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NLM Citation: Wang H, Falk MJ, Wensel C, et al. Cohen Syndrome. 2006 Aug 29 [Updated 2016 Jul 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Cohen Syndrome

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Created: August 29, 2006; Updated: July 21, 2016.

Summary

Clinical characteristics

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

Diagnosis/testing

The diagnosis of Cohen syndrome is based on clinical findings, but no consensus diagnostic criteria exist. Identification of biallelic pathogenic variants in *VPS13B* (also known as *COH1*) on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Spectacle correction of refractive errors, low-vision 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 (G-CSF) for the treatment of neutropenia.

Surveillance: Annual ophthalmologic and hematologic evaluations; monitor growth and weight gain.

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Agents/circumstances to avoid: Caution should be used regarding medications with the potential to decrease the neutrophil count.

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). Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants have been identified in an affected family member.

Diagnosis

Suggestive Findings

Cohen syndrome **should be suspected** in individuals with the following findings [Chandler et al 2003a, Falk et al 2004, Kolehmainen et al 2004, Seifert et al 2006, El Chehadeh-Djebbar et al 2013]:

- Retinal dystrophy appearing by mid-childhood
- Progressive high myopia
- Acquired microcephaly
- Non-progressive intellectual disability and global developmental delay
- Hypotonia
- Joint hypermobility
- Typical Cohen syndrome facial gestalt: thick hair and eyebrows, long eyelashes, wave-shaped palpebral fissures, broad nasal tip, smooth or short philtrum, and hypotonic appearance
- Short stature
- Small or narrow hands and feet
- Truncal obesity appearing in or after mid-childhood
- Friendly disposition
- Neutropenia

Establishing the Diagnosis

The diagnosis of Cohen syndrome **is established** in a proband with at least six of the following eight cardinal features [Kolehmainen et al 2004] and/or by identification of biallelic pathogenic variants in *VPS13B* (*COH1*) on molecular genetic testing (see Table 1).

Cardinal features

- Retinal dystrophy and high myopia
- Microcephaly
- Developmental delay
- Joint hypermobility
- Typical Cohen syndrome facial gestalt
- Truncal obesity with slender extremities
- Overly sociable behavior
- Neutropenia

Molecular testing approaches can include the following:

- **Single-gene testing** begins with sequence analysis of *VPS13B* (*COH1*), followed by deletion/duplication analysis if only one or no pathogenic variant is found (see Table 1). Because of the high proportion of deletion and/or duplication alleles [Parri et al 2010, El Chehadeh-Djebbar et al 2011], it may be appropriate to perform sequence analysis and deletion/duplication analysis concurrently.
- **Targeted analysis** for pathogenic variants can be performed first in Old Order Amish or individuals of Finnish ancestry. Two founder pathogenic variants, c.8459T>C in exon 46 and 9258_9259insT in exon 51 have been identified in Old Order Amish. These variants are found *incis* and segregate together, so either may be used for targeted variant testing. A 2-bp deletion (c.3348_3349delCT) accounts for 75% of pathogenic alleles in Finland [Kolehmainen et al 2003]. Some individuals of Finnish ancestry heterozygous for this 2-bp deletion were found to have a multiexon deletion on the other *VPS13B* allele [Balikova et al 2009]; thus, deletion/duplication analysis may be appropriate for affected individuals with only a single detectable *VPS13B* pathogenic variant.
- **A multigene panel** that includes *VPS13B* and other genes of interest (see Differential Diagnosis) may also be used. 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

Table 1. Molecular Genetic Testing Used in Cohen Syndrome

Gene [1]	Test Method	Proportion of Probands with a Pathogenic Variant Detectable by This Method
VPS13B (*COH1*)	Targeted analysis for pathogenic variants • c.8459T>C or 9258_9259insT • c.3348_3349delCT	>99% in Old Order Amish [2] 75% of mutated alleles in Finland [3]
	Sequence analysis [4]	~70% [5]
	Gene targeted deletion/duplication analysis [6]	~30% [7]

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. H Weng, personal observation
3. Kolehmainen et al [2003]
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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.
5. Homozygous or compound heterozygous pathogenic variants are identified in approximately 70% of individuals with Cohen syndrome [Balikova et al 2009, Seifert et al 2009, El Chehadeh-Djebbar et al 2011].
6. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; methods used may include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
7. El Chehadeh-Djebbar et al [2011]

Clinical Characteristics

Clinical Description

Phenotypic features of Cohen syndrome among the more than 200 affected individuals reported to date are variable and include progressive retinochoroidal dystrophy and myopia, acquired microcephaly, developmental delay, hypotonia, joint laxity, characteristic facial features, truncal obesity, cheerful disposition, and neutropenia.

Note: Certain statistics presented here are from National Cohen Syndrome Database (NCSD) in which approximately 50% of individuals are Old Order Amish; the diagnosis of Cohen syndrome has been confirmed by molecular genetic testing in the vast majority of individuals.

Ophthalmologic. Individuals with Cohen syndrome had a first ophthalmologic visit and were prescribed their first pair of glasses at an average age of 4.5 years. Defective dark adaptation/night blindness (nyctalopia) 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, markedly progress in severity over time with many individuals developing a bull's eye maculopathy.

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 (iridodonesis) because of lens subluxation and/or microspherophakia.

More than 70% of individuals in the NCSD fall often or trip easily, most likely because of constriction of peripheral visual fields secondary to retinal degeneration. Among ten individuals from nine families of Italian heritage with Cohen syndrome, 90% had retinal dystrophy and 80% had high myopia [Katzaki et al 2007]. Twenty percent of individuals in the Greek cohort developed blindness [Douzgou & Petersen 2011, Douzgou et al 2011], although progression to complete blindness has not been reported in other ethnic groups to the authors' knowledge.

Other reported ophthalmic features include astigmatism, strabismus, microcornea, microphthalmia, sluggish pupillary reaction, iris atrophy and oval pupil, cataracts, optic atrophy, bull's-eye maculopathy, coloboma of the retina or lids, congenital ptosis, and exophthalmos [Taban et al 2007]. Corneal changes and early-onset cataracts are frequently observed in individuals of Greek ancestry, but not in other ethnic groups [Douzgou & Petersen 2011, Douzgou et al 2011]. A few individuals have developed retinal detachments [E Traboulsi, personal observation].

Microcephaly develops during the first year of life and continues into adulthood. Although 80% of mothers providing data to the NCSD 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 et al 2003a, Hennies et al 2004].

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 et al 2003a, Nye et al 2005]. Overall, children with Cohen syndrome attain developmental milestones at a rate slower than average (Table 2), and once achieved, psychomotor skills do not regress. 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 sibs [Horn et al 2000].

Table 2. Timing of Achievement of Developmental Milestones 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 et al [2003a]
3. Nye et al [2005]

Hypotonia. Half of mothers whose children are included in the NCSD recalled reduced fetal movement during an otherwise normal pregnancy. 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] and appears 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].

Joint laxity and additional musculoskeletal features including 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 et al 2003a].

Distinctive facial features have been described in different ethnic populations. Features include hypotonic facies, thick hair, low hairline, high-arched and wave-shaped eyelids, long and thick eyelashes, thick eyebrows, prominent nasal root, high and narrow palate, smooth or short philtrum, and prominent upper central incisors; the latter two together result in an open-mouth appearance. Lack of the frontonasal angle, together with a short philtrum, made the nose appear "overly long" in a cohort from Greece [Bugiani et al 2008]. Horn et al [2000] and Falk et al [2004] also found that although quite consistent among affected individuals within a particular ethnic group, facial gestalt appears to be inconsistent across ethnic populations. However, taking into consideration that reported individuals with Cohen syndrome are evaluated by different clinicians, the distinctive facial features that are shared by individuals from different ethnic backgrounds are fairly impressive. In fact, a significant number of parents in the NCSD noted distinct facial features in their children and discussed them with clinicians as the first clues leading to the late diagnosis of Cohen syndrome.

Systematic anthropometric and cephalometric analysis of 14 individuals confirmed microcephaly, short philtrum, forward-inclined upper incisors, and maxillary prognathia [Hurmerinta et al 2002]. Long-term evaluation of six individuals with Cohen syndrome from three consanguineous families showed that the clinical features are stable over time [Peeters et al 2008].

Endocrine and obesity. Children with Cohen syndrome tend to manifest failure to thrive in infancy and early childhood, but subsequently 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 noticeably decreased.

Among individuals in the NCSD, the prevalence of short stature is approximately 65% and delayed puberty 74%; clinical endocrinologic evaluations did not identify explanations for these findings. Adult height in six affected individuals from three families was at or below the 3rd centile, with body mass index (BMI) ranging from 20.1 to 30.8 [Peeters et al 2008]. A study of ten affected individuals from nine families ranging in age from five to 52 years found short stature in seven and truncal obesity in eight; BMI ranged from 21.8 to 32.2 [Katzaki et al 2007]. Extensive endocrine evaluations of pituitary, adrenal, and thyroid function in the cohort of Finnish descent showed no significant abnormalities [Kivitie-Kallio et al 1999a].

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 who had growth hormone deficiency displayed catch-up growth following initiation of growth hormone replacement therapy [Author, personal observation]. The prevalence of growth hormone deficiency in Cohen syndrome is unknown.

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 intellectual disability [Kivitie-Kallio et al 1999b, Chandler et al 2003b, 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 et al 1999b, Chandler et al 2003b, Karpf et al 2004]. Detailed psychometric and behavioral analyses did not identify any severe behavioral problems in six affected adults but confirmed a wide range of dysfunction related to individual degree of intellectual and visual disability [Peeters et al 2008].

Hematologic. Neutropenia, defined as an absolute neutrophil count (ANC) lower than 1,500/mm^3 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 affected individuals [Falk et al 2004] (see **Immunologic and rheumatologic**, following). 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 frank neutropenia. However, 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.

More than 65% of affected individuals experience repeated oral mucosal ulcers and gingival infections, prophylactic granulocyte colony-stimulating factor (G-CSF) therapy has been commonly used in these 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 hematologic malignancies have been reported.

Immunologic and rheumatologic. While neutropenia may contribute to the compromise of immune function in some individuals with Cohen syndrome, it is not clear if it is the sole cause of the dysfunction. 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 appears to correlate poorly with ANC; individuals with frequent infections have an ANC in the same range as those without increased infections (500-1,200/mm^3). 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 et al [2002] found rheumatoid arthritis in an individual with Cohen syndrome, and frequent uveitis and recurrent pericarditis have been seen in affected individuals [H Wang, personal observation].

Musculoskeletal. Individuals with Cohen syndrome have characteristic narrow hands and feet, and slender fingers that have frequently been falsely reported to be long. The fingers are in fact short, as shown by hand x-ray analysis of the metacarpophalangeal pattern [Kivitie-Kallio et al 1999a].

Neurologic. Seizures have been reported in a minority of individuals with Cohen syndrome [Coppola et al 2003, Atabek et al 2004]. Anecdotally, two individuals in the NCSD cohort with epilepsy requiring anticonvulsants have phenotypes at the more severe end of the Cohen syndrome spectrum, characterized by an 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 epileptiform foci [Kivitie-Kallio et al 1999b].

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

Electromyography is reported to be normal [Kivitie-Kallio et al 1999b].

Cardiovascular. The cardiovascular system is not commonly affected in individuals with Cohen syndrome. An earlier report of mitral valve prolapse in individuals with Cohen-like syndrome of Ashkenazi Jewish ancestry [Sack & Friedman 1980] (see Differential Diagnosis) may be referring to another syndrome. Cardiac evaluation in 22 individuals of Finnish descent identified decreased left ventricular function with advancing age but no evidence for clinically significant mitral valve prolapse [Kivitie-Kallio et al 1999a]. Of the approximately 20 individuals in the NCSD who have had echocardiograms, none showed evidence of mitral valve prolapse.

Other. A majority of infants with Cohen syndrome (95% of those of Amish ancestry and 65% of non-Amish) have an unusually high-pitched and weak cry. Overall, 80% of parents with children in the NCSD 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 cause the "mewing cry" seen in *cri-du-chat* syndrome have also been found in some individuals with Cohen syndrome [Chandler et al 2003a].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

Cohen et al [1973] described a pattern of abnormalities – intellectual deficiency, hypotonia, obesity, high nasal bridge, and prominent central incisors – observed in a pair of sibs and one unrelated individual.

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

Prevalence

About 200 individuals have been reported in the literature since the first description by Cohen et al [1973]. The disorder has 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, Katzaki et al 2007, Taban et al 2007, Bugiani et al 2008, Peeters et al 2008, Balikova et al 2009].

There is little doubt that Cohen syndrome is one of the more commonly underdiagnosed conditions. An early study by Rauch et al [2006] indicated that Cohen syndrome accounted for approximately 0.7% of 1070 individuals with unexplained developmental delay or intellectual disability, ranking it as the fifth most common diagnosis, immediately after fragile X syndrome (1.2%). A recent study of 2000 consecutive undiagnosed individuals who had undergone clinical exome sequencing identified two individuals with Cohen syndrome among 504 individuals who received a molecular diagnosis during the study [Yang et al 2014].

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 et al 2003a].

Cohen syndrome is overrepresented in the Amish population. 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 one in 500 and providing evidence for a founder effect.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *VPS13B*.

Differential Diagnosis

There are several disorders for which the phenotype may overlap with Cohen syndrome, particularly in the first year(s) of life. Individuals with Cohen syndrome are often suspected of having the following disorders:

- **Cohen-like syndrome** or "Jewish-type Cohen" was first reported in a cohort of individuals from Israel [Sack & Friedman 1986]. The concept has since been challenged [Chandler & Clayton-Smith 2002]. The originally reported 39 individuals of Jewish descent in 32 families were 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" or Cohen-like syndrome did not have neutropenia or chorioretinal dysplasia – manifestations that are found in all affected individuals of Finnish ancestry [Norio et al 1984]. In fact, no *VPS13B* pathogenic variants have been found in individuals with "Jewish-type Cohen" or Cohen-like syndrome [Kolehmainen et al 2004]; the authors therefore conclude that these individuals have a clinical and genetic etiology that is distinct from Cohen syndrome. It is notable that this historical mislabeling has caused significant confusion in the characterization of the Cohen syndrome phenotype.
- **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. Motor milestones and language development are delayed. 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 and manifests as genital hypoplasia, incomplete pubertal development, and, in most, infertility. PWS is caused by absence of the paternally

derived PWS/AS region of chromosome 15 by one of several genetic mechanisms. Individuals with PWS do not have retinal dystrophy. 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 intellectual disability, 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 retinal dystrophy, truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic 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; 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 demonstrate severe cognitive 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. Pathogenic variants in at least 19 genes are known to be associated with Bardet-Biedl syndrome. Inheritance is autosomal recessive.
- ***Cri-du-chat* syndrome** (OMIM 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, intellectual disability (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 *ELN*, the gene encoding elastin; the deletion can be detected using fluorescent in situ hybridization (FISH) or targeted analysis for pathogenic variants. Inheritance is autosomal dominant; most affected individuals have a *de novo* contiguous gene deletion.
- **Mirhosseini-Holmes-Walton syndrome** (OMIM 268050) was described in 1972 in two brothers with pigmentary retinal degeneration, cataracts, microcephaly, severe intellectual disability, 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 Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Cohen syndrome, the following evaluations are recommended:

- Ophthalmologic evaluation to assess visual acuity, position and size of the lens, refractive error, and severity of the retinal dystrophy
- Developmental assessment
- Hematologic evaluation including a white blood cell count with differential to identify neutropenia
- Consultation with a clinical geneticist and/or genetic counselor

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
- Low vision assessment with training as needed for the visually impaired
- Psychosocial support for affected individuals and their families

Early intervention and physical, occupational, and speech therapy are appropriate to address gross developmental delay, hypotonia, joint hypermobility, and motor clumsiness.

If neutropenia is documented, consideration may 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 and to hydrocortisone was subnormal in 12 of 14 individuals and in eight of 16 individuals, respectively. However, recombinant G-CSF, administered to three individuals in the study, caused granulocytosis in all three.

Recurrent infections should be treated per standard therapy.

Surveillance

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

Annual hematologic evaluation should include complete blood count and differential to assess neutropenia. More frequent monitoring may be needed for individuals with lower ANC or more frequent infections.

Growth and weight gain should be monitored.

Agents/Circumstances to Avoid

Caution should be used regarding medications with the potential to decrease the neutrophil count.

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 www.ClinicalTrialsRegister.eu 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.

Other

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

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. —ED.

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 (i.e., carriers of one *VPS13B* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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 of a *VPS13B* pathogenic variant is 2/3.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with Cohen syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *VPS13B*.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier of a *VPS13B* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *VPS13B* pathogenic variants in the family.

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.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *VPS13B* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

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.

- **Cohen Syndrome Association**

  The Cohen Syndrome Association was founded by parents to raise awareness of this disease with the goal of educating parents and professionals to assure earlier diagnosis and medical interventions.

  Email: info@cohen-syndrome.org

  www.cohensyndrome.org

- **National Neutropenia Network: North America Patient and Family Support Group**

  PO Box 1693

  Brighton MI 48116

  Phone: 877-326-7117

  Email: kate@neutropenianet.org

  www.neutropenianet.org

- **Neutropenia Support Association Inc.: Canada Patient and Family Support Group**

  971 Corydon Avenue

  P.O. Box 243

  Winnipeg Manitoba R3M 3SR

  Canada

  Phone: 204-489-8454; 800-663-8876 (within Canada and U.S.)

  Email: stevensl@neutropenia.ca

  www.neutropenia.ca

- **Macular Degeneration Support**

  Free information and personal assistance for people dealing with macular degeneration and similar retinal diseases

  3600 Blue Ridge Boulevard

  Grandview MO 64030

  Phone: 816-761-7080

  Email: director@mdsupport.org

  www.mdsupport.org

- **National Center on Birth Defects and Developmental Disabilities**

  Phone: 800-232-4636 (toll-free)

  Email: cdcinfo@cdc.gov

  Facts About Intellectual Disability

- **European Society for Immunodeficiencies (ESID) Registry**

  Dr. Gerhard Kindle

University Medical Center Freiburg Centre of Chronic Immunodeficiency
Engesserstr. 4
79106 Freiburg
Germany
Phone: 49-761-270-34450
Email: esid-registry@uniklinik-freiburg.de
ESID Registry

- **Severe Chronic Neutropenia International Registry: Australia, India, and Southeast Asia**
  St. Vincent's Hospital, Department of Medicine
  Fitzroy Victoria 3065
  Australia
  Phone: 61-3-9231-2574
  Email: ffirkin@bigpond.net.au
- **Severe Chronic Neutropenia International Registry: Europe, Africa, and Middle East**
  Carl-Neuberg-Str., 30625
  Hannover
  Germany
  Phone: 49-511-546-0918
  Fax: 49-511-557-106
  Email: zeidler.cornelia@mh-hannover.de
  Severe Chronic Neutropenia International Registry Hannover
- **Severe Chronic Neutropenia International Registry: North and South America**
  1107 Northeast 45th Street
  Suite 345
  Seattle WA 98105
  Phone: 206-543-9749; 800-726-4463 (within U.S.)
  Fax: 206-543-3668
  Email: bolyard@uw.edu
  Severe Chronic Neutropenia International Registry Seattle

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. Cohen Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

VPS13B	8q22.2	Vacuolar protein sorting-associated protein 13B	VPS13B	VPS13B

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 Cohen Syndrome (View All in OMIM)

216550	COHEN SYNDROME; COH1
607817	VACUOLAR PROTEIN SORTING 13 HOMOLOG B; VPS13B

Gene structure. The longest *VPS13B* transcript (NM_017890.4; 14,100 bp) is widely expressed and is transcribed from 62 exons that span a genomic region of approximately 864 kb [Kolehmainen et al 2003]. *VPS13B* contains 66 exons, including four alternative exons; the translation start codon is in exon 2 [Velayos-Baeza et al 2004]. *VPS13B* 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] (see **Normal gene product** and Table A, **Gene**).

Benign variants. While several missense variants have been described in clinically affected individuals, the absence of a functional assay leaves the possibility that these represent rare benign variants. Indeed, a large number of silent and missense amino acid changes detected in the coding region of *VPS13B* (18 of 114 reported *VPS13B* sequence variants) do not cause a Cohen syndrome phenotype [Kolehmainen et al 2004, Seifert et al 2009].

Pathogenic variants. Common founder pathogenic variants have been identified in the Finnish and Old Order Amish populations.

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

There is no evidence for a major mutational hot spot in individuals with Cohen syndrome who are of non-Finnish, non-Amish ancestry [Hennies et al 2004].

Extensive allelic heterogeneity has now been described in a wide range of ethnic and geographically distributed populations, with more than 100 novel pathogenic variants throughout *VPS13B* (primarily null alleles caused by nonsense or frameshift variants resulting in a premature stop codon, or intragenic deletion or duplication) subsequently identified [Hennies et al 2004, Kolehmainen et al 2004, Mochida et al 2004, Seifert et al 2006].

Altered splicing or deletion/duplication of *VPS13* exon(s) also results in pathogenic alleles [Kolehmainen et al 2004, Balikova et al 2009, Parri et al 2010]. Analyzing the data pooled from several different studies, El Chehadeh-Djebbar et al [2011] concluded that copy number variations including deletion and duplication may be detected in 33% of families with Cohen syndrome.

Deletions in *VPS13B* are postulated to result from non-homologous end-joining (NHEJ) due to sequence microhomology, small deletions and insertions at the junction, and the variation in size and affected region of deletions in affected individuals [Balikova et al 2009]. A higher frequency of LINEs, SINEs, and DNA repeat elements occurs in *VPS13B* in comparison to the average for autosomal sequences, and deletion breakpoints have mainly been found in interspersed repetitive sequences – predominantly in the sequence between introns 16 and 21 [Balikova et al 2009].

The full-length splice form (NM_017890.4, 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].

Table 3. Selected *VPS13B* (*COH1*) Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.3348_3349delCT	p.Cys1117PhefsTer8	NM_017890.4 NP_060360.3
c.8459T>C	p.Ile2820Thr	
c.9259dupT (9258_9259insT)	p.Leu3087PhefsTer20	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Normal gene product. *VPS13B* encodes vacuolar protein sorting 13B (VPS13B), a putative transmembrane protein of 4,022 amino acids with a complex domain structure [Kolehmainen et al 2003]. Homology to the *Saccharomyces cerevisiae* VPS13 protein suggests a role for VPS13B in intracellular vesicle-mediated sorting and protein transport [Kolehmainen et al 2003]. The complex domain structure of VPS13B 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 *VPS13B* 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. The full-length *VPS13B* transcript containing exon 28b now appears to be the major, ubiquitously expressed transcript in both humans and mice, although human brain and retina show differential splicing of exon 28 (NM_017890.3) [Seifert et al 2009]. Diagnostic testing should include exon 28b.

Wide expression of *VPS13B* is seen on northern blot analysis of 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 mouse ortholog (Coh1) in brain showed wide expression in neurons of the postnatal brain but only at low levels in the embryonic brain, suggesting that *VPS13B* 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.

Seifert et al [2011] demonstrated that VPS13B is a peripheral Golgi membrane protein that strongly colocalizes with the *cis*-Golgi protein GM130 and plays an essential role for Golgi integrity. Further studies showed that the VPS13B protein physically and functionally interacts with the small GTPase RAB6 at the Golgi complex, where depletion of VPS13B in primary neurons negatively interfered with neurite outgrowth [Seifert et al 2015].

As the Golgi complex is the place where glycosylation of newly synthesized proteins occurs, VPS13B deficiency could lead to glycosylation defects. Indeed, Duplomb et al [2014] demonstrated a very unusual pattern of glycosylation of the serum proteins in individuals with Cohen syndrome. This was characterized by a significant accumulation of agalactosylated fucosylated structures as well as asialylated fucosylated structures, although transferrin and α1-AT profiles (two liver-derived proteins) were normal. Intercellular cell adhesion molecule 1 and LAMP-2 (two highly glycosylated cellular proteins) were also found to have an altered migration profile on

SDS-PAGE in peripheral blood mononuclear cells from individuals with Cohen syndrome. These new findings may become a critical element in deciphering the pathogenic mechanisms of Cohen syndrome.

Abnormal gene product. The majority of *VPS13B* pathogenic variants detected to date result in a premature termination signal because of nonsense or deletion variants, although no mutational hot spot has been identified [Seifert et al 2009]. As the majority of mutated 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 *VPS13B* transcripts 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.

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Chapter Notes

Author Notes

Website for Dr Wang

Revision History

- 21 July 2016 (sw) Comprehensive update posted live
- 10 March 2011 (me) Comprehensive update posted live
- 24 October 2006 (cd) Revision: sequence analysis of the entire coding region clinically available
- 29 August 2006 (me) Review posted live
- 18 April 2006 (mjf) Original submission

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