GENEReviews

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Cohen Syndrome

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Summary

Disease characteristics. Cohen syndrome is characterized by failure to thrive in infancy and childhood and truncal obesity in the teen years, early-onset hypotonia and developmental delays, microcephaly developing during the first year, moderate to profound psychomotor retardation, progressive retinochoroidal dystrophy and myopia, neutropenia in many and recurrent infections and aphthous ulcers in some, a cheerful disposition, joint hyperextensibility, and often, characteristic facial features.

Diagnosis/testing. The diagnosis of Cohen syndrome is based on clinical findings, but no consensus diagnostic criteria exist. *COH1* (also known as *VPS13B*) is the only gene known to be associated with Cohen syndrome. Molecular genetic testing is clinically available. Mutation detection rate varies by ethnicity.

Management. Management includes spectacle correction of refractive errors, training for the visually impaired, and psychosocial support. Early intervention and physical, occupational, and speech therapy help address developmental delay, hypotonia, joint hyperextensibility, and motor clumsiness. Recurrent infections are treated per standard therapy; consideration should be given to use of granulocyte-colony stimulating factor (GCSF) for the treatment of neutropenia. Surveillance includes annual ophthalmologic evaluation and repeat white blood cell counts with differential to identify intermittent neutropenia.

Genetic counseling. Cohen syndrome is inherited in an autosomal recessive manner. Each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Offspring of an

individual with Cohen syndrome are obligate heterozygotes (carriers). Prenatal testing for at-risk pregnancies and carrier testing for at-risk family members is clinically available once the disease-causing mutations have been identified in an affected relative.

Diagnosis

Clinical Diagnosis

Although diagnostic criteria have been proposed by several groups based on studies of individuals with confirmed *COH1(VPS13B)* gene mutations, no clinically based diagnostic criteria have been widely accepted at this time.

Prior to identification of the causative gene *COH1* in 2003, Kivitie-Kallio & Norio (2001) and Chandler, Kidd et al (2003) identified a variety of clinical features most suggestive of Cohen syndrome including facial dysmorphism, pigmentary retinopathy, neutropenia, and neurologic abnormalities (psychomotor retardation, motor clumsiness, hypotonia, microcephaly).

Subsequently, evaluation of individuals in different ethnic populations with known *COH1* mutations revealed that overall "facial gestalt" was an unreliable indicator of Cohen syndrome [Falk et al 2004]. However, specific facial features were seen across ethnicities including thick hair and eyebrows, long eyelashes, wave-shaped palpebral fissures, bulbous nasal tip, smooth or shortened philtrum, and hypotonic appearance.

In contrast to facial gestalt, features common to almost all individuals with *COH1* mutations appear to be better clinical indicators of Cohen syndrome:

- Retinal dystrophy appearing by mid-childhood
- Progressive high myopia
- Acquired microcephaly
- Non-progressive mental retardation, global developmental delay
- Hypotonia
- Joint hyperextensibility

Other features suggestive of Cohen syndrome are seen in a minority of individuals from various ethnic backgrounds with proven *COH1* mutations [Falk et al 2004]:

- Short stature
- Small or narrow hands and feet
- Truncal obesity appearing in or after mid-childhood
- Friendly disposition
- Non-cyclic granulocytopenia or low total white blood cell count with or without aphthous ulcers

Kolehmainen et al (2004) studied 76 individuals from 59 families with a provisional diagnosis of Cohen syndrome to correlate molecular and clinical findings. The individuals were assessed for eight clinical criteria:

- High myopia and/or retinal dystrophy
- Microcephaly
- Developmental delay

- Joint hypermobility
- Typical Cohen syndrome facial gestalt
- Truncal obesity with slender extremities
- Overly sociable behavior
- Neutropenia

Individuals fulfilling six or more criteria were considered likely to have "true Cohen syndrome." Those fulfilling five or fewer criteria were considered to have a provisional "Cohen-like syndrome."

Using the above criteria, Kolehmainen et al (2004) found 22 different *COH1* mutations in probands identified as having "true Cohen syndrome." In addition, they identified another three novel mutations in individuals with incomplete clinical data. By contrast, no *COH1* mutations were found in individuals who only met the provisional diagnosis of "Cohen-like syndrome."

The broad clinical spectrum of Cohen syndrome and difficulty establishing definitive clinical diagnostic criteria were confirmed recently by Seifert et al (2006), who identified 25 different *COH1* mutations in 24 ethnically diverse individuals age two to 60 years. The "typical facial gestalt" was seen in 23/24 individuals. Early-onset progressive myopia was present in all individuals older than age five years (14/14) while widespread pigmentary retinopathy was found in 12/14. Some individuals did not have the characteristic facial gestalt and pigmentary retinopathy at school age. Development and growth parameters varied significantly.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Gene. *COH1* (also known as *VPS13B* as first identified in yeast) is the only gene known to be associated with Cohen syndrome.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** The common Finnish mutation c.3348_3349delCT accounts for 75% of mutant alleles in Finland [Kolehmainen et al 2003].
- **Sequence analysis of select exons.** Sequence analysis of exon 23 detected mutations in 26 of 27 individuals of Finnish heritage [Kolehmainen et al 2003]; the mutation detection rate in other populations is unknown.

Molecular genetic testing: Research

- **Targeted mutation analysis.** Two mutations are common in individuals of Amish heritage [Falk et al 2004]:
  - A frameshift mutation with 1-bp insertion, c.9258_9259insT

- A missense substitution, c.8459T>C (p.I2820T)

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Cohen Syndrome

Test Methods	Mutations Detected	Mutation Detection Rate [1]	Test Availability
Targeted mutation analysis	c.3348_3349delCT	75% of mutant alleles in Finland [2]	Clinical Testing
Sequence analysis of exon 23	*COH1(VPS13B)* sequence variants	26/27 in the Finnish population; unknown in other populations	
Sequence analysis		Unknown	
Targeted mutation analysis	c.9258_9259insT, c.8459T>C	Observed in the Amish	Research only

1. Mutation detection rate depends on diagnostic criteria used and ethnicity.
2. Kolehmainen et al 2003

Interpretation of test results. Because the mutations in *COH1* are distributed throughout the gene, only sequencing of the entire gene can confirm or exclude a diagnosis of Cohen syndrome. However, it should be noted that currently the clinical availability of such testing is limited because of the large size of the *COH1* gene.

For other issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

- In the Finnish, the common founder mutation present in at least 75% of mutant alleles is c.3348_3349delCT [Kolehmainen et al 2003].
- In individuals of other ethnic backgrounds, full *COH1* sequence analysis is available clinically. However, the percentage of individuals with clinically diagnosed Cohen syndrome who have identifiable mutations in *COH1* is not yet known.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *COH1*.

Clinical Description

Natural History

Phenotypic features of Cohen syndrome variably include moderate to severe psychomotor retardation, motor clumsiness, acquired microcephaly, childhood hypotonia and joint laxity, progressive retinochoroidal dystrophy and myopia, neutropenia, truncal obesity, a cheerful disposition, and generally, characteristic facial features. Clinical features among the approximately 100 individuals with Cohen syndrome reported to date have been variable, leading to the impression of disease heterogeneity.

The following are prominent clinical features of Cohen syndrome, presented by system.

Note: Among individuals included in the NCSD, the diagnosis of Cohen syndrome has been confirmed by molecular genetic testing primarily in those of Amish heritage; the diagnosis has been genetically confirmed in a limited number of individuals of other ethnic backgrounds.

- **Perinatal.** Half of mothers whose children are included in the NCSD recalled reduced fetal movement during an otherwise normal pregnancy. Although most infants were born at term (average gestational age: 38.5 weeks), average birth weight (2.5 kg) length (47.8 cm) were in the 10th to 25th centile.

Infants with Cohen syndrome frequently have feeding and breathing difficulties during the first days of life, likely related to hypotonia. The majority of newborns with Cohen syndrome are hypotonic. Hypotonia is present in all infants by age one year [Kivitie-Kallio & Norio 2001].

A majority of infants with Cohen syndrome have an unusually high-pitched and weak cry. In the NCSD, this is seen in 95% of children of Amish ancestry and 65% of non-Amish children. Overall, 80% of parents with children in the NCSD database recall this cry as resembling a kitten mewing. However, this unique cry is frequently overlooked by clinicians and has not been reported in the medical literature. The cause of the unusual cry in Cohen syndrome remains unknown, although laryngeal abnormalities postulated to be cause for the "mewing cry" seen in cri-du-chat syndrome have also been found in some individuals with Cohen syndrome [Chandler, Kidd et al 2003].

- **Craniofacial.** Microcephaly develops during the first year of life and continues into adulthood. Although 80% of mothers providing data to the NCSD database reported that their infants had a small head size at birth, the average birth head circumference (35 cm) was in fact in the 50th centile. Earlier studies also reported normal head circumference at birth [Kivitie-Kallio & Norio 2001; Chandler, Kidd et al 2003; Hennies et al 2004].

  Distinctive features have been variably described in different ethnic populations. Features include thick hair, low hairline, high-arched, waved-shaped eyelids, long and thick eyelashes, thick eyebrows, prominent nasal root, high and narrow palate, short philtrum and prominent upper central incisors; the latter two together result in an open-mouth appearance. Horn et al (2000) and Falk et al (2004) both concluded that although quite consistent among affected individuals within a particular ethnic group, facial gestalt appears to be inconsistent between ethnic populations.

  Despite some variability in the facial appearance, several specific features can be identified in affected individuals of different ethnicities. These include thick hair and eyebrows, long eyelashes, wave-shaped palpebral fissures, bulbous nasal tip, smooth or shortened philtrum, and hypotonic appearance [Falk et al 2004]. Systematic anthropometric and cephalometric analysis of 14 individuals confirmed microcephaly, short philtrum, forward-inclined upper incisors, and maxillary prognathia [Hurmerinta et al 2002].

- **Developmental.** All children with Cohen syndrome have delayed developmental milestones in the first year of life. Analysis of individuals in the NCSD showed fairly consistent findings on certain developmental milestones compared with other cohorts with Cohen syndrome (Table 2) [Kivitie-Kallio & Norio 2001;Chandler, Kidd et al 2003;Nye et al 2005]. The psychomotor retardation in children with Cohen syndrome appears non-progressive and non-regressive. All but one of the individuals in the NCSD is able to walk without assistance, but at least 20% are unable to communicate verbally. The degree of developmental delay varies considerably, even among siblings [Horn et al 2000].

Table 2. Timing of Developmental Milestone Achievement in Cohen Syndrome

Developmental Milestone	Age at Milestone Achievement		
	Finnish Cohort [1]	English Cohort [2]	NCSD (US) Cohort [3]
Roll over	4-12 months	—	7 months
Sit independently	10-18 months	12 months	11 months
Walk independently	2-5 years	2.5 years	2.5 years
Speak first words	1-5 years	2.5 years	3.2 years
Speak in sentences	5-6 years	5 years	4.2 years

1. Kivitie-Kallio & Norio 2001
2. Chandler, Kidd et al 2003
3. Nye et al 2005

- **Ophthalmologic.** The range of ophthalmologic findings first identified in affected individuals of Finnish descent includes decreased visual acuity, night blindness, constricted visual fields, chorioretinal dystrophy with bull's-eye-like maculae and retinal pigmentary deposits, optic atrophy, and abnormal (isoelectric) electroretinograms (ERGs) [Norio et al 1984].

  Many of the same ophthalmologic findings have since been confirmed in individuals of non-Finnish descent. Individuals registered in the US NCSD had a first ophthalmologic visit and first pair of glasses at an average age of 4.5 years. Defective dark adaptation/night blindness was typically noticed after age seven years. However, studies of younger individuals with Cohen syndrome demonstrate that abnormal retinal findings and ERG changes are present much earlier in life [Kivitie-Kallio et al 2000, Chandler et al 2002]. The studies further show that the two most prominent ophthalmologic findings, myopia and retinal dystrophy, progress markedly in severity over time. The progressive myopia and late-onset lens subluxation that occur in some individuals result from progressive laxity of zonules and progressive rounding up of the lens (spherophakia). Older individuals can have tremulousness of the iris and lens (phako-iridodonesis).

  More than 70% of individuals in the NCSD fall often or trip easily, most likely because of limited peripheral visual fields from retinal degeneration.

  Congenital ptosis has also been noted in some individuals.

- **Endocrine and metabolism.** Among individuals in the NCSD, the prevalence of short stature is approximately 65%, delayed puberty 74%, and obesity 60%; clinical endocrinologic evaluations were negative.

  Extensive endocrine evaluations of pituitary, adrenal, and thyroid function in the cohort of Finnish descent showed no significant abnormalities [Kivitie-Kallio, Eronen et al 1999].

  Growth hormone deficiency was reported in a girl who was clinically diagnosed with Cohen syndrome [Massa et al 1991] but whose phenotype differed considerably from that seen in individuals with genetically confirmed Cohen syndrome. Three other individuals with Cohen syndrome with growth hormone deficiency displayed catch-up growth with growth hormone replacement therapy [author, personal observation]. The prevalence of growth hormone deficiency in Cohen syndrome is unknown.

  Individuals with Cohen syndrome tend to manifest failure to thrive in infancy and early childhood, but then proceed to become significantly overweight in their teenage

years. More than 80% of individuals in the NCSD were reported to be underweight during early childhood, but overweight afterward. The obesity tends to be truncal in nature. The average age of the onset of obesity is 11.3 years (14.6 years in individuals of Amish descent and 8.4 years in individuals of non-Amish ancestry). The authors have noted that this change usually occurs very rapidly, with a weight gain of 10-15 kg seen over a period of four to six months. In contrast to Prader-Willi syndrome, appetite and food intake are not increased during this time period and activity is not decreased.

- **Hematologic.** Neutropenia, defined as an absolute neutrophil count (ANC) lower than 1,500/mm^3, was initially documented in individuals of Finnish ancestry [Norio et al 1984] and later found in many who were not of Finnish descent [De Ravel, Dillen et al 2002; Chandler, Kidd et al 2003]. The neutropenia is mild to moderate, non-cyclic, and usually not fatal [Kivitie-Kallio et al 1997; author, unpublished data]. However, recurrent infections and aphthous ulcers have been described in some individuals [Falk et al 2004] (see Immunologic section below). ANC usually falls into the range of 500 to 1,200/mm^3 in all age groups [author, unpublished data]. Furthermore, low-normal neutrophil counts are common in individuals who do not have neutropenia.

  More than 65% of affected individuals experience repeated oral mucosal ulcers and gingival infections, with at least three individuals requiring prophylactic granulocyte colony-stimulating factor (G-CSF) therapy.

  The neutropenia may not necessarily result in an overall low white blood cell count and therefore may be overlooked for many years in some individuals. The etiology of the neutropenia remains unclear. Bone marrow examination performed by the Finnish groups showed a normocellular or hypercellular marrow, with a left-shifted granulopoiesis in about half of those affected. No bone marrow malignancies have been seen.

  Whether other hematologic findings reported in clinically diagnosed individuals — including combined deficiency of protein C, protein S, and antithrombin III causing venous thrombosis [Schlichtemeier et al 1994] in one individual and asymptomatic thrombocytopenia in another [De Ravel, Dillen et al 2002] — are present in individuals with molecularly confirmed Cohen syndrome remains to be determined.

- **Immunologic and rheumatologic.** While neutropenia may contribute to compromised immune dysfunction in some individuals with Cohen syndrome, it is not clear if it is the sole cause. More than 80% of children in the NCSD have had more than five episodes of otitis media per year and most of them had tympanostomy tubes placed during early childhood. The majority of children also had an average of 2.5 lifetime episodes of pneumonia.

  The frequency and severity of infections in individuals with Cohen syndrome seems to correlate poorly with ANC; affected individuals are generally more symptomatic than non-affected individuals with an ANC in the same range (500-1,200/mm^3). The authors have also observed that when treated with immunomodulators, some individuals with Cohen syndrome appear to have significantly fewer oral ulcers with no change in ANC. Indeed, increased neutrophil adhesive capability has been reported in an individual with Cohen syndrome [Olivieri et al 1998].

  Other immune disturbances have been observed; De Ravel, Azou et al (2002) found rheumatoid arthritis in an individual with Cohen syndrome. In addition to rheumatoid arthritis, frequent uveitis and recurrent pericarditis have been seen in affected individuals [Wang, personal observation].

- **Neurologic.** Seizures have been reported in a minority of individuals with Cohen syndrome [Coppola et al 2003, Atabek et al 2004]. Anecdotally, two individuals with epilepsy in the NCSD currently on anticonvulsants have phenotypes at the more severe end of the Cohen syndrome spectrum, characterized by inability to communicate verbally. Most individuals, however, particularly those older than age five years in the Finnish cohort, were reported to have low-voltage EEGs without irritative spikes or epileptoform foci [Kivitie-Kallio, Larsen et al 1999].

  Childhood hypotonia, one of the most common features in Cohen syndrome, seems to improve over time regardless of intervention. The mechanism of hypotonia is unknown but speculated to be of central nervous system origin [Kivitie-Kallio et al 1998].

  Magnetic resonance imaging (MRI) of 18 individuals with Cohen syndrome found normal gray and white matter signal intensity and a relatively enlarged corpus callosum compared to 26 controls [Kivitie-Kallio et al 1998]. Although this abnormal finding appeared to be subtle and nonspecific, it warrants further study.

  Electromyography (EMG) is reported to be normal [Kivitie-Kallio, Larsen et al 1999].

- **Musculoskeletal.** Joint hypermobility, kyphosis, scoliosis, and *pes planovalgus* are most likely the consequence of hypotonia. The relatively disease-specific motor clumsiness appears to be quite common [Kivitie-Kallio et al 2000; Chandler, Kidd et al 2003].

  Individuals with Cohen syndrome have characteristic narrow hands and feet, and slender fingers that have frequently been falsely reported to be long. In fact, the fingers are short, based on the hand x-ray analysis of the metacarpophalangeal pattern [Kivitie-Kallio, Eronen et al 1999].

- **Psychological and behavioral.** Individuals with Cohen syndrome are typically described as having a "cheerful and friendly disposition."

  While cognitive ability varies, the majority of affected individuals fall into the moderate-to-profound range of mental retardation [Kivitie-Kallio, Larsen et al 1999; Chandler, Moffett et al 2003; Karpf et al 2004]. Independence levels are generally poor but socialization skills are relatively less impaired; indeed, sociability is characteristic of individuals with Cohen syndrome. In contrast, psychological evaluations performed in previous studies have identified maladaptive and autistic-type behavior in some individuals [Kivitie-Kallio, Larsen et al 1999; Chandler, Moffett et al 2003; Karpf et al 2004].

- **Cardiovascular.** The cardiovascular system is not commonly affected in individuals with Cohen syndrome. Mitral valve prolapse has been reported in individuals with Cohen-like syndrome of Ashkenazi Jewish ancestry [Sack & Friedman 1980] but not in individuals with classic Cohen syndrome who have documented *COH1* mutations. Cardiac evaluation in 22 individuals of Finnish descent identified decreased left ventricular function with advancing age but no evidence for clinically significant mitral prolapse [Kivitie-Kallio, Eronen et al 1999]. Of the approximately 20 individuals in the NCSD who have had echocardiograms, none showed evidence of mitral valve prolapse.

  Similarly, while carotid aneurysms and tortuous descending aortas have been reported in the literature [Schlichtemeier et al 1994], they have not been found in individuals with a confirmed *COH1* mutation.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

Cohen et al (1973) described a pattern of abnormalities including mental deficiency, hypotonia, obesity, high nasal bridge, and prominent central incisors, observed in a sib pair and an unrelated individual.

Norio et al (1984) observed six individuals of Finnish descent with the same disorder, known by them as the "Pepper syndrome," from the family name. They identified consanguinity among two pairs of parents (confirming the autosomal recessive inheritance of the disorder), intermittent granulocytopenia, and marked ophthalmologic changes including decreased visual acuity, hemeralopia, constricted visual fields, chorioretinal dystrophy with bull's-eye-like maculae and pigmentary deposits, optic atrophy, and isoelectric electroretinogram.

Prevalence

The worldwide prevalence of Cohen syndrome is not known. More than 100 individuals have been reported in the literature since the first individual was described in 1973 by Cohen et al.

As more than 80% of individuals with molecularly confirmed Cohen syndrome who are registered in the National Cohen Syndrome Database (NCSD) have not been reported in the literature, it is estimated that at least 500 to 1,000 individuals have been diagnosed, and many more undiagnosed, worldwide.

Cohen syndrome has now been confirmed on almost all continents and in a wide variety of ethnic groups [Falk et al 2004, Hennies et al 2004, Kolehmainen et al 2004, Mochida et al 2004, Kondo et al 2005].

Cohen syndrome is overrepresented in the Finnish population [Kolehmainen et al 2003], with more than 35 individuals diagnosed in Finland to date. The Finnish phenotype is comparable to that seen in individuals of non-Finnish descent [Chandler, Kidd et al 2003].

Cohen syndrome is overrepresented in the Amish population. Of the more than 60 individuals with Cohen syndrome from around the US currently registered in the National Cohen Syndrome Support Center, approximately 50% are Amish. Since the first report of Cohen syndrome in the Ohio Geauga Old Order Amish settlement in 2004 [Falk et al 2004], more than 30 affected individuals have been identified in this highly consanguineous, isolated population of approximately 15,000 — indicating a prevalence as high as 1 in 500 and providing evidence for a founder effect.

The concept of a Jewish type of Cohen syndrome, first reported in a cohort of individuals from Israel [Sack & Friedman 1986] has since been challenged [Chandler & Clayton-Smith 2002]. The originally reported 39 individuals of Jewish descent in 32 families appeared macrocephalic and tall with generalized obesity, as opposed to being microcephalic and short with truncal obesity as seen in classic Cohen syndrome. Furthermore, the individuals reported with "Jewish-type" Cohen syndrome did not have neutropenia or chorioretinal dysplasia — manifestations found in all affected individuals of Finnish ancestry [Norio et al 1984]. The likelihood that these individuals belong to a completely different clinical entity is supported by the fact that no *COH1* mutations have been found in individuals with Jewish-type Cohen or Cohen-like syndrome [Kolehmainen et al 2004]. Thus, the incidence of classic Cohen syndrome may not be increased in the Ashkenazi Jewish ethnic group.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The lack of widely accepted clinically based diagnostic criteria and clinically available laboratory testing for Cohen syndrome are some of the barriers to accurate diagnosis. However, many of the disorders in the differential diagnosis can be diagnosed with clinically available genetic tests.

Individuals with Cohen syndrome are often suspected of having the following disorders.

- **Prader-Willi syndrome** (PWS) is characterized by severe hypotonia and feeding difficulties in early infancy, followed in later infancy or early childhood by excessive eating and, unless eating is externally controlled, gradual development of morbid obesity. All individuals have some degree of cognitive impairment. A distinctive behavioral phenotype (with temper tantrums, stubbornness, manipulative behavior, and obsessive-compulsive characteristics) is common. Hypogonadism is present in both males and females. PWS is caused by absence of the paternally derived PWS/AS region of chromosome 15 by one of several genetic mechanisms.The mainstay of diagnosis is DNA-based methylation testing to detect abnormal parent-specific imprinting within the Prader-Willi critical region (PWCR); this testing identifies more than 99% of affected individuals.
- **Angelman syndrome** (AS) is characterized by severe developmental delay or mental retardation, severe speech impairment, gait ataxia and/or tremulousness of the limbs, and a unique behavior with an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. Microcephaly and seizures are common. AS is caused by the loss of the maternally imprinted contribution in the 15q11.2-q13 (AS/PWS) region that can occur by one of at least five different known genetic mechanisms. Molecular genetic testing (methylation analysis and *UBE3A* sequence analysis) identifies alterations in about 90% of individuals.
- **Bardet-Biedl syndrome** (BBS) is characterized by cone-rod dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotrophic hypogonadism, complex female genitourinary malformations, and renal dysfunction. The visual prognosis for children with Bardet-Biedl syndrome is poor: night blindness is usually evident by age seven to eight years; the mean age at which affected individuals become legally blind is 15.5 years. Birth weight is usually normal, but significant weight gain begins within the first year and becomes a lifelong issue for most individuals. A majority of individuals have significant learning difficulties, but only a minority have severe impairment on IQ testing. Renal disease is a major cause of morbidity and mortality. The diagnosis of Bardet-Biedl syndrome is established by clinical findings. Nine genes are known to be associated with Bardet-Biedl syndrome. Inheritance is autosomal recessive, with some cases possibly caused by triallelic inheritance.
- **Cri-du-chat syndrome** (MIM 123450) is a multiple congenital anomaly syndrome involving microcephaly and a cat-like cry. It is caused by deletions of chromosome 5p.
- **Williams syndrome** (WS) is characterized by cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvular aortic stenosis, hypertension), distinctive facies, connective tissue abnormalities, mental retardation (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, and endocrine abnormalities (hypercalcemia, hypercalciuria,

hypothyroidism, and early puberty). Hypotonia and hyperextensible joints can result in delayed attainment of motor milestones. More than 99% of individuals with the clinical diagnosis of WS have a contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) encompassing the elastin *(ELN*) gene that can be detected using fluorescent in situ hybridization (FISH) or targeted mutation analysis. Inheritance is autosomal dominant; most cases are *de novo* occurrences.

- **Mirhosseini-Holmes-Walton syndrome** (MIM 268050) was described in 1972 in two brothers with pigmentary retinal degeneration, cataracts, microcephaly, severe mental retardation, hyperextensible joints, scoliosis, and arachnodactyly [Mirhosseini et al 1972]. It has been hypothesized that the disorder in this family is allelic to Cohen syndrome [Horn et al 2000].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Ophthalmologic evaluation to assess visual acuity and pigmentary retinopathy
- Hematologic evaluation including a white blood cell count with differential to identify neutropenia

Treatment of Manifestations

Ophthalmologic issues are among the most concerning for families of individuals with Cohen syndrome registered in the National Cohen Syndrome Database. Management includes the following:

- Spectacle correction of refractive errors
- Training as needed for the visually impaired
- Psychosocial support for affected individuals and their families

If neutropenia is documented, consideration should be given to the use of granulocyte-colony stimulating factor (G-CSF). In a study reported by Kivitie-Kallio et al (1997) response to adrenaline stimulation was subnormal in 12 of 14 individuals, and to hydrocortisone in eight of 16 individuals, but administration of recombinant G-CSF caused granulocytosis in all three individuals studied.

Recurrent infections should be treated per standard therapy; full immunologic evaluation should be considered.

Early intervention and physical, occupational, and speech therapyare appropriate to address gross developmental delay, hypotonia, joint hyperextensibility, and motor clumsiness.

Surveillance

Annual ophthalmologic evaluation should assess visual acuity, refractive error, and/or retinal dystrophy.

Repeat testing of white blood cell count with differential over time to identify intermittent neutropenia is indicated.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Anecdotal reports notwithstanding, pycnogenol, a standard French maritime pine bark extract effective in improving visual acuity in retinal vascular leakage conditions [Schonlau & Rohdewald 2001, Spadea & Balestrazzi 2001], has not been proven an effective treatment for the pigmentary retinopathy observe in Cohen syndrome.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Cohen syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with Cohen syndrome are obligate heterozygotes (carriers) for a disease-causing mutation in the *COH1* gene.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is clinically available once the disease-causing mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Cohen Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
VPS13B	8q22-q23	Vacuolar protein sorting 13B

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Cohen Syndrome

216550	COHEN SYNDROME; COH1
607817	COH1 GENE; COH1

Table C. Genomic Databases for Cohen Syndrome

Gene Symbol	Entrez Gene	HGMD
VPS13B	157680 (MIM No. 607817)	VPS13B

For a description of the genomic databases listed, click here.

Normal allelic variants: The longest *COH1(VPS13B)* transcript (14,093 bp) is widely expressed and is transcribed from 62 exons that span a genomic region of approximately 864 kb [Kolehmainen et al 2003]. *COH1* contains 66 exons, including four alternative exons; the translation start codon is in exon 2 [Velayos-Baeza et al 2004]. The *COH1* gene has a complicated pattern of alternative splicing that potentially leads to the use of four different

termination codons and to three additional in-frame, alternatively spliced forms [Kolehmainen et al 2003].

Pathologic allelic variants: Common founder mutations have been identified in the Old Order Amish and Finnish populations.

- The common mutation described in the Finnish population is homozygosity for c. 3348_3349delCT, seen in 75% of mutant alleles [Kolehmainen et al 2003].
- Affected individuals of Amish descent have been found to be homozygous for both a nonsense mutation involving a 1-bp insertion (c.9258_9259insT) and a missense mutation involving a c.8459T>C (p.I2820T) substitution [Falk et al 2004].

Extensive allelic heterogeneity has now been described in a wide range of ethnic and geographically distributed populations, with more than 40 novel mutations (mostly null alleles resulting from nonsense or frameshift mutations resulting in a premature stop codon) subsequently identified throughout *COH1* [Hennies et al 2004, Kolehmainen et al 2004, Mochida et al 2004]. Mutations resulting in altered splicing or in the deletion of one or more exons have also been described [Kolehmainen et al 2004]. While several missense mutations have been described in clinically affected individuals, the absence of a functional assay leaves the possibility that these represent rare non-pathogenic variants [Kolehmainen et al 2004]. No major mutational hotspot in individuals with Cohen syndrome of non-Finnish, non-Amish ancestry appears to exist [Hennies et al 2004].

The full-length splice form (exons 1-62) with the complete C-terminal VPS13 domain is essential for normal development and, when absent, results in classic Cohen syndrome [Kolehmainen et al 2004]. However, no clear genotype-phenotype correlation has been forthcoming.

Normal gene product: *COH1* encodes vacuolar protein sorting 13B (COH1), a putative transmembrane protein of 4,022 amino acids with a complex domain structure [Kolehmainen et al 2003]. The exact function of COH1 is unknown. Homology to the *Saccharomyces cerevisiae* VPS13 protein suggests a role for COH1 in intracellular vesicle-mediated sorting and protein transport [Kolehmainen et al 2003]. The complex domain structure of COH1 includes ten predicted transmembrane domains, a potential vacuolar targeting motif, an endoplasmic reticulum retention signal in the C terminus, and two peroxisomal matrix protein targeting signal-2 (PTS2) consensus sequences, one near the N terminus and the other near the C terminus [Kolehmainen et al 2003]. Various COH1 isoforms may have different functions within the cell. Velayos-Baeza et al (2004) described several alternative splicing variants, at least two transcripts of which are major forms.

Wide expression of *COH1* is seen on northern blot analysis in human tissues, with differential expression of different transcripts. Transcripts of approximately 2.0 and 5.0 kb are expressed in fetal brain, lung, liver, and kidney, and in all adult tissues analyzed. A transcript of approximately 12-14 kb is expressed in prostate, testis, ovary, and colon in the adult. Expression is very low in adult brain tissue [Kolehmainen et al 2003]. In contrast, expression analysis of the COH1 homologue (Coh1) in mouse brain shows it to be widely expressed in neurons of the postnatal brain but only expressed at low levels in the embryonic brain, suggesting that COH1 may be more important in neuronal differentiation than in proliferation [Mochida et al 2004]. The expression pattern was found by Velayos-Baeza et al (2004) to be ubiquitous, with some tissue-specific differences between several transcript variants.

Abnormal gene product: Eight of nine mutations initially identified in *COH1* were predicted to result in premature protein truncation. As the majority of mutant alleles in individuals with Cohen syndrome are null (nonsense or frameshift), the effects are predicted to be premature

protein truncation or mRNA instability. It is not known whether proteins encoded by mutated *COH1* are expressed or degraded. The mechanism by which premature protein truncation or mRNA instability results in the clinical manifestations of Cohen syndrome is not currently understood.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Macular Degeneration Support
The MD Support web site offers free information and personal assistance for people dealing with macular degeneration and similar retinal diseases
3600 Blue Ridge
Grandview MS 64030
Phone: 816-761-7080 (toll call)
Email: director@mdsupport.org
www.mdsupport.org

National Center on Birth Defects and Developmental Disabilities
Mental retardation

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Author Notes

Web site for Dr Wang: www.ddcclinic.org

Revision History

- 24 October 2006 (cd) Revision: sequence analysis of the entire coding region clinically available
- 29 August 2006 (me) Review posted to live Web site
- 18 April 2006 (mjf) Original submission