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Aymé-Gripp Syndrome

Shivarajan Manickavasagam Amudhavalli, MD,[1] Randi Gadea, MS,[1] and Karen Gripp, MD[2]

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Summary

Clinical characteristics

Aymé-Gripp syndrome is classically defined as the triad of bilateral early cataracts, sensorineural hearing loss, and characteristic facial features in combination with neurodevelopmental abnormalities. The facial features are often described as "Down syndrome-like" and include brachycephaly, flat facial appearance, short nose, long philtrum, narrow mouth, and low-set and posteriorly rotated ears. Hearing loss is often congenital. Other features may include postnatal short stature, seizure disorder, nonspecific brain abnormalities on head imaging, skeletal abnormalities, and joint limitations. A subset of individuals have been found to have pericarditis or pericardial effusion during the neonatal or infantile period. All affected individuals have had developmental delay, but the degree of cognitive impairment is extremely variable. Other features including gastrointestinal and endocrine abnormalities, ectodermal dysplasia (i.e., nail dystrophy and mammary gland hypoplasia), dental anomalies, and chronic glomerulopathy with proteinuria have been reported in rare affected individuals.

Diagnosis/testing

The diagnosis of Aymé-Gripp syndrome is established in a proband with cataracts, sensorineural hearing loss, and suggestive facial features and a heterozygous pathogenic variant in a specific region of *MAF* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic and ideally involves multidisciplinary care. Hearing aids or cochlear implant for sensorineural hearing loss; surgical intervention and eye glasses for cataracts and refractive errors, respectively; physical therapy for milder joint limitations; hip replacement for those with chondrolysis; standard therapy for developmental delay / cognitive impairment, seizure disorder, scoliosis, congenital heart defects / pericardial issues, oligodontia, and hypothyroidism.

Surveillance: Dental evaluation every six months; assessment for new neurologic manifestations, progressive joint restriction in major joints, and developmental and educational needs at each visit; clinical examination for

Author Affiliations: 1 Children's Mercy Hospitals and Clinics, Kansas City, Missouri; Email: samudhavalli@cmh.edu; Email: rngadea@cmh.edu. 2 AI duPont Hospital for Children, Wilmington, Delaware; Email: kgripp@nemours.org.

scoliosis at each visit until skeletal maturity; at least annual audiology and ophthalmology evaluations; assessment of thyroid function as clinically indicated.

Genetic counseling

Aymé-Gripp syndrome is inherited in an autosomal dominant manner. Almost all individuals reported to date have been simplex cases (i.e., a single occurrence in a family) resulting from a *de novo* pathogenic variant. Once the causative genetic alteration has been identified in the proband, parental testing may be offered. Each child of an individual with Aymé-Gripp syndrome has a 50% chance of inheriting the *MAF* pathogenic variant. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant in an affected family member is known.

Diagnosis

Aymé-Gripp syndrome is classically defined as the triad of cataract, sensorineural hearing loss, and characteristic facial features in combination with neurodevelopmental abnormalities [Amudhavalli et al 2018]. Formal clinical diagnostic criteria for Aymé-Gripp syndrome have not been established.

Suggestive Findings

Aymé-Gripp syndrome **should be suspected** in individuals with the following major and minor clinical features and imaging findings.

Major clinical features

- Distinctive facial features (Figure 1), often described as similar to those seen in individuals with Down syndrome, including:
  - Brachycephaly
  - Flat facial appearance
  - Short nose
  - Long philtrum
  - Narrow mouth
  - Dental abnormalities (small, abnormally shaped teeth)
  - Low-set and posteriorly rotated ears
- Sensorineural hearing loss
- Cataracts
- Developmental delay / intellectual disability
- Short stature

Minor clinical features

- Seizures (variable, from febrile seizures to epilepsy)
- Congenital radioulnar synostosis
- Pericardial effusion
- Mammary gland hypoplasia
- Ectodermal abnormalities (sparse scalp hair, dystrophic nails)

Imaging findings

- Congenital radioulnar synostosis
- Radial head subluxation
- Chondrolysis of the hip (in a young adult)
- Carpal/tarsal long bone defects

Figure 1. Individuals with a molecularly confirmed diagnosis of Aymé-Gripp syndrome with characteristic facial features including midface retrusion, high forehead, flat nasal bridge, long philtrum, and thin vermillion of the upper lip

Individual 1 shown at age three years (1a), four years (1b) and seven years (1c). Note the progression of the facial phenotype.

Individual 2 is an affected adult (age unknown).

From Amudhavalli et al [2018]

Establishing the Diagnosis

The diagnosis of Aymé-Gripp syndrome **is established** in a proband with cataracts, sensorineural hearing loss, and suggestive facial features AND a heterozygous pathogenic (or likely pathogenic) variant in a specific region of *MAF* identified by molecular genetic testing (see Table 1 and Molecular Genetics).

Note: Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

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

Gene-targeted testing requires that the clinician determine which gene is likely involved, whereas genomic testing does not. Because the phenotype of Aymé-Gripp syndrome is broad, 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 Aymé-Gripp syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of Aymé-Gripp syndrome molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *MAF* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis.

  Note: No exon/multiexon deletions/duplications have been reported to result in Aymé-Gripp syndrome.

- **An intellectual disability multigene panel** that includes *MAF* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. 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. (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 diagnosis of Aymé-Gripp syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene is likely involved) is the best option. **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 Aymé-Gripp Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
MAF	Sequence analysis [3]	19/19 [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Amudhavalli et al [2018], Alkhunaizi et al [2019], Niceta et al [2020]

Clinical Characteristics

Clinical Description

Individuals with Aymé-Gripp syndrome frequently have the triad of bilateral early cataracts, sensorineural hearing loss, and dysmorphic features that are often described as "Down syndrome-like" facies [Gripp et al 1996, Aymé & Philip 1997, Amudhavalli et al 2018, Niceta et al 2020]. To date, 21 affected individuals from 19 families have been reported [Amudhavalli et al 2018, Alkhunaizi et al 2019, Niceta et al 2020]. Clinical features in these individuals are summarized in Table 2.

Table 2. Features of Aymé-Gripp Syndrome

Feature	# of Persons w/Feature	Comment
Cataract	21/21	Often congenital but may be noted as late as young adulthood
Characteristic facial features	20/21	
Sensorineural hearing loss	20/21	Typically congenital
DD / Cognitive impairment	20/21	Degree of cognitive impairment is highly variable.
Skeletal defects	20/21	Variably affecting skull, hip, & limbs
Postnatal short stature	17/21	
Seizure disorder	15/21	
Nonspecific brain anomalies on imaging	12/21	
Joint limitations	12/21	
Pericardial effusion	8/21	

DD = developmental delay

Characteristic facial features. Dysmorphic facial features typically include brachycephaly (~80%), flat facial profile, midface retrusion, short nose, long philtrum, thin vermilion of the upper lip, and small mouth. Other features include widely spaced eyes, broad/sparse eyebrows, long philtrum, and high anterior hairline.

Audiologic manifestations. Early-onset or congenital sensorineural hearing loss has been reported in all but one affected individual. One affected mother was noted to have normal hearing as an adult [Alkhunaizi et al 2019].

- Hearing loss is frequently bilateral and often diagnosed early in childhood.
- Hearing loss can vary from mild to severe, with a few affected individuals requiring hearing aids or cochlear implant.

Ophthalmologic manifestations. Almost all affected individuals reported have congenital or early-onset cataract as a presenting feature. Cataract can be noted as early as infancy to as late as adolescence or even adulthood.

- One affected individual, age 18 months at presentation, had bilateral retinal hemorrhage and optic disc anomaly [Amudhavalli et al 2018].
- One affected individual was reported to have bilateral cataracts diagnosed at age 14 months. This individual developed aphakic glaucoma and went blind at age two years [Alkhunaizi et al 2019].
- Two affected parents were reported to have cataracts extracted after age 40 years [Javadiyan et al 2017, Alkhunaizi et al 2019].

Growth. Most affected individuals have mild-to-moderate short stature, with height 1.25-2 SD below the mean for age. Short stature usually develops postnatally, with birth length in the normal range. Weight and head circumference are typically within normal ranges for all age groups.

Intellectual development. Both speech and gross motor delays have been reported. Some affected individuals have been diagnosed with an autism spectrum disorder. Developmental delay has been reported in all but one affected individual, but the degree of intellectual impairment is highly variable. For example, an affected mother and son had only mild learning delays and were both able to complete secondary education [Javadiyan et al 2017], whereas an affected individual age 29 years was nonverbal and used sign language to communicate

[Amudhavalli et al 2018]. One parent found to have a pathogenic *MAF* variant was reported to have normal development and no history of learning difficulties, and graduated from university with a bachelor's degree.

Neurologic manifestations

- Seizures have been reported in 15 of 21affected individuals, with five having febrile seizures [Amudhavalli et al 2018]. The age of onset ranges from age six months to 12 years in reported individuals.
- Nonspecific brain abnormalities such as ventriculomegaly, Chiari 1 malformation, obstructive hydrocephalus, empty sella, and cerebral atrophy have been noted in slightly more than half of individuals who have undergone brain imaging. One individual was reported to have calcifications of the basal ganglia [Alkhunaizi et al 2019].

Joint and skeletal manifestations. Joint manifestations, ranging from congenital radioulnar synostosis with forearm shortening to mild restriction in the range of motion, have been reported in most affected individuals. For an in-depth analysis of the skeletal features seen in Aymé-Gripp syndrome, see the review by Niceta et al [2020].

- Congenital radioulnar synostosis, radial head subluxation, and shortened forearm as individual findings or in various combinations are the most common joint manifestations.
- Clino/campto/brachydactyly, pectus excavatum, scoliosis without vertebral anomalies, delayed skeletal maturation and carpal/tarsal bone defects, short fourth metatarsal, and hip joint chondrolysis have also been reported.
- Coronal craniosynostosis requiring surgical repair is reported as a rare feature.
- One affected individual was reported to have early fusion of the growth plates, spontaneous fractures, and exostosis [Niceta et al 2020].
- Some affected adults have required hip replacement for hip joint chondrolysis.

Cardiac manifestations

- At least eight of 21 individuals have been noted to have pericarditis or pericardial effusion during the neonatal or infantile period:
  - Four affected individuals presented in the neonatal period with cardiac murmurs for which echocardiogram was performed, revealing pericardial effusion [Amudhavalli et al 2018, Niceta et al 2020].
  - One of these affected infants had persistent effusion and underwent effusion aspiration and eventually a pericardial window.
- Atrial septal defect and patent ductus arteriosus have been reported in a single individual each.

Ectodermal manifestations

- **Bilateral mammary gland hypoplasia** may be seen in females.
- **Hair.** Sparse scalp hair has been reported in both children and adults. Mild-to-moderate premature hair loss has been seen in some affected adults.
- **Nails.** Dystrophic or double nails (rudimentary or accessory nails that grow on top of an existing nail) have been observed [Javadiyan et al 2017, Niceta et al 2020].
- **Dental abnormalities** may include small teeth, abnormally shaped teeth, and/or oligodontia, present in slightly fewer than half of affected individuals

Hypothyroidism was identified in three of 15 affected individuals. Hypothyroidism was not congenital in nature but was diagnosed in childhood and responded to thyroid hormone replacement therapy. Other endocrine abnormalities have rarely been documented.

Rare manifestations may include the following:

- Hiatal hernia and diaphragmatic hernia
- Transient hematuria
- Proteinuria and/or microalbuminuria (reported as a late-onset feature)
- Glomerulonephropathy
- Nephrotic syndrome (which did not recur after treatment with prednisone)

Genotype-Phenotype Correlations

MAF has an N-terminal transactivation domain and a C-terminal DNA binding domain (see Molecular Pathogenesis).

- Pathogenic variants causing Aymé-Gripp syndrome occur at serine, threonine, and proline residues in the N-terminal transactivation domain [Niceta et al 2015].
- A subset of pathogenic variants in the C-terminal DNA binding domain have been associated with isolated congenital cataracts [Anand et al 2018] (see Genetically Related Disorders).

Penetrance

For this disorder, penetrance is felt to be 100%; however, there is variability in presentation as illustrated by a report from Javadiyan et al [2017] and Alkhunaizi et al [2019] in which an affected mother had a substantially milder phenotype than her child.

Prevalence

This disorder is rare and exact prevalence estimates are unknown. Only 21 individuals representing 19 families have been reported in the literature.

Genetically Related (Allelic) Disorders

Heterozygous pathogenic variants in *MAF* are also known to be associated with isolated ocular findings (cataract, iris coloboma, microphthalmia, and anterior chamber dysgenesis) in the absence of other findings of Aymé-Gripp syndrome (OMIM 610202) [Jamieson et al 2002].

Differential Diagnosis

Table 4. Disorders to Consider in the Differential Diagnosis of Aymé-Gripp Syndrome

DiffDx Disorder	Gene(s)	MOI	Key Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/Aymé-Gripp syndrome	Distinguishing from Aymé-Gripp syndrome
Stickler syndrome	*COL2A1* *COL9A1* *COL9A2* *COL9A3* *COL11A1* *COL11A2*	AD AR [1]	• Cataract • Midface hypoplasia • Short stature • SNHL	• Absence of congenital radio ulnar synostosis, pericardial effusion, & ID/DD • Distinct facial features (incl malar hypoplasia, broad or flat nasal bridge, & micro/retrognathia)
Myhre syndrome	*SMAD4*	AD	• Hearing loss • ID/DD [2] • Joint contractures & camptodactyly • Mid face hypoplasia • Short stature	• Absence of cataract & pericardial effusion • Distinct facial features (incl short palpebral fissures, deep-set eyes, maxillary underdevelopment, short philtrum, narrow mouth, & prognathism)

Table 4. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Key Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/Aymé-Gripp syndrome	Distinguishing from Aymé-Gripp syndrome
Zellweger spectrum disorder	*PEX1* *PEX6* *PEX12* [3]	AR	• Cataracts • Flat facial appearance • SNHL	• Abnormal liver function • Brain anomalies such as cortical gyral anomalies, heterotopias, & subependymal cysts • Large fontanelle

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; SNHL = sensorineural hearing loss

1. Stickler syndrome caused by pathogenic variants *COL2A1*, *COL11A1*, or *COL11A2* is inherited in an autosomal dominant manner; Stickler syndrome caused by pathogenic variants in *COL9A1*, *COL9A2*, or *COL9A3* is inherited in an autosomal recessive manner.

2. Mild-to-moderate intellectual disability and developmental delay are common in Myhre syndrome; however, cognition can be within the normal range.

3. Biallelic pathogenic variants in *PEX1*, *PEX6*, *PEX12* account for 60.5%, 14.5%, and 7.6% of Zellweger spectrum disorder (ZSD), respectively. ZSD is also known to be caused by biallelic pathogenic variants in *PEX2*, *PEX3*, *PEX10*, *PEX5*, *PEX11β*, *PEX13*, *PEX14*, *PEX16*, *PEX19*, or *PEX26*.

Fine-Lubinsky syndrome, characterized by brachycephaly, deafness, cataract, microstomia, and intellectual disability (OMIM 601353), should also be considered in the differential diagnosis of Aymé-Gripp syndrome. Fine-Lubinsky syndrome likely represents a distinct disorder (i.e., not associated with mutation of *MAF*) but the genetic basis of the disorder is currently unknown. Since there are very few reports of affected individuals, a robust clinical delineation of this syndrome is currently not possible.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Aymé-Gripp syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Aymé-Gripp Syndrome

System/Concern	Evaluation	Comment
Ears	Audiologic exam	To evaluate for hearing loss
Eyes	Ophthalmologic exam	To evaluate for cataracts & vision
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Psychiatric	Neuropsychiatric eval	In persons age >12 mos: screen for traits suggestive of ASD.
Neurologic	Neurologic eval	To incl EEG & consideration of brain MRI if seizures are suspected
Skeletal	Consider radiographs of forearm, hand/foot, elbow, chest, spine, pelvis.	To assess for radioulnar synostosis, carpal/tarsal bone defects, radial/femoral head dislocation, pathologic fractures, & scoliosis
Cardiac	Echocardiogram	To assess for pericardial effusion & congenital heart defects
Dental	Dental eval	To assess for oligodontia & other dental anomalies
Endocrine	Thyroid function tests [1]	To assess for hypothyroidism, particularly in those w/poor growth velocity

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family supports/resources	Assess need for: • Community or online resources such as Parent To Parent; • Social work involvement for parental support.

ASD = autism spectrum disorder
1. Including a free T4 and TSH

Treatment of Manifestations

Treatment of this disorder is symptomatic and ideally involves multidisciplinary care, which may include an ophthalmologist, otolaryngologist, developmental and behavior specialist, speech therapist, occupational therapist, physiotherapist, orthopedist, endocrinologist, cardiologist, and neurologist, depending on the affected person's specific needs.

Table 6. Treatment of Manifestations in Individuals with Aymé-Gripp Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Sensorineural hearing loss	Hearing aids may be helpful as per otolaryngologist. [1]	Community hearing services through early intervention or school district
Cataracts / Refractive error	Surgical intervention & eye glasses as per ophthalmologist	Consideration of early intervention to help stimulate visual development
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Seizures	Standardized treatment w/ASM by experienced neurologist.	• Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [2]
Joint limitations	PT in children & adults w/milder joint limitations involving knees, fingers, & hips	Consider chondrolysis & need for hip replacement in young adults.
Scoliosis	Standard treatment as per orthopedist	
Congenital heart defects / Pericardial effusion	Standard treatment as per cardiologist	
Oligodontia	Standard treatment as per orthodontist	
Hypothyroidism	Standard treatment as per endocrinologist	

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; PT = physical therapy
1. Cochlear implant has been used to treat severe hearing loss on occasion.
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 and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if 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 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.
- In the US:
  - Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a 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.

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 support 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 is typically performed one on one with a board-certified behavior analyst.

Surveillance

Table 7. Recommended Surveillance for Individuals with Aymé-Gripp Syndrome

System/Concern	Evaluation	Frequency
Ears	Routine audiologic evals & monitoring of hearing aid function	At least annually; more frequently as clinically indicated
Eyes	Ophthalmologic eval	
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures, changes in tone, movement disorders.	
Skeletal	Assess for progressive joint restriction in major joints.	
	Clinical exam for scoliosis	At each visit until skeletal maturity
Dental	Dental eval	Every 6 mos
Endocrine	Monitoring of thyroid function	As clinically indicated

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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

Aymé-Gripp syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with Aymé-Gripp syndrome have the disorder as the result of a *de novo MAF* pathogenic variant.

  The proportion of cases caused by a *de novo* pathogenic variant is approximately 90% in families in which both the mother and father of the proband were available for analysis [Niceta et al 2015, Javadiyan et al 2017, Amudhavalli et al 2018].

- In two families reported to date, a proband with Aymé-Gripp syndrome had the disorder as the result of an *MAF* pathogenic variant inherited from his mildly affected mother [Javadiyan et al 2017, Alkhunaizi et al 2019].

- Molecular genetic testing is recommended for the parents of a proband who has an identifiable *MAF* pathogenic variant.

- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, the pathogenic variant was most likely *de novo* in the proband. Another possible explanation is germline mosaicism in a parent. Though theoretically possible, no instances of a proband inheriting a pathogenic variant from an apparently unaffected parent with germline (or somatic) mosaicism have been reported.

- Although almost all individuals with Aymé-Gripp syndrome represent simplex cases (i.e., the only affected individual in the family), the family history may appear to be negative due to failure to recognize features of the disorder in mildly affected family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

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

- If a parent of the proband has the *MAF* pathogenic variant, the risk to the sibs of inheriting the variant is 50%.
- If the *MAF* pathogenic variant identified 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 the parents have not been tested for the *MAF* pathogenic variant but appear to be clinically unaffected, the risk to the sibs of a proband appears to be low but greater than that of the general population because of the possibility of a very mild phenotype in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with Aymé-Gripp syndrome has a 50% chance of inheriting the *MAF* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *MAF* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence

of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *MAF* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. 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.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**

  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)

  Fax: 202-337-8314

  Email: info@agbell.org

  Listening and Spoken Language Knowledge Center

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**

  Phone: 202-387-1968

  Fax: 202-387-2193

  www.aaidd.org

- **American Society for Deaf Children**

  Phone: 800-942-2732 (ASDC)

  Email: info@deafchildren.org

  deafchildren.org

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  babyhearing.org

- **CDC - Developmental Disabilities**

  Phone: 800-CDC-INFO

Email: cdcinfo@cdc.gov

Intellectual Disability

- **MedlinePlus**

  Intellectual Disability

- **VOR: Speaking out for people with intellectual and developmental disabilities**

  Phone: 877-399-4867

  Email: info@vor.net

  www.vor.net

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. Ayme-Gripp Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MAF	16q23.2	Transcription factor Maf	MAF @ LOVD	MAF	MAF

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 Ayme-Gripp Syndrome (View All in OMIM)

177075	MAF bZIP TRANSCRIPTION FACTOR; MAF
601088	AYME-GRIPP SYNDROME; AYGRP

Molecular Pathogenesis

MAF encodes transcription factor Maf (MAF), a basic leucine zipper (b-ZIP) containing transcription factor of the AP1 family [Niceta et al 2015]. The MAF 373-amino-acid protein is important in lens and eye development but also controls multiple physiologic processes during embryonic development, including chondrocyte and skin cell differentiation. MAF is phosphorylated by GSK3 [Niceta et al 2015].

MAF has a C-terminal extended homology region, a b-ZIP domain mediating DNA binding, and an N-terminal transactivation domain required for transcriptional and regulatory activity [Niceta et al 2015]. *MAF* pathogenic variants causing Aymé-Gripp syndrome specifically reported to date affect residues located within the GSK3 recognition motifs at the N-terminal transactivation domain, including: p.Ser54, p.Ser57, p.Thr58, p.Pro59, p.Thr62, p.Pro63, p.Ser66, p.Pro69 (see also Genotype-Phenotype Correlations).To date, the most frequently affected residue is p.Pro59: p.Pro59His has been reported in three unrelated individuals, p.Pro59Leu in two unrelated individuals, and p.Pro59Arg in two related individuals.

Impaired phosphorylation of the GSK3 binding sites affects MAF ubiquitination, and in turn, this impairs protein degradation [Niceta et al 2015]. Pathogenic variants in this domain are postulated to disrupt dimerization, protein stability, and function, resulting in the syndromic phenotype [Anand et al 2018].

Chapter Notes

Revision History

- 6 February 2020 (ma) Review posted live
- 7 March 2019 (sma) Original submission

References

Literature Cited

Alkhunaizi E, Koenekoop RK, Saint-Martin C, Russell L. Maternally inherited MAF variant associated with variable expression of Aymé-Gripp syndrome. Am J Med Genet A. 2019;179:2233–6. PubMed PMID: 31390148.

Amudhavalli SM, Hanson R, Angle B, Bontempo K, Gripp KW. Further delineation of Aymé-Gripp syndrome and use of automated facial analysis tool. Am J Med Genet A. 2018;176:1648–56. PubMed PMID: 30160832.

Anand D, Agrawal SA, Slavotinek A, Lachke SA. Mutation update of transcription factor genes FOXE3,HSF4, MAF, and PITX3 causing cataracts and other developmental ocular defects. Hum Mutat. 2018;39:471–94. PubMed PMID: 29314435.

Aymé S, Philip N. Apparently new syndrome of congenital cataracts, sensorineural deafness, Down syndrome-like facial appearance, short stature, and mental retardation. Am J Med Genet. 1997;70:333–5. PubMed PMID: 9188678.

Gripp KW, Nicholson L, Scott CI Jr. Apparently new syndrome of congenital cataracts, sensorineural deafness, Down syndrome-like facial appearance, short stature, and mental retardation. Am J Med Genet. 1996;61:382–6. PubMed PMID: 8834052.

Jamieson RV, Perveen R, Kerr B, Carette M, Yardley J, Heon E, Wirth MG, van Heyningen V, Donnai D, Munier F, Black GC. Domain disruption and mutation of the bZIP transcription factor, MAF, associated with cataract, ocular anterior segment dysgenesis and coloboma. Hum Mol Genet. 2002;11:33–42. PubMed PMID: 11772997.

Javadiyan S, Craig JE, Sharma S, Lower KM, Casey T, Haan E, Souzeau E, Burdon KP. Novel missense mutation in the bZIP transcription factor, MAF, associated with congenital cataract, developmental delay, seizures and hearing loss (Aymé-Gripp syndrome). BMC Med Genet. 2017;18:52. PubMed PMID: 28482824.

Niceta M, Barbuti D, Gupta N, Ruggiero C, Tizzano EF, Graul-Neumann L, Barresi S, Nishimura G, Valenzuela I, Grondona FL, Fernandez Alvarez P, Leoni C, Zweier C, Tzschach A, Stellacci E, Del Fattore A, Dallapiccola B, Zampino G, Tartaglia M. Skeletal abnormalities are common features in Aymé-Gripp syndrome. Clin Genet. 2020;97:362–9. PubMed PMID: 31600839.

Niceta M, Stellacci E, Gripp KW, Zampino G, Kousi M, Anselmi M, Traversa A, Ciolfi A, Stabley D, Bruselles A, Caputo V. Mutations impairing GSK3-mediated MAF phosphorylation cause cataract, deafness, intellectual disability, seizures, and a Down syndrome-like facies. Am J Hum Genet. 2015;96:816–25. PubMed PMID: 25865493.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

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