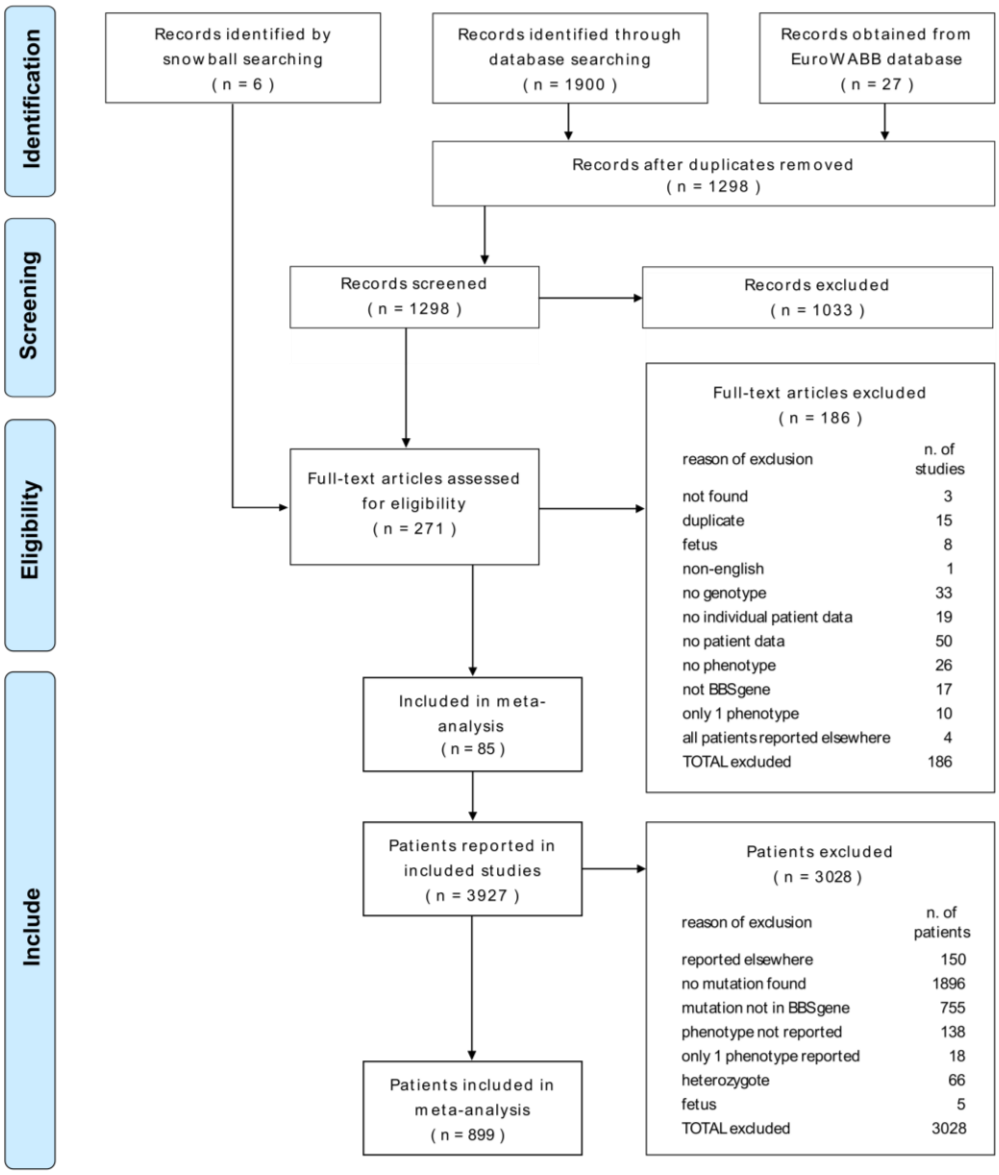
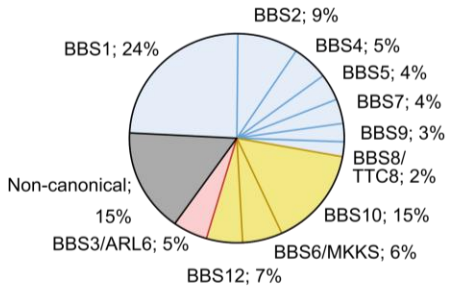
Supp. Figure S1. Flow diagram of the literature search for the meta-analysis. The flow diagram was assembled using the Prisma 2009 guidelines (Moher et al., 2009).



Supp. Figure S2. Characteristics of all reported BBS patients. (A) Pie chart showing the distribution of causative BBS genes in the whole set of BBS patients (n = 899). Blue – mutations in the BBSome-encoding genes, red – mutations in *BBS3/ARL6*, yellow – mutations in the chaperonin-encoding genes. **(B-D)** Sex and age distribution (when available) in the specified subsets of BBS patients. **(E)** Frequency of symptoms in BBS patients calculated as a ratio of patients with reported presence of the symptom to patients with reported presence or absence of the symptom. RD – retinal dystrophy (n = 834 patients with reported presence of absence of this symptom), OBE – obesity (n = 749), DD – developmental delay (n = 299), PD – polydactyly (n = 730), CI – cognitive impairment (n = 665), REP – reproductive system anomalies (n = 443), REN – renal anomalies (n = 672), LIV – liver anomalies (n = 282), HRT – heart anomalies (n = 225). P-value was calculated using chi-square test.

A



B

	BBSome	BBS3/ARL6	Chaperonins	Non-canonical
Number of patients	466	47	250	136
Sex available (n)	274	28	153	41
% Males	50%	57%	58%	39%
% Females	50%	43%	42%	61%
Distribution of sex groups				
Age available (n)	257	26	149	43
% Age 0-9	14%	0%	17%	12%
% Age 10-19	27%	27%	40%	44%
% Age 20-39	42%	58%	32%	37%
% Age 40+	17%	15%	11%	7%

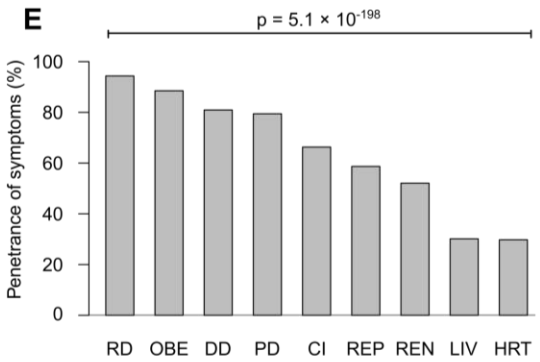
C

	BBS1	BBS2	BBS4	BBS5	BBS7	BBS8/ TTC8	BBS9	BBS18/ BBIP1
Number of patients	214	85	49	34	37	17	29	1
Sex available (n)	150	39	18	18	22	14	12	1
% Males	45%	59%	44%	44%	68%	50%	58%	100%
% Females	55%	41%	56%	56%	32%	50%	42%	0%
Distribution of sex groups								
Age available (n)	140	39	19	11	21	13	13	1
% Age 0-9	9%	38%	16%	0%	14%	8%	23%	0%
% Age 10-19	17%	28%	42%	36%	52%	62%	23%	0%
% Age 20-39	48%	31%	42%	45%	29%	23%	54%	0%
% Age 40+	26%	3%	0%	18%	5%	8%	0%	100%

D

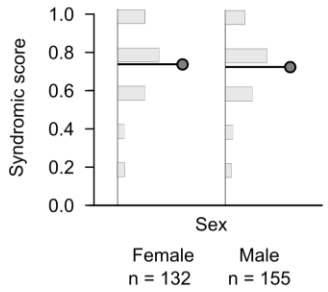
	BBS6/MKKS	BBS10	BBS12
Number of patients	58	133	59
Sex available (n)	25	95	33
% Males	56%	59%	55%
% Females	44%	41%	45%
Distribution of sex groups			
Age available (n)	19	94	36
% Age 0-9	16%	17%	17%
% Age 10-19	37%	47%	25%
% Age 20-39	42%	28%	39%
% Age 40+	5%	9%	19%

E



Supp. Figure S3. Characteristics of the subset of BBS patients used for the *syndromic score* analysis. (A) *Syndromic score* in female vs. male patients. **(B-D)** Sex and age distribution within the indicated genetic subsets of BBS patients in the *'set* used for the calculation of *syndromic score*.
Data information: **(A)** Black lines with dots represent the mean. Histograms were normalized to max.

A



B

	BBSome	BBS3/ARL6	Chaperonins	Non-canonical
Number of patients	242	32	131	21
Sex available (n)	165	15	91	16
% Males	52%	40%	64%	38%
% Females	48%	60%	36%	63%
Distribution of sex groups				
Age available (n)	146	15	91	18
% Age 0-9	14%	0%	16%	6%
% Age 10-19	26%	13%	42%	39%
% Age 20-39	42%	80%	30%	39%
% Age 40+	18%	7%	12%	17%

C

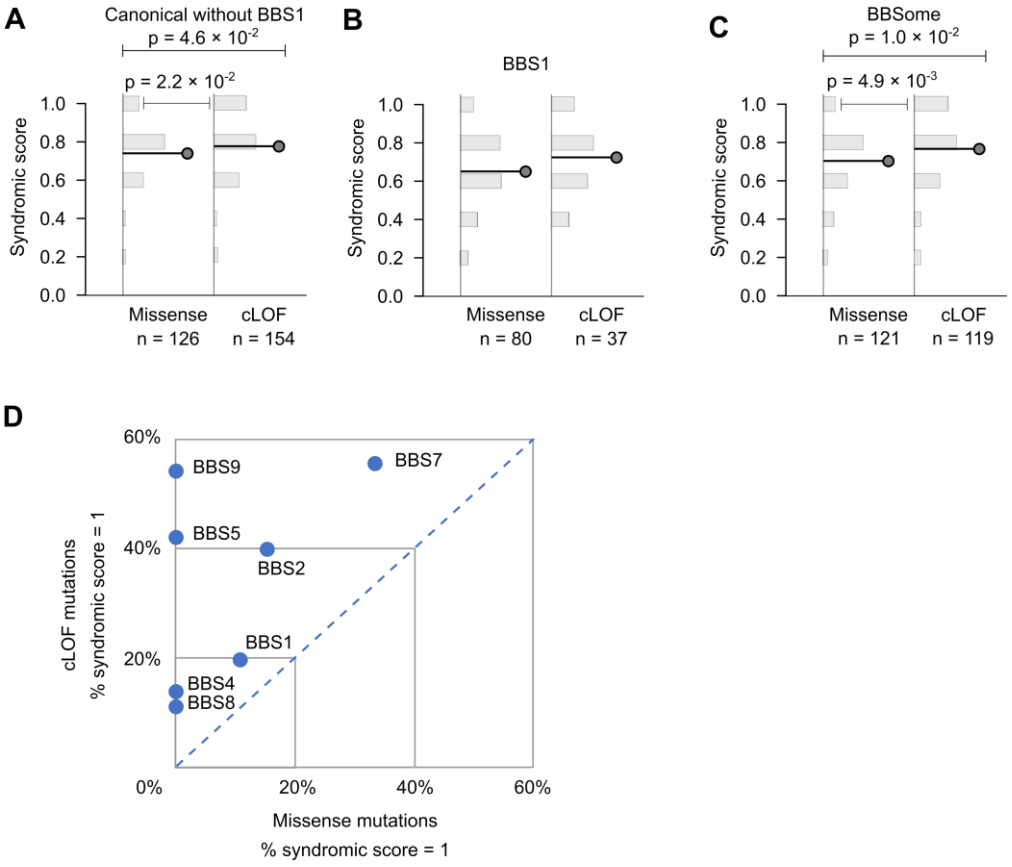
	BBS1	BBS2	BBS4	BBS5	BBS7	BBS8/ TTC8	BBS9	BBS18/ BBIP1
Number of patients	117	33	22	18	27	11	13	1
Sex available (n)	86	24	8	14	16	10	6	1
% Males	48%	58%	50%	36%	69%	60%	50%	100%
% Females	52%	42%	50%	64%	31%	40%	50%	0%
Distribution of sex groups								
Age available (n)	70	26	9	7	16	10	7	1
% Age 0-9	11%	27%	22%	0%	0%	10%	29%	0%
% Age 10-19	11%	35%	22%	43%	56%	50%	29%	0%
% Age 20-39	49%	35%	56%	29%	38%	30%	43%	0%
% Age 40+	29%	4%	0%	29%	6%	10%	0%	100%

D

	BBS6/MKKS	BBS10	BBS12
Number of patients	27	72	32
Sex available (n)	19	55	17
% Males	53%	71%	53%
% Females	47%	29%	47%
Distribution of sex groups			
Age available (n)	14	57	20
% Age 0-9	14%	21%	5%
% Age 10-19	50%	44%	30%
% Age 20-39	36%	23%	45%
% Age 40+	0%	12%	20%

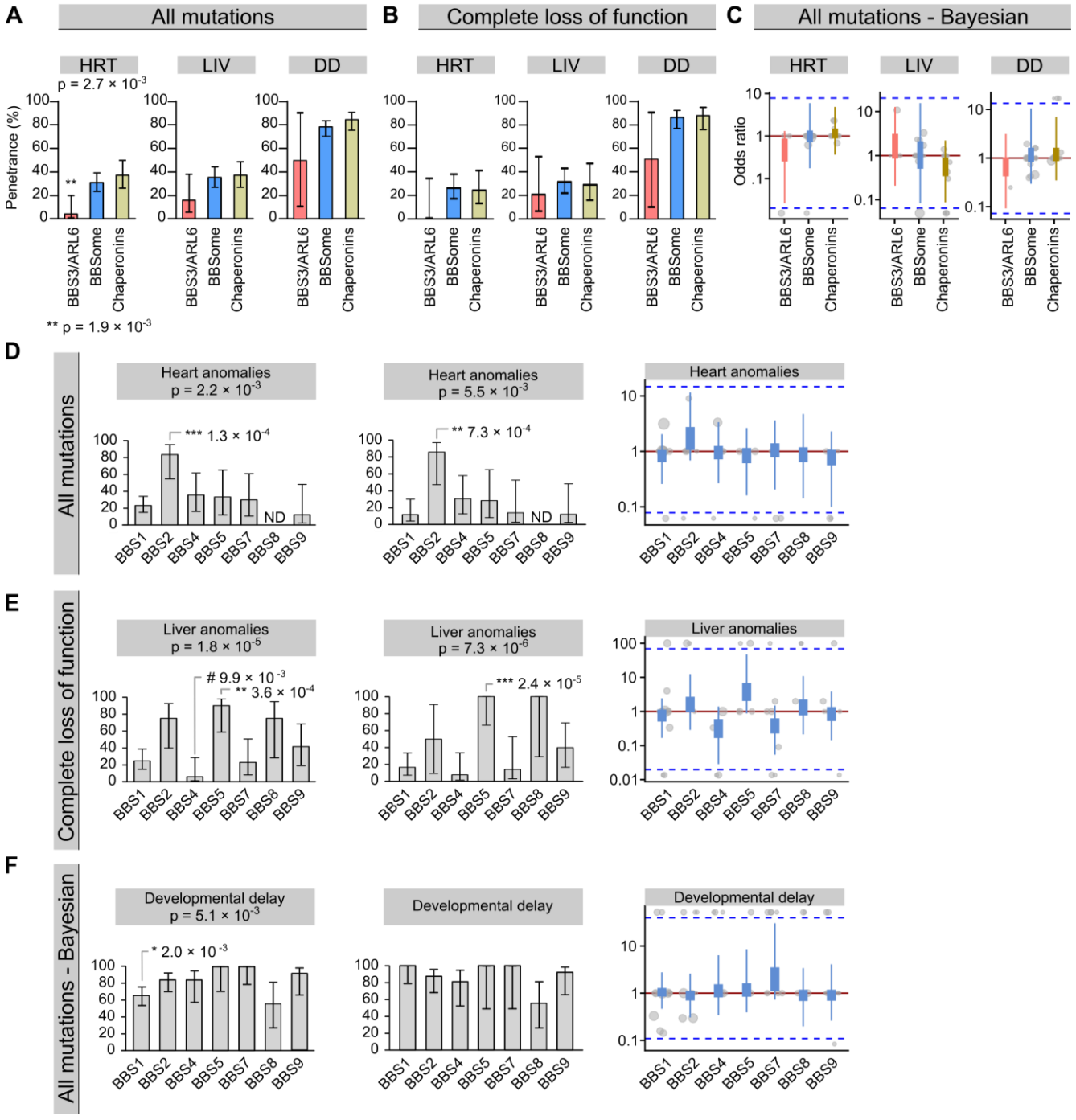
Supp. Figure S4. The disease outcome in patients with missense mutations and assumed complete loss of function mutations. (A-C) Syndromic score in indicated BBS patients with missense mutations (mono- or biallelic single amino acid substitutions or small in-frame deletions) and in patients with assumed complete loss of function mutations (large deletions, frameshift mutations, splicing defects). cLOF – assumed complete loss of function. **(D)** Percentages of patients with missense mutations (x axis) or loss of function mutations (y axis) presenting with the maximal *syndromic score*. Blue dots represent mutations in particular BBSome subunits.

Data information: (A-C) Black lines with dots represent the mean. Histograms were normalized to max. P-values higher than 0.05 are not indicated in any graphs. Statistical significance of difference between the two groups of patients was determined by Mann-Whitney test. Statistical significance of the difference between the frequency of patients presenting with the highest *syndromic score* was calculated using the Fisher's exact test.

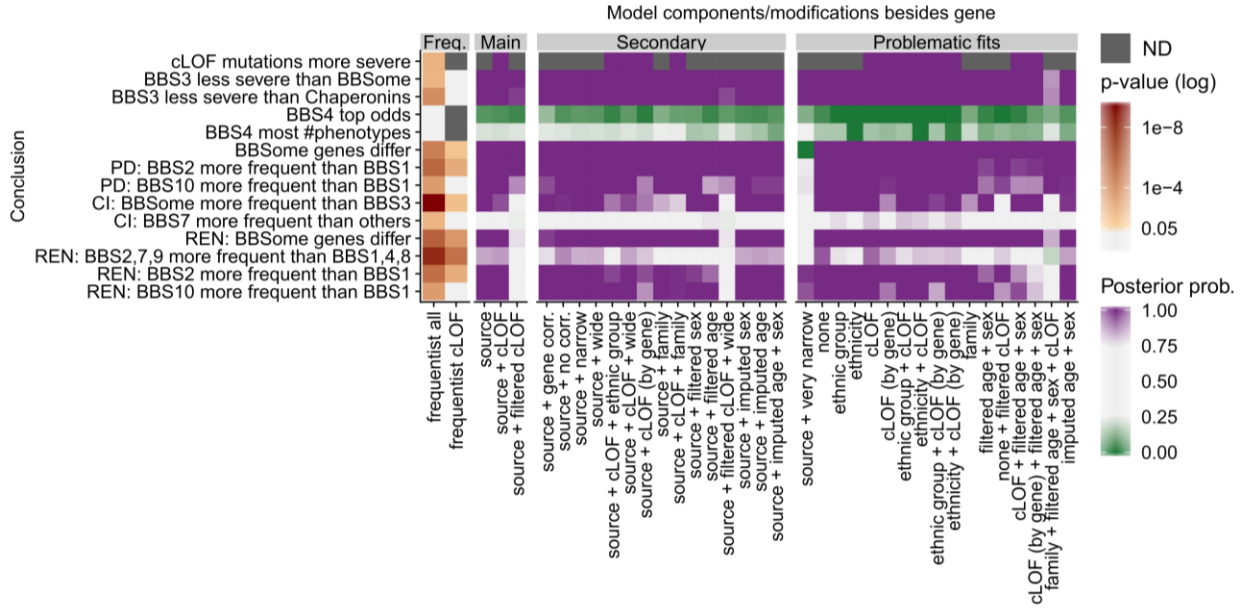


Supp. Figure S5. Penetrance of heart and liver anomalies and developmental delay in patients with mutations in particular BBS genes. (A) The frequency of the indicated symptoms in BBS patients with mutations in the indicated functional groups of BBS genes. The error bars represent 95% posterior credible intervals assuming uniform prior on the proportions. Numbers of patients (BBS3/ARL6, BBSome, Chaperonins): HRT – 25, 130, 63; LIV – 19, 109, 72; DD – 2, 165, 96. HRT – heart, LIV – liver, DD – developmental delay. **(B)** The frequency of the indicated symptoms in BBS patients with assumed complete loss of function mutations in the indicated functional groups of BBS genes. The error bars represent 95% posterior credible intervals assuming uniform prior on the proportions. Numbers of patients (BBS3/ARL6, BBSome, Chaperonins): HRT – 8, 67, 34; LIV – 10, 73, 29; DD – 2, 82, 43. HRT – heart, LIV – liver, DD – developmental delay. **(C)** Bayesian model: Posterior 95% (thin) and 50% (thick) credible intervals for ratio of odds for a phenotype given a mutation within the indicated functional group to odds for the phenotype given a mutation across all groups shown. Number of patients is the same as in A. Gray dots show the odds ratio calculated similarly for individual studies included in the meta-analysis. Dots outside of the dashed lines correspond to studies where the empirical odds ratio is 0 or infinity. Dot size corresponds to the number of relevant cases in the study. The model assumes odds ratios (but not the absolute odds) are the same regardless of whether the mutation is LOF. **(D)** The frequency of the indicated symptoms in BBS patients with mutations in the indicated BBSome subunits. The error bars represent 95% posterior credible intervals assuming uniform prior on the proportions. Numbers of patients (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8/TTC8, BBS9): heart anomalies – 77, 12, 14, 9, 10, 0, 8; liver anomalies – 47, 8, 15, 10, 13, 4, 12; developmental delay – 67, 39, 13, 9, 14, 9, 13. **(E)** The penetrance of the indicated symptoms in BBS patients with assumed complete loss of function mutations in the indicated BBSome-encoding genes. The error bars represent 95% posterior credible intervals assuming uniform prior on the proportions. Numbers of patients (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8/TTC8, BBS9): heart anomalies – 25, 7, 13, 7, 7, 0, 8; liver anomalies – 32, 2, 12, 8, 7, 2, 10; developmental delay – 16, 24, 11, 4, 4, 9, 13. **(F)** Bayesian model: Posterior 95% (thin) and 50% (thick) credible intervals for ratio of odds for a phenotype given a mutation in the indicated BBSome-encoding gene to odds for the phenotype given a mutation across all groups shown. Numbers of patients are the same as in D. Gray dots show the odds ratio calculated similarly for individual studies included in the metanalysis. Dots outside of the dashed lines correspond to studies where the empirical odds ratio is 0 or infinity. Dot size corresponds to the number of relevant cases in the study. The model assumes odds ratios (but not the absolute odds) are the same regardless of whether the mutation is LOF.

Data information: (A, B, D, E) Statistical significance of differences among all groups of patients was determined by Fisher's exact test. Statistical significance of differences between individual groups was determined post hoc using Fisher's exact test (one group vs all other groups taken together) with the Sidak correction for multiple comparions. #, *, **, ***, and **** represent the significance of p-values corresponding to $p < 0.1$, $p < 0.05$, $p < 0.01$, $p < 0.001$, and $p < 0.0001$, respectively, after the Sidak correction. The error bars represent 95% posterior credible intervals assuming uniform prior on the proportions. P-values higher than 0.1 are not indicated in any graphs. **(C, F)** Detailed description of the Bayesian model can be found in the Supplemental Statistical Analysis.


A
All mutations
HRT
LIV
DD
p = 2.7 × 10-3
Penetrance (%)
**
BBS3/ARL6
BBSome
Chaperonins
** p = 1.9 × 10-3
B
Complete loss of function
C
All mutations - Bayesian
Odds ratio
D
All mutations
Heart anomalies
p = 2.2 × 10-3
*** 1.3 × 10-4
ND
Heart anomalies
p = 5.5 × 10-3
** 7.3 × 10-4
Heart anomalies
E
Complete loss of function
Liver anomalies
p = 1.8 × 10-5
# 9.9 × 10-3
** 3.6 × 10-4
Liver anomalies
p = 7.3 × 10-6
*** 2.4 × 10-5
Liver anomalies
F
All mutations - Bayesian
Developmental delay
p = 5.1 × 10-3
* 2.0 × 10-3
Developmental delay
Developmental delay
BBS1
BBS2
BBS4
BBS5
BBS7
BBS8
BBS9

Supp. Figure S6. Robustness of main conclusions to analytical decisions.
The heatmap shows the statistical evaluation of the selected statements by the Bayesian model (posterior probability) and the frequentist statistics (p-value). Two frequentist analyses were performed, one including the complete dataset, second focusing on mutations with complete LOF (cLOF). All Bayesian models include gene as covariate but may also include additional covariates: source, age, sex, cLOF, family, ethnicity - either as a global covariate or allowed to vary by gene. Since age and sex are not available for all data, we can either fit the model only to patients where those are reported (filtered) or impute missing data (imputed). Instead of using cLOF as a covariate, we can fit the model using only patients with cLOF mutations (filtered cLOF). For most models, we include a correlation structure across phenotypes (e.g., that two phenotypes occur frequently together across all genes), but this structure may be absent (no corr.) or replaced with a correlation structure across genes (gene corr. - e.g., that two genes have similar pattern of effects across all phenotypes). We also tried modifying the width of prior distributions (wide, narrow, very narrow). ND indicates that the question could not be evaluated for the given model. The "Problematic fits" category is reserved for models we know fit the data badly. PD – polydactyly, CI – cognitive impairment, REN – renal anomalies.
Data information: The p-values not specified in previous figures were calculated using one-tailed Fisher's exact test. See Supplemental Statistical Analysis for the exact formulation of the statements in the Bayesian analysis. See Supplemental Statistical Analysis for a detailed description of all models and the imputation procedure as well as for assessments of model fit. All models ever examined over the course of this project are included.



Supp. Table S1. PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	9, 33
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4, 33
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	34-35
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	33-34
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	33
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	34, Supp. Table S2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	35-37
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	35-36
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	37-38
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	37, Supp. Table S2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	37, Supp. Table S2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	38-41, Supplemental Statistical Analysis

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10-11, Supp. Figure S1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supp. Table S2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supp. Table S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supp. Table S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-21, Figure 2, Figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	26-27
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	32
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28-32, Figure 4C
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1, 41

Supp. Table S2. Summary of the included studies and evaluation of the risk of bias.
Supp. Table S3. Database of all reported BBS patients.
Supp. Table S4. List of the BBS-causing mutations occurring in our dataset.

Supp. Tables S2, S3 and S4 were provided as separate MS Word/MS Excel files.

Supp. Table S5. List of the ethnicities/countries of origin and the matching ethnic groups of the included patients.

Ethnic groups (EG) and the original ethnicities/countries of origin of the patients	Count
EG-A	**273**
Algerian	1
Arabica	3
Ashkenazi Jewish	4
Egyptian	4
Iraqi	4
Israel	2
Israel Arab	2
Jordanian	1
Kuwait	1
Lebanese	10
Middle Eastern	2
Moroccan	2
Omani	5
Saudi Arabian	187
Tunisian	15
Turkey	1
Turkish	29
EG-B	**117**
East Indian	2
Gypsy	4
India	3
Indian	24
Iranian	19
Pakistani	65
EG-C	**55**
Canada	8
Canadian	5
Hutterite	3
Newfoundland	18
USA	21
EG-D	**330**
Belgian	1
British	5
British/Canadian/French/German	1
British/Irish	1
Caucasian	13
Croatian	2
Danish/Dutch/Norwegian	1
English	1
English/German/Canadian	1
English/Irish	2
English/Irish/Scotish	2
English/Irish/Scottish	1
English/Scottish/French/Canadian	1
English/Scottish/German/Iceland	1
Europe	6
European	16
European/American	13
Faroe Islands	10
French	67
French/Canadian	4
German	5
German/Irish/Swedish/Hungarian	1
German/Italian	4

Irish	1
Irish/English/German/Norwegian	1
Italian	21
N. European	28
Netherland	5
Northern European	7
Polish	4
Portugese	2
Romanian	1
Russian	3
Scandinavian	14
Spanish	57
Swedish	2
Swiss	1
United Kingdom	5
White European	19
EG-E	**18**
Chinese	3
Japanese	9
Japanese/Paraguayan	1
Korean	4
Malay	1
EG-F	**9**
Canadian Native Indian	2
Denea	7
EG-G	**8**
Ghanian	1
Somalian	2
South African Black	5
EG-H	**10**
El-Salvadorian	1
Guyanese	1
Latino	3
Mexican	2
Nicaraguan	1
Peruvian	1
Peruvian/Spanish	1
Not Available (NA)	**79**
La Réunion	2
Melanesian	2
Mexican/Norwegian/Danish	1
South African Black/European/Asian	4
NA	70

Supp. Table S6. Data of the *'set* of BBS patients used for the syndromic score analysis.
Supp. Table S7. Previously published observations about BBS genotype-phenotype correlations.

Supp. Tables S6 and S7 were provided as separate MS Word/MS Excel files.