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CLINICAL UTILITY GENE CARD

Clinical utility gene card for: Bardet–Biedl syndrome

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1. DISEASE CHARACTERISTICS

1.1 Name of the disease (synonyms)

Bardet–Biedl syndrome (BBS); Laurence–Moon–Bardet–Biedl syndrome; Laurence–Moon–Biedl syndrome.

Other synonyms include ARL6-related Bardet–Biedl syndrome, BBS1-related Bardet–Biedl syndrome, BBS2-related Bardet–Biedl syndrome, BBS4-related Bardet–Biedl syndrome, BBS5-related Bardet–Biedl syndrome, BBS7-related Bardet–Biedl syndrome, BBS9-related Bardet–Biedl syndrome, BBS10-related Bardet–Biedl syndrome, BBS12-related Bardet–Biedl syndrome, CEP290-related Bardet–Biedl syndrome, MKKS-related Bardet–Biedl syndrome, MKS1-related Bardet–Biedl syndrome, TRIM32-related Bardet–Biedl syndrome, TTC8-related Bardet–Biedl syndrome.

1.2 OMIM# of the disease

209900.

1.3 Name of the analysed genes or DNA/chromosome segments

Gene	*Name*	*Locus*
BBS1	*BBS1 gene*	11q13
BBS2	*BBS2 gene*	16q21
BBS3/ARL6	*BBS3 gene/ADP-Ribosylation Factor-like 6*	3p12–q13
BBS4	*BBS4 gene*	15q23
BBS5	*BBS5 gene*	2q31
BBS6/MKKS	*BBS6 gene; MKKS gene*	20p12
BBS7	*BBS7 gene*	4q27
BBS8/TTC8	*BBS8 gene/Tetratricopeptide repeat domain 8*	14q32.1
BBS9/B1	*BBS9 gene/Parathyroid hormone-responsive B1 gene*	7p12–p14
BBS10	*BBS10 gene*	12q21.2
BBS11/TRIM32	*BBS11 gene/Tripartite motif-containing protein 32*	9q31–34.1
BBS12	*BBS12 gene*	4q27
BBS13MKS1	*BBS13 gene/MKS1 gene*	17q23
BBS14/CEP290	*BBS14 gene/Centrosomal protein, 290 KD (CEP290)*	12q21.3

1.4 OMIM# of the gene(s)

BBS1 209901; *BBS2 606151*; *BBS3/ARL6 608845*; *BBS4 600374*; *BBS5 603650*; *BBS6/MKKS 604896*; *BBS7 607590*; *BBS8/TTC8 608132*; *BBS9 607968*; *BBS10 610148*; *BBS11/TRIM32 602290*; *BBS12 610683*; *BBS13/MKS1 609883*; *BBS14/CEP290 610142*.

1.5 Mutational spectrum

BBS1 has a common mutation, p.Met390Arg (p.M390R), which accounted for 18% of the total number of mutated alleles in 259 individuals with BBS.[1] A frameshift mutation, C91fsX95, is commonly found in 48% of the patients with *BBS10* mutations, but mutation hotspots are otherwise rare throughout the BBS genes.

Gene	*Mutational spectrum*	*Estimated frequency*[a] (%)
BBS1	M, N, S, F	23–39
BBS2	M, N, S, F	8–9
BBS3/ARL6	M, N	0.4–2
BBS4	M, N, S, F, Del	1–3
BBS5	N, S, Del	0.4–3
BBS6/MKKS	M, N, F	4–5.8
BBS7	M, F, Del	1.5–2.0
BBS8/TTC8	S, Del	1.2
BBS9/B1	M, N, S, F	6
BBS10	M, N, F	20
BBS11/TRIM32	M	0.4
BBS12	M, N, F, Del	5
BBS13MKS1	M, F, Del	4.5
BBS14/CEP290	N	0.6

Abbreviations: Del, intragenic deletion; F, frameshift mutation; M, missense mutation; N, nonsense mutation; S, splice site mutation.
[a]Estimated mutation frequency.[2–4]
After Table 9.3.[2]

1.6 Analytical methods

Genomic sequencing of the coding regions of the commonest causative genes has been most frequently employed to search for BBS mutations. Gene-sequencing panels have more recently become available (see Section 2.3). Large deletions and genomic rearrangements are rare and array comparative genomic hybridization and karyotyping are not routinely performed.[2]

1.7 Analytical validation

Sequence alterations that could be mutations are bidirectionally sequenced and can be re-sequenced in normal, ethnically matched controls to exclude polymorphisms.

1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

The incidence of BBS has been estimated to be 1 in 100 000 to 1 in 160 000 live births in both the North American and European populations.[5,6]

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1.9 If applicable, prevalence in the ethnic group of investigated person

BBS has a higher prevalence in populations with a high incidence of consanguinity or that are subject to possible founder effects. In the Bedouin from the mixed Arab population of Kuwait, prevalence ranged from 1 in 13 500 to 1 in 36 000.[7,8] In New Foundland, the frequency of BBS was estimated to be 1 in 17 500.[9]

1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	☒	☐
B. Predictive testing	☒	☐
C. Risk assessment in relatives	☒	☐
D. Prenatal	☒	☐

Comment:
Mutation testing in BBS is used mainly to confirm a suspected clinical diagnosis. A list of laboratories that perform clinical and research testing of the BBS genes can be found on the GeneTests website (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests). Predictive testing without disease manifestations is less common. Prenatal testing is available for families with known mutations.

2. TEST CHARACTERISTICS

	Genotype or disease		A: true positives B: false positives	C: false negative D: true negative
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Negative	C	D	Positive predictive value:	A/(A+B)
			Negative predictive value:	D/(C+D)

2.1 Analytical sensitivity
(proportion of positive tests if the genotype is present)
The sensitivity for genomic sequencing approaches 100% for mutation detection, but errors can be made due to polymorphisms causing allele dropout. Deletions of whole exons or whole gene deletions are not usually detected by sequencing, and mutations outside the coding exons in promoters or enhancers are likely to be missed. However, these mutational mechanisms are probably uncommon in BBS.

2.2 Analytical specificity
(proportion of negative tests if the genotype is not present)
Analytical specificity is nearly 100%. False positives in genomic sequencing are rare.

2.3 Clinical sensitivity
(proportion of positive tests if the disease is present)
The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Mutation frequency for the 14 known BBS genes has been provided in Section 1.5.

Panels that screen multiple causative genes in BBS can achieve a higher sensitivity than single-gene analysis. Using clinical panels for screening multiple BBS genes leads to an estimated sensitivity of 70%.[10]

It is important to note that many of the clinical manifestations of BBS are age dependent, and that the average age of diagnosis in a study of 109 individuals was 9 years.[6]

2.4 Clinical specificity
(proportion of negative tests if the disease is not present)
The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Clinical specificity is nearly 100%.

2.5 Positive clinical predictive value
(lifetime risk to develop the disease if the test is positive)
BBS has two modes of inheritance – autosomal recessive and triallelic/oligogenic inheritance. For BBS inherited as an autosomal recessive trait, non-penetrance is rare and positive clinical predictive value approaches 100%, although milder BBS phenotypes have been described.[11] Triallelic/oligogenic inheritance requires two disease-causing mutations at one BBS locus, with a third mutation at a different locus. In families with triallelic/oligogenic inheritance, two disease-causing mutations may be insufficient to cause clinical features, although this type of inheritance is infrequent in BBS.

2.6 Negative clinical predictive value
(probability of not developing the disease if the test is negative)
Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:
Nearly 100%.

Index case in that family had not been tested:
Genetic heterogeneity with undiscovered genes means that 20–30% of individuals who test negative for all of the currently known BBS genes may still have the condition.

3. CLINICAL UTILITY

3.1 (Differential) diagnosis: The tested person is clinically affected
(To be answered if in 1.10 'A' was marked)

3.1.1 Can a diagnosis be made other than through a genetic test?

No	☐ (continue with 3.1.4)	
Yes	☒	
	Clinically	☒
	Imaging	☐
	Endoscopy	☐
	Biochemistry	☐
	Electrophysiology	☐
	Other (please describe):	The clinical diagnostic criteria for BBS have been subdivided into major (primary) and secondary criteria. Either four primary criteria or three primary criteria and two secondary criteria were sufficient for a clinical diagnosis of BBS.[6] It is crucial that clinicians are aware of the age dependency of some of the more important diagnostic findings, with onset of obesity after infancy, developmental differences in early childhood and the onset of visual impairment in later childhood or teenage years.

Major criteria	Secondary criteria
Rod-cone dystrophy	Speech disorder or speech delay
Polydactyly	Strabismus or cataracts or astigmatism[a]
Obesity	Brachydactyly or syndactyly
Learning difficulties	Developmental delay
Hypogenitalism in males	Polyuria and polydipsia
Renal anomalies	Ataxia and/or poor coordination
	Mild spasticity
	Diabetes mellitus
	Dental crowding or hypodontia or small roots or a high arched palate
	Left ventricular hypertrophy or congenital heart disease
	Hepatic fibrosis

[a]Strabismus, cataracts and astigmatism can be non-specific findings associated with retinal dystrophy and this criteria should be included with caution.

3.1.2 Describe the burden of alternative diagnostic methods to the patient

A clinical diagnosis may require at a minimum a history and physical examination, measurement of growth parameters, an optical fundus examination and/or an electroretinogram, a renal ultrasound scan, and a developmental assessment.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged?

Although an accurate clinical assessment can substantiate the diagnosis of BBS and therefore establish the need for appropriate monitoring and management, genetic testing remains useful for genetic counseling and prenatal testing.

3.1.4 Will disease management be influenced by the result of a genetic test?

No	☐	
Yes	☒	
	Therapy (please describe)	Caloric restriction and exercise for obesity, speech and developmental assessments with special services as appropriate, evaluation for visual aids and support services for the visually impaired, monitoring of blood pressure, renal function, urinalysis, fasting blood glucose, HbA1C and lipid levels should be performed. Evaluations for other BBS manifestations may include an audiology assessment, renal ultrasound scan and a cardiac echocardiogram.
	Prognosis (please describe)	Genetic testing alone does not often determine prognosis and there is considerable phenotypic variability.
	Management (please describe)	Multidisciplinary clinic management is optimal, but often single-specialist referrals are obtained, including ophthalmology, nephrology, nutrition and endocrinology.

3.2 Predictive Setting: The tested person is clinically unaffected but carries an increased risk based on family history

(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention?

If the test result is positive (please describe):

See above (Section 3.1).

If the test result is negative (please describe):

Follow-up required.

3.2.2 Which options in view of lifestyle and prevention does a person at risk have if no genetic test has been done (please describe)?

Similar to Section 3.2.1.

3.3 Genetic risk assessment in family members of a diseased person

(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family?

Yes.

3.3.2 Can a genetic test in the index patient save genetic or other tests in family members?

No – if testing is positive for BBS in the index patient, it can reduce the need for testing for other genetic conditions in family members by providing a diagnosis. However, testing for BBS may still be required in other clinically affected family members.

3.3.3 Does a positive genetic test result in the index patient enable a predictive test in a family member?

Yes, the full manifestations of BBS may not be present at birth or in early childhood, and testing during this time period can enable a molecular genetic diagnosis of BBS prior to the development of clinical features.

3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 Does a positive genetic test result in the index patient enable a prenatal diagnostic?

Prenatal diagnosis can be performed as for a common autosomal recessive condition. Testing for two known familial mutations in one gene can be performed on DNA from a fetus obtained by chorion villus sampling or amniocentesis.

4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe)

Testing has medical consequences as described above.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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