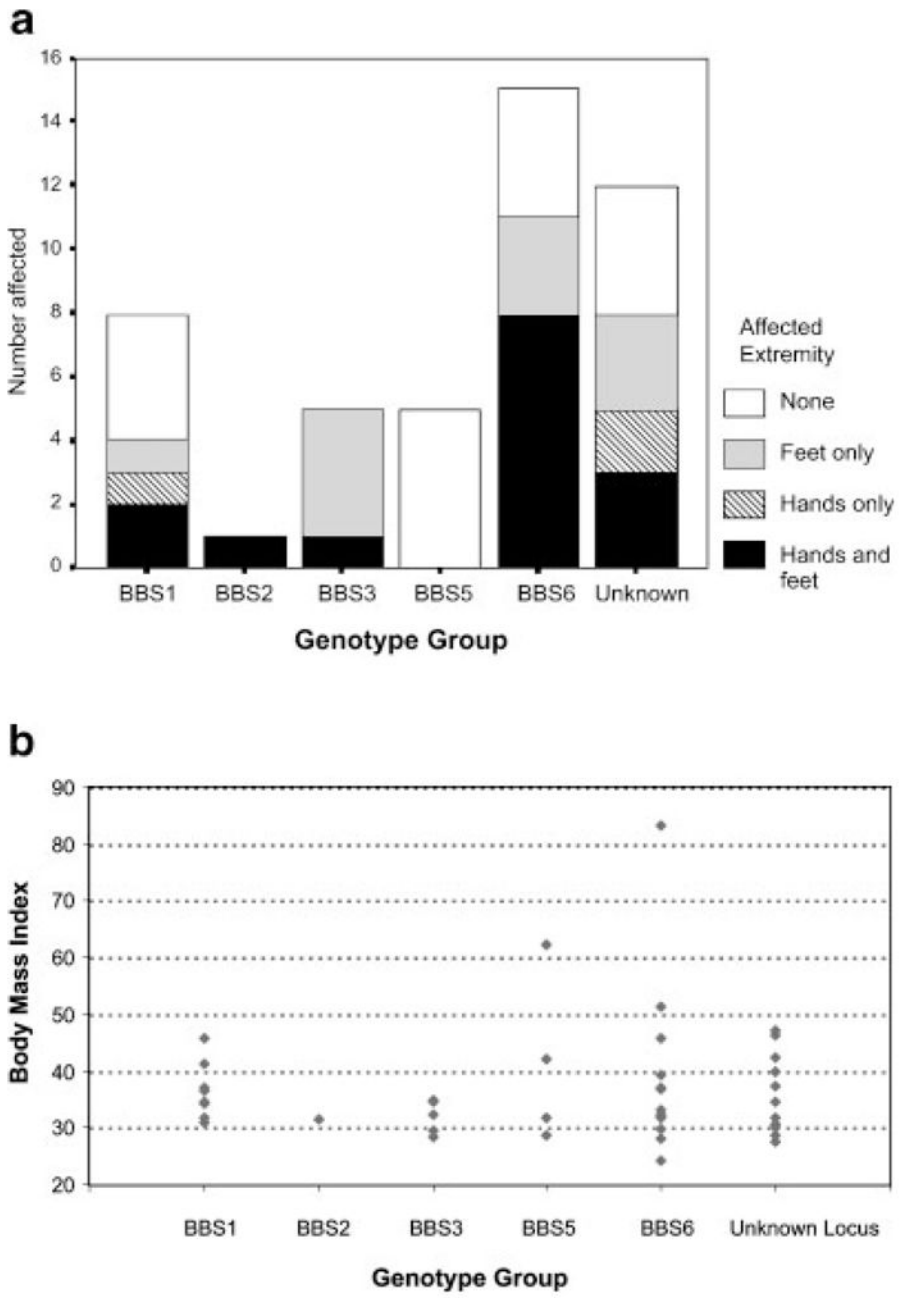

Fig. 3.

a: Polydactyly by genotype group in Bardet–Biedl syndrome; (**b**) maximum body mass index by genotype group in Bardet–Biedl syndrome.

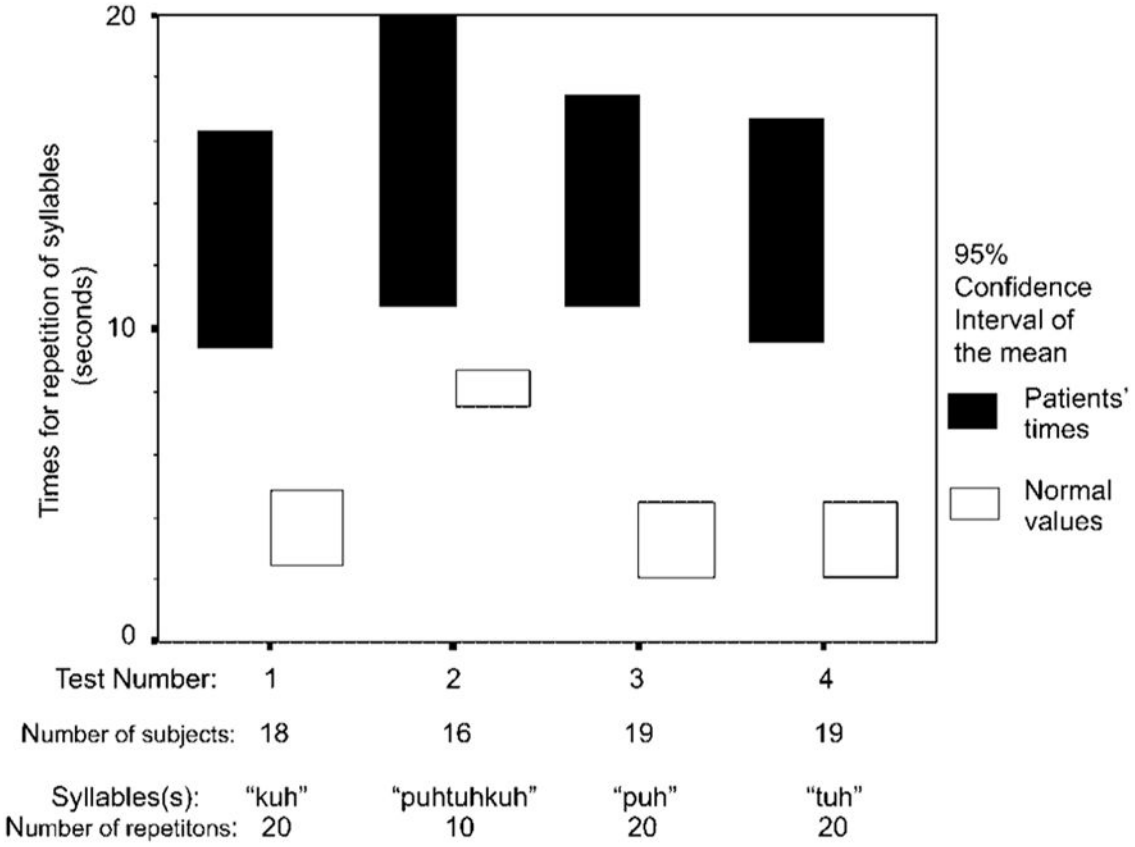

Fig. 4.
Diadochokinetic speech tests in Bardet–Biedl syndrome.

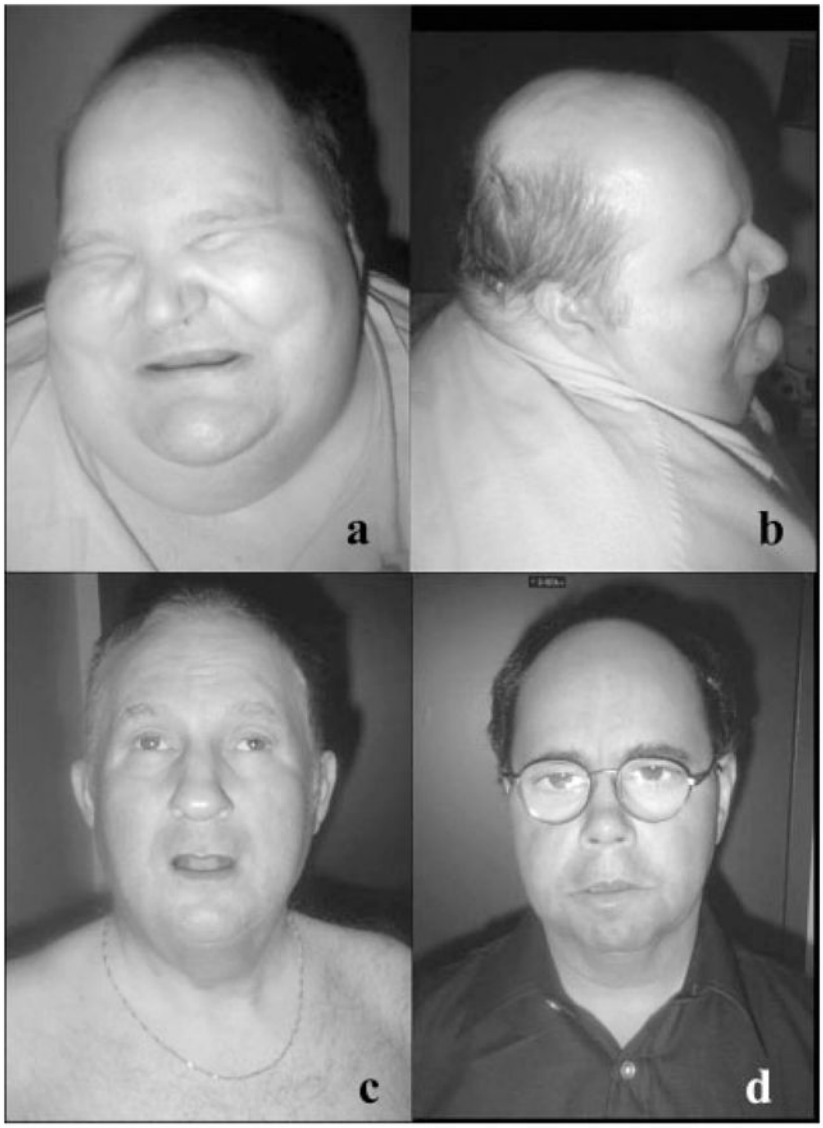

Fig. 5.

Craniofacial features of three unrelated male Newfoundland BBS patients, showing frontal balding (all), bitemporal narrowing (**a**, **c**), short narrow palpebral fissures (a, c), ptosis (**d**), long smooth philtrum (c, d), thin upper lip (all), small mouth (c), downturned mouth (a, d). Lateral view (**b**) shows brachycephaly and long ears. Patients (a, b and d) have mutations in the *MKKS/BBS6* gene, patient (c) links to the *BBS5* locus.

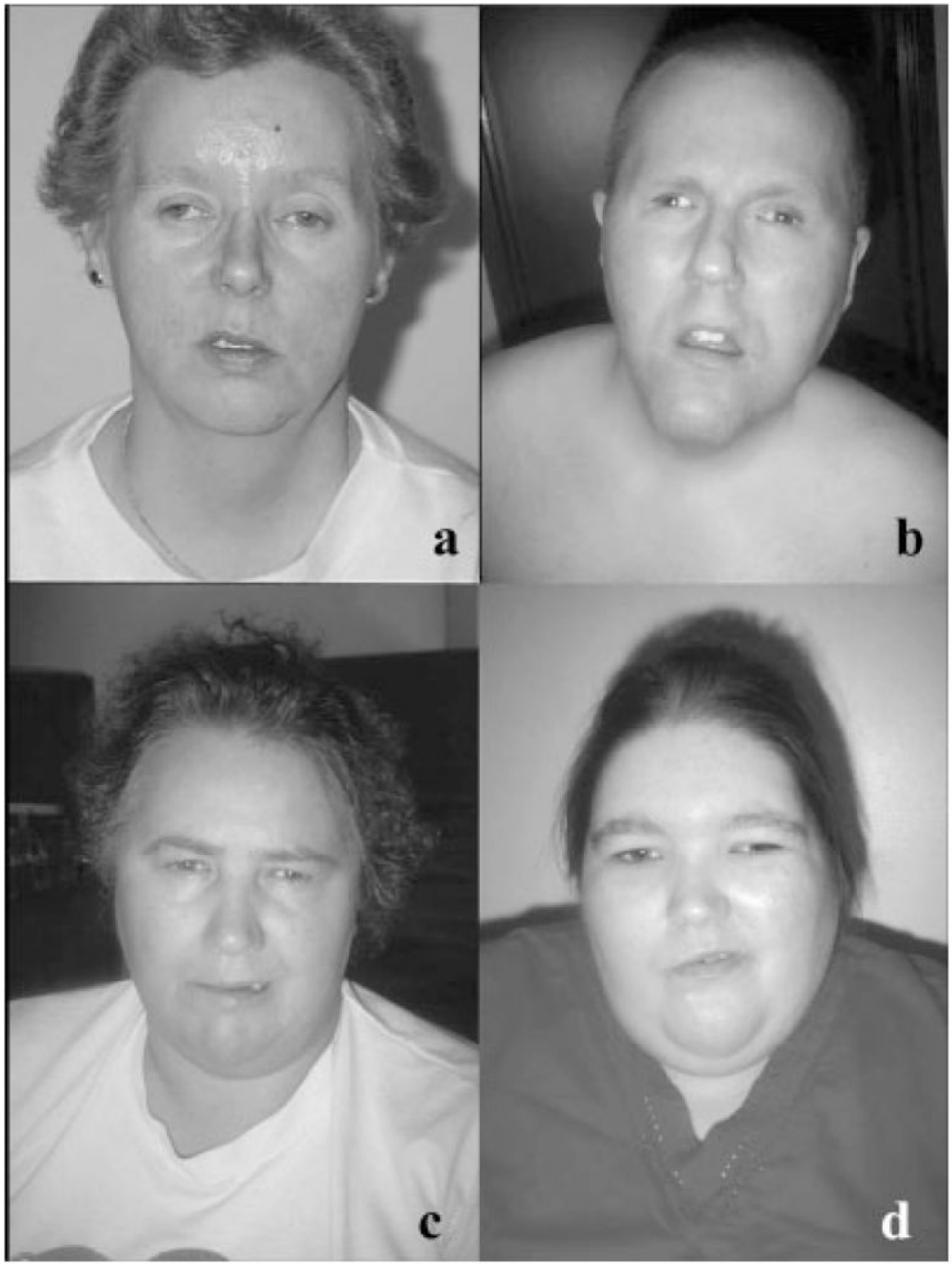

Fig. 6.

Facial features of four unrelated BBS Newfoundland patients showing asymmetric, expressionless facies, bitemporal narrowing, short narrow palpebral fissures, long shallow philtrum (**b**), small downturned mouth and thin upper lip (**a**, b, and **d**). Patient (a) has a mutation in the *BBS1* gene, patients (b) and (**c**) have mutations in the *MKKS/BBS6* gene, and patient (d) shows linkage to the *BBS5* locus.

TABLE I

Mutations in Patients With BBS Identified in the Newfoundland Population

# Patients (family #)	Gene/Locus	Mutation
8 (NF-B7, B8, B10, B15, B19, B23)	BBS1	M390R homozygous
1 (NF-B12)	BBS2	Y24X homozygous, and A242S heterozygote for BBS6
5 (NF-B2)	BBS3	Gene not identified
5 (NF-B9)	BBS5	Gene not Identified
4 (NF-B13, B20)	BBS6	D143fsX157 homozygous
8 (NF-B3, B4, B16, B25)	BBS6	F94fsX103 homozygous
2 (NF-B1)	BBS6	D143fsX157/F94fsX103
1 (NF-B5)	BBS6	F94fsX103/L277P
2 (NF-B6)[a]	Excluded from all eight *BBS* loci	
4 (NF-B11, B12, B21)[a]	Molecular investigations inconclusive due to family structure	
6 (NF-B17, 18, 22, 24, 26)[a]	No DNA available	

[a]All these patients are classified as “unknown” genotype group.

TABLE II

Genital Abnormalities in BBS Patients by Genotype Group

Abnormality	Prevalence	Genotype group of affected
Male		
Small penile length (<10th centile)	92% (12/13)	BBS 1, 2, 3, 5, 6, unknown
Undescended testes	11% (3/26)	BBS 6, unknown
Hypospadias	8% (2/26)	BBS 6, unknown
Phimosis	8% (2/26)	BBS 1, 6
Urethral strictures	8% (2/26)	BBS 5, 6
Posterior urethral valves	4% (1/26)	BBS 6
Female		
Vaginal atresia	10% (2/20)	BBS6, unknown
Hypoplastic labia minora	25% (3/12)	BBS6, unknown
Absent urethral opening	5% (1/20)	Unknown

TABLE III

Craniofacial Dysmorphic Features in BBS Patients

Feature	Prevalence
Brachycephaly	92% (24/26)
Macrocephaly[a]	58% (15/26)
Bitemporal narrowing	65% (17/26)
Long ears[a]	61% (16/26)
Short palpebral fissures[a]	77% (20/26)
Narrow palpebral fissures	81% (21/26)
Ptosis	27% (7/26)
Shallow philtrum	35% (9/26)
Long philtrum[a]	35% (9/26)
Thin upper lip	54% (14/26)
Small mouth[a]	38% (10/26)
Downturned mouth	58% (15/26)
High arched palate	86% (19/22)
Frontal balding in adult males	92% (11/12)

Other features are judgements of examination or photographs.

[a]Measurements are more than two standard deviations from the mean [Hall et al., 1995].

TABLE IV

Additional Medical Disorders in the Newfoundland BBS Patients

	Prevalence	Genotype group of affected
Gastro-intestinal		
Cholecystectomy for gall stones	17/46 (37%)	BBS 1, 3, 5, 6, unknown
Elevated liver enzymes	8/33 (24%)	BBS 1, 2, 3, 6
Gastro-esophageal reflux	8/46 (17%)	BBS 1, 5, 6, unknown
Colonic dysmotility	7/46 (15%)	BBS 1, 6, unknown
Celiac disease	2/46 (4%)	BBS 1, unknown
Peptic ulcer disease	3/46 (6.5%)	BBS 5, unknown
Skeletal/connective tissue		
Kyphoscoliosis	5/46 (11%)	BBS 6, unknown
Talipes equinovarus	2/46 (4%)	BBS 3, 6
Skin		
Pigmented nevi	6/25 (24%)	BBS 1, 5, 6, unknown
Eczema	5/46 (11%)	BBS 1, 3, 5, 6, unknown
Psoriasis	3/46 (6.5%)	BBS 3, 6
Neurological		
Epilepsy	5/46 (11%)	BBS 6, unknown
Miscellaneous		
Asthma	13/46 (28%)	BBS 1, 2, 5, 6, unknown
Hyperhidrosis (hands and feet)	10/46 (22%)	BBS 1, 2, 5, 6, unknown
Chronic serous otitis media	9/46 (20%)	BBS 2, 3, 6, unknown
Idiopathic edema	8/46 (17%)	BBS 1, 3, unknown
Thyroid disease	6/46 (13%)	BBS 1, 3, unknown
Myocardial infarction	6/46 (13%)	BBS 1, 3, 6, unknown
Congenital heart disease	3/46 (6.5%)	BBS 6, unknown