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Bachmann-Bupp Syndrome

Synonym: *ODC1*-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

Bachmann-Bupp syndrome (BABS) is characterized by a distinctive type of alopecia, global developmental delay in the moderate to severe range, hypotonia, nonspecific dysmorphic features, behavioral abnormalities (autism spectrum disorder, attention-deficit/hyperactivity disorder) and feeding difficulties. Hair is typically present at birth but may be sparse and of an unexpected color with subsequent loss of hair in large clumps within the first few weeks of life. Rare findings may include seizures with onset in later childhood and conductive hearing loss.

Diagnosis/testing

The finding of abnormal polyamine pathway metabolites (including increased N-acetylputrescine) on metabolomic profiling is suggestive of a diagnosis of BABS. The diagnosis is established in a proband with suggestive findings and a heterozygous pathogenic variant in *ODC1* identified by molecular genetic testing. Heterozygous pathogenic variants in *ODC1* that cause BABS are typically gain-of-function variants.

Management

Treatment of manifestations: Feeding therapy with a low threshold for a clinical feeding evaluation and/or gastrostomy tube placement; nutritional intervention for those with obesity; stool softeners, prokinetics, osmotic agents or laxatives for constipation; standard treatment for epilepsy, developmental delay / intellectual disability, refractive error, strabismus, hearing loss, follicular cysts, and congenital heart defects.

Surveillance: Measurement of growth parameters, evaluation of nutritional status and safety of oral intake, monitoring for signs and symptoms of constipation, assessment of mobility and self-help skills, monitoring of developmental progress and educational needs, and assessment for new manifestations (seizures, changes in tone) at each visit. Complete skin evaluation for follicular cysts at least annually. Behavioral assessment for signs

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of autism spectrum disorder, attention, and aggressive or self-injurious behaviors annually. Ophthalmology and audiology evaluations annually or as clinically indicated.

Therapies under investigation: An experimental targeted treatment with difluoromethylornithine (DFMO) is being explored on a compassionate use basis; it is not currently an FDA-approved treatment for BABS.

Genetic counseling

BABS is expressed in an autosomal dominant manner and typically caused by a *de novo ODC1* pathogenic variant. Therefore, the risk to other family members is presumed to be low. Once an *ODC1* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Bachmann-Bupp syndrome (BABS) have been published.

Suggestive Findings

BABS **should be considered** in individuals with the following clinical, suggestive laboratory, and imaging findings.

Clinical findings

- Prenatal history of polyhydramnios
- An unusual pattern of noncongenital alopecia due to sudden-onset hair loss shortly after birth with congenitally absent or sparse eyebrows and eyelashes
- Developmental delay, typically in the moderate to severe range
- Hypotonia
- Macrocephaly, defined as OFC of >97th percentile for age and sex
- Macrosomia (defined as weight and length >95th percentile for age and sex) in early infancy
- Recurrent follicular cysts

Suggestive laboratory findings. Metabolomic profile showing abnormal polyamine pathway metabolites, including increased N-acetylputrescine

Brain MRI findings

- Nonspecific white matter hyperintensities
- Cystic lesions, primarily in the periventricular region but occasionally in other areas, potentially associated with in utero intraventricular hemorrhage

Establishing the Diagnosis

The diagnosis of BABS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ODC1* identified by molecular genetic testing (see Table 1 and Molecular Genetics).

NOTE: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to pathogenic variants in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *ODC1* variant of uncertain significance does not establish or rule out the diagnosis of this disorder. (3) Heterozygous pathogenic variants in *ODC1* that cause BABS are typically gain-of-function variants (see Molecular Genetics).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of BABS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and supportive laboratory findings suggest the diagnosis of BABS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *ODC1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Note: Because the mechanism of disease causation is gain of function, gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications is typically not required.
- **An intellectual disability multigene panel** that includes *ODC1* and other genes of interest (see Differential Diagnosis) may be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. Because BABS is a rare condition, this gene may not be represented on a multigene panel. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by developmental delay and growth abnormalities, **comprehensive genomic testing**, which does not require the clinician to determine which gene is likely involved, may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Bachmann-Bupp Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ODC1	Sequence analysis [3]	9/9 (100%) [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Bupp et al [2018], Rodan et al [2018], VanSickle et al [2021]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available. As this condition is thought to be due to a gain of function, it is not anticipated that whole-exon or gene deletions or duplications will lead to this phenotype (see Molecular Genetics).

Clinical Characteristics

Clinical Description

To date, nine individuals from nine families have been reported with a pathogenic variant in *ODC1* [Bupp et al 2018, Rodan et al 2018, Rajasekaran et al 2021, VanSickle et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Bachmann-Bupp Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Alopecia	9/9 (100%)	
Nonspecific dysmorphic features	9/9 (100%)	No specific pattern identified
Developmental delay [1]	8/8 (100%)	
Hypotonia [1]	8/8 (100%)	
Macrocephaly	6/9 (66%)	
Pregnancy notable for polyhydramnios	5/9 (55.5%)	
Skin findings [1]	4/8 (50%)	Keratosis pilaris and follicular cysts
Constipation [1]	3/8 (37.5%)	
Macrosomia	2/5 (40%)	Measured in infancy; growth parameters tend to normalize w/age.
Seizures [1]	1/8 (12.5%)	

1. One reported case was of a late-term stillbirth; thus, some features pertaining to this person are unknown [Rodan et al 2018].

Alopecia appears to be the most distinctive feature of BABS, but it does have some variability.

- Hair is typically present at birth but is sometimes sparse and sometimes has atypical color (darker or lighter than anticipated).
- Loss of hair, if present, begins in the first few weeks of life with hair falling out in large clumps.
- Absent or sparse eyebrows and eyelashes are typically congenital.

- Some affected individuals undergo regrowth of scalp hair that usually remains sparse, although one affected individual had full, thick hair with no reported loss of hair postnatally but absent eyebrows and eyelashes.

Nonspecific dysmorphic features. Dysmorphic features have been identified in most affected individuals, but not with any discernible pattern or consistency.

Developmental delay / intellectual disability. Developmental delay is evident early in life with both motor and speech delays. Walking was achieved between age 17 months and four years, although two affected individuals still had not walked when reported at ages three and five years. First words were said between ages three and six years; three affected individuals were nonverbal when reported at ages ten months, 32 months, and 16 years.

Hypotonia is uniform and likely contributes to motor developmental delay.

Behavior. Attention-deficit/hyperactivity disorder (ADHD), autism, and aggression have all been reported in five of the nine published individuals.

- Behavioral concerns evolved in one affected individual treated with difluoromethylornithine (DFMO) (see Therapies Under Investigation), resulting in a diagnosis of autism.
- It is unclear whether DFMO treatment accelerated the development of autistic symptoms that would have developed in any case (although more slowly) without treatment, or whether the treatment itself affected brain function through the alteration of polyamine levels.

Growth. Larger head circumference for age and sex is often seen. One affected individual with a normal head circumference had sagittal craniosynostosis, which has not been seen in any other reported individuals.

Macrosomia at birth has been reported; in four of five affected individuals measured, length was >95% percentile, and in two of five weight was >95% percentile. However, growth parameters tend to normalize with age: at later childhood examination, only two of eight had height >95% percentile and none had weight >95% percentile.

Gastrointestinal and feeding. Ability to feed varies with developmental level, with some affected individuals requiring gastrostomy tube. Others can take food by mouth. Constipation has been seen and may be related to hypotonia.

Skin findings including keratosis pilaris, recurrent follicular cysts (particularly on the back, axilla, and posterior of head), and dry skin have been observed in childhood. Cysts were noted in the first few years of life and resolved with DFMO treatment (see Therapies Under Investigation).

Seizures are seen in one individual, at age 23 years the oldest known with BABS. His seizures emerged at age 14 years, and multiple seizure types have been observed including atypical absence, atonic, and generalized tonic-clonic. Treatment has been challenging as no controlling medication has been identified [VanSickle et al 2021].

Brain MRI findings. Abnormalities identified on brain MRI vary quite broadly without a unifying pattern, although cystic lesions have been reported, and nonspecific white matter changes (loss, hyperintensity, signal abnormality) have been observed in six of nine affected individuals.

Other. Because this is a newly recognized condition, it is unclear if the following findings are associated with BABS or represent rare co-occurrences, as the findings have been found in a small number of affected individuals.

- **Hearing loss.** One individual had unilateral congenital sensorineural hearing loss. Three individuals have required myringotomy.

- **Congenital heart disease.** Mild pulmonary stenosis has been reported in one affected individual and ventricular septal defect (self-resolved) was reported in another.
- **Nail anomalies.** Two affected individuals had brittle nails and another had hypoplastic toenails.
- **Ophthalmologic findings.** One reported individual had esotropia, pseudostrabismus, and bilateral myopic astigmatism.

Prognosis. The availability of experimental targeted treatment options (see Table 7) may change the natural history of this condition. It is unclear if diagnosis prior to symptom onset, coupled with targeted therapies, will decrease the morbidity and mortality of this condition in the future.

Genotype-Phenotype Correlations

Gain-of-function variants located in the C terminus are associated with BABS. For example, pathogenic variants resulting in a premature termination codon within the last exon, escaping nonsense-mediated decay and causing a gain-of-function terminus, are associated with BABS.

Loss-of-function variants may be enriched with neurologic phenotypes (see Genetically Related Disorders).

Nomenclature

Bachmann-Bupp syndrome may also be referred to as *ODC1*-related neurodevelopmental disorder based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

The prevalence of Bachmann-Bupp syndrome is unknown. Nine affected individuals have been reported in the literature to date. Three additional affected individuals are known to these authors but have not been reported in the medical literature.

Genetically Related (Allelic) Disorders

It is unclear whether loss-of-function variants in *ODC1* lead to a distinct phenotype, although current evidence suggests that loss-of-function variants are unlikely to be deleterious. One missense variant was enriched in a population of individuals with neurologic conditions (0.68% of such individuals) [Prokop et al 2021].

Sporadic tumors (including colorectal, gastric, skin, breast, prostate cancer and neuroblastoma) occurring as single tumors frequently harbor somatic pathogenic variants in *ODC1* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more information, see Cancer and Benign Tumors.

Differential Diagnosis

Table 3. Selected Genetic Disorders in the Differential Diagnosis of Bachmann-Bupp Syndrome

Gene(s)	DiffDx Disorder	MOI	Features Observed in DiffDx Disorder & BABS	Features Distinguishing from BABS
CHD3	Snijders Blok-Campeau syndrome (SNIBCPS; OMIM 618205)	AD	DD, macrocephaly, hypotonia	In SNIBCPS: ventriculomegaly, common dysmorphic features, & joint laxity
DCAF17	Woodhouse-Sakati syndrome (OMIM 241080)	AR	Alopecia totalis, dystonia	Hypogonadism, diabetes mellitus

Table 3. continued from previous page.

Gene(s)	DiffDx Disorder	MOI	Features Observed in DiffDx Disorder & BABS	Features Distinguishing from BABS
LSS	*LSS*-related neurodevelopmental disorder (OMIM 618840)	AR	Alopecia, DD, epilepsy	Alopecia is congenital in persons w/*LSS*-related neurodevelopmental disorder.
PAK1	Intellectual developmental disorder with macrocephaly, seizures, & speech delay (IDDMSSD; OMIM 618158)	AD	DD, macrocephaly, seizures	In IDDMSSD: ataxia & absence of consistent hair & skin abnormalities
PTEN	Cowden syndrome (See *PTEN* Hamartoma Tumor Syndrome.)	AD	DD, macrocephaly	Facial trichilemmomas, acral keratoses, papillomatous papules, ↑ risk for breast, thyroid, & endometrial cancers
Ectodermal dysplasias including the following:				
EDA *EDAR* *EDARADD* *WNT10A*	Hypohidrotic ectodermal dysplasia	XL, AD, AR	Hypotrichosis: thin, lightly pigmented, slow-growing scalp hair	• Ectodermal dysplasia is not typically assoc w/DD or hypotonia. Alopecia is congenital in most ectodermal dysplasia. • BABS is not assoc w/dental issues. Only 1 person w/BABS was reported to have ↓ sweating.
GJB6	Hidrotic ectodermal dysplasia 2	AD	Partial-to-complete alopecia	
HOXC13	Ectodermal dysplasia 9, hair/nail type (OMIM 614931)	AR	Generalized congenital atrichia	
KRT74	Ectodermal dysplasia 7, hair/nail type (OMIM 614929)	AR	Generalized hypotrichosis or atrichia	
KRT85	Ectodermal dysplasia 4, hair/nail type (OMIM 602032)	AR	Sparse or absent scalp hair; absent eyebrows, eyelashes, pubic & axillary hair	

AD = autosomal dominant; AR = autosomal recessive; BABS = Bachmann-Bupp syndrome; DD = developmental delay; DiffDx = differential diagnosis; MOI = mode of inheritance; XL = X-linked

Management

No clinical practice guidelines for Bachmann-Bupp syndrome (BABS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with BABS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Bachmann-Bupp Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To evaluate for overgrowth in infancy/childhood

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval for aspiration risk, nutritional status, & signs & symptoms of constipation • May require use of special nipple &/or nasogastric tube in infancy • Consider eval for gastric tube placement in those w/dysphagia &/or aspiration risk.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl ADHD, aggression &/or traits suggestive of ASD
Neurologic	Neurologic eval	Consider EEG & brain MRI if seizures are a concern.
Eyes	Ophthalmologic eval	To assess for eye alignment & refractive error
Ears/Hearing	Audiology eval	To assess for presence & type of hearing loss
Skin/Hair	Physical exam for follicular cysts	Consider referral to dermatologist
Cardiovascular	Auscultation for heart murmur	Consider echocardiogram, as clinically indicated
Genetic counseling	By genetics professionals [1]	To inform patients & families re nature, MOI, & implications of BABS in order to facilitate medical & personal decision making
Family support & resources		Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; BABS = Bachmann-Bupp syndrome; EEG = electroencephalogram; MOI = mode of inheritance; MRI = magnetic resonance imaging
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

An experimental targeted treatment for BABS is being investigated (see Therapies Under Investigation) but is not currently FDA approved for use in this disorder.

Table 5. Supportive Treatment of Manifestations in Individuals with Bachmann-Bupp Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Feeding difficulties	• Feeding therapy • Special nipple or nasogastric tube may be required. • Gastrostomy tube placement may be considered for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Obesity/ Overgrowth	Nutritional intervention	Consider restricting caloric intake.
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	Incl social/behavioral concerns

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for BABS. • In 1 person, epilepsy was refractory to multiple ASMs, ketogenic diet, & vagal nerve stimulators. [1] • Education of parents/caregivers [2]
Refractive error &/or strabismus	Standard treatment(s) as recommended by ophthalmologist	
Hearing loss	Standard treatment per audiologist	
Follicular cysts	Standard treatment per dermatologist	May require surgical drainage
Congenital heart defects	Standard treatment per cardiology	
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability

1. VanSickle et al [2021]

2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- Individualized education plan (IEP) services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.

- Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
- Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
- PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
- As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public-school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather promote optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder (ADHD), when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 6. Recommended Surveillance for Individuals with Bachmann-Bupp Syndrome

System/Concern	Evaluation	Frequency
Growth/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Gastrointestinal	Monitor for constipation.	
Musculoskeletal	OT/PT assessment of mobility & self-help skills	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for signs of ASD, attention, & aggressive or self-injurious behavior	Annually
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
	Assess for new manifestations such as seizures & changes in tone.	
Eyes	Assessment by an ophthalmologist	Annually or as clinically indicated
Hearing	Assessment for signs & symptoms of hearing loss	
Skin/hair	Complete skin eval for follicular cysts	At least annually
Miscellaneous/ Other	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	At each visit

ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Difluoromethylornithine (DFMO). A compassionate-use protocol investigating the use of this drug in the targeted treatment of individuals with BABS is being used through investigational new drug approval by FDA. Table 7 summarizes the proposed protocol.

Table 7. Experimental Targeted Treatment of Manifestations in Individuals with Bachmann-Bupp Syndrome

Targeted Treatment	Dosage	Consideration
Difluoromethylornithine (DFMO) [1]	• Escalating 500 mg/m^2/dose orally BID for 3 mos to 750 mg/m^2/dose orally for 3 mos • 1000 mg/m^2/dose orally BID for maintenance	• This dosing strategy was used for 3 patients w/BABS under FDA-approved Single Patient IND based on previous data from pediatric dosing for neuroblastoma treatment. • Future treatment strategies for DFMO may be influenced by ongoing safety & efficacy data.

BID = twice a day; FDA = Food and Drug Administration; IND = investigational new drug
1. Also called eflornithine

Other ODC inhibitors and DFMO analogs with pharmacokinetic profiles superior to DFMO are under investigation. Also, various nature-derived molecules, including allicin and curcumin, are being studied. Finally, polyamine-restricted diets (Nutrialys) that could be of use in lowering the dietary intake of polyamines are being developed. Special tables exist with precise quantities of each polyamine in various foods and drinks, allowing the design of a tailored putrescine-low diet.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Bachmann-Bupp syndrome (BABS) is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with BABS whose parents have also undergone molecular genetic testing have the disorder as the result of a *de novo ODC1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If the *ODC1* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If a parent of the proband is known to have the *ODC1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.

Offspring of a proband

- Each child of an individual with BABS has a 50% chance of inheriting the *ODC1* pathogenic variant.
- To date, individuals with BABS are not known to reproduce; however, many are not yet of reproductive age.

Other family members. Given that all probands with BABS reported to date have the disorder as the result of a *de novo ODC1* pathogenic variant, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo ODC1* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **MedlinePlus**
  Intellectual Disability

See Chapter Notes for information about the Authors' clinical research program.

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Bachmann-Bupp Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ODC1	2p25.1	Ornithine decarboxylase	ODC1 database	ODC1	ODC1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Bachmann-Bupp Syndrome (View All in OMIM)

165640	ORNITHINE DECARBOXYLASE 1; ODC1
619075	BACHMANN-BUPP SYNDROME; BABS

Molecular Pathogenesis

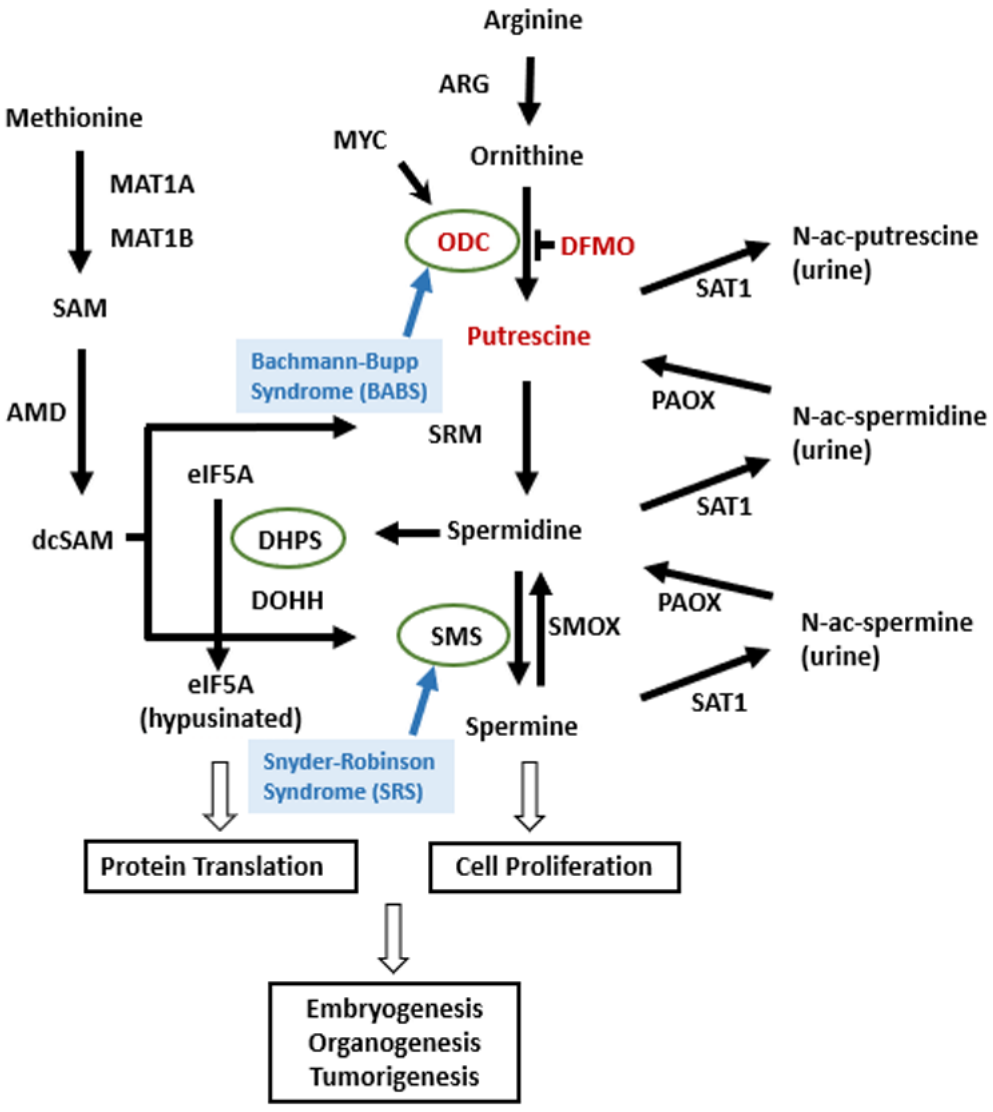

Figure 1. The polyamine metabolic pathway and associated genetic disorders

ODC and polyamines are intrinsically involved in the regulation of embryogenesis, organogenesis, and tumorigenesis. This occurs through tight regulation of putrescine, spermidine, and spermine, all of which control cell division and proliferation. Spermidine is substrate to eIF5A and essential for its hypusination (activation) and therefore directly affects eIF5A-mediated protein translation

events. Many polyamine pathway-linked genes including *ODC1*, *SMS*, and *DHPS* and their gene products (green circles) have recently been identified to cause syndromes with a common finding of global developmental delays in childhood. Other polyamine-associated genes such as *DOHH*, *AMD1*, *eIF5A*, *MAT1A/B*, *MYC*, or *MYCN* may also be involved in similar genetic disorders. Collectively, they represent a new condition, which the authors refer to as polyaminopathy spectrum disorder (PSD).

Figure and legend republished from Schultz et al [2019]

ODC1 codes for ornithine decarboxylase (ODC), a rate-limiting enzyme in the polyamine pathway, converting ornithine into the polyamine metabolite putrescine (see Figure 1). Polyamines (putrescine, spermidine, spermine) are polycationic molecules involved in many physiologic and cell development processes. The C terminus of ODC contains a 37-amino acid region (amino acids 425-461 using the NM_002539.3 transcript) which is functionally important as a destabilization region. In vitro deletions in this region cause a functional ODC protein that is more stable due to reduced proteasomal degradation, resulting in elevated ODC protein and polyamine levels, mainly putrescine and N-acetyl-putrescine.

When intracellular putrescine and other polyamine levels are elevated, these metabolites are acetylated. Acetylated polyamines are shuttled out of the cell in an attempt to regain homeostasis, resulting in elevated plasma N-acetylputrescine. In cell experiments using high-performance liquid chromatography (HPLC), increased putrescine is observed because HPLC is not able to separate putrescine from N-acetylputrescine; however, mass spectrometry does have this capability.

A transgenic mouse model created in 1995 in which a C-terminally deleted ODC (p.Pro427Ter) protein was overexpressed showed higher ODC enzyme levels and increased polyamine metabolites [Megosh et al 1995]. Phenotypically these mice demonstrated skin, nail, and hair follicle abnormalities after birth similar to those seen in humans [Soler et al 1996]. Treatment of the mice with DFMO prevented hair loss and allowed partial regrowth of hair [Soler et al 1996].

Mechanism of disease causation. Gain of function. All pathogenic variants reported to date are in exon 12 (amino acids 414-461 using the NM_002539.3 transcript) or at the intronic splice site before exon 12, resulting in deletion of the C-terminal region.

Cancer and Benign Tumors

Due to its role in regulating cell growth and proliferation, the polyamine pathway and ODC are known to be involved in neoplastic cell growth, specifically in neuroblastoma and in breast, colon, lung, prostate, and skin cancers [Nowotarski et al 2013]. ODC is a transcriptional target of the *MYC* oncogene, which mediates cell apoptosis, differentiation, metabolism, and proliferation. Therefore, difluoromethylornithine (DFMO) has been studied as a potential treatment for or preventative of neuroblastoma, glioblastoma, and prostate, skin, breast, and colon cancers. While oral DFMO has not yet been FDA approved, it has been approved for other routes of administration, specifically via intravenous administration for trypanosomiasis and topical administration for hirsutism. Oral DFMO has been studied in Phase I/II clinical trials in individuals with neuroblastoma and was found to be safe and well tolerated in the study population through two years of maintenance therapy [Saulnier Sholler et al 2015, Lewis et al 2020].

Chapter Notes

Author Notes

The **Spectrum Health/Michigan State University International Center for Polyamine Disorders (ICPD)** is a collaborative translational and clinical research program operated under the auspices of Michigan State University and Spectrum Health West Michigan in Grand Rapids, Michigan. The ICPD launched in summer 2020 and includes a polyaminopathy patient biobank, a state-of-the-art translational research lab core, and a

clinical genetics team at Spectrum Health West Michigan. The ICPD offers innovative ways to study polyaminopathies and associated disabilities and to develop strategies for treatment and prevention. This collaborative effort between Spectrum Health and Michigan State University brings world leading experts in the field from the bench and clinic together to study these rare genetic diseases.

www.grc.org/polyamines-conference/2019/

cancer.msu.edu/faculty/bachmann-andre

www.phd.msu.edu/index.php/research/faculty-staff/andre-s-bachmann

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