CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2011: 79: 501–506
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CLINICAL GENETICS
doi: 10.1111/j.1399-0004.2011.01669.x

Review

Clinical variability of genetic isolates of Cohen syndrome

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Douzgou S, Petersen MB. Clinical variability of genetic isolates of Cohen syndrome.
Clin Genet 2011: 79: 501–506. © John Wiley & Sons A/S, 2011

Cohen syndrome (CS) (OMIM#216550) is an uncommon autosomal recessive developmental disorder that has been attributed to mutations in the *COH1* gene in at least 200 patients of diverse ethnic background so far. The clinical heterogeneity of CS is evident when comparing patients of different ethnic backgrounds, especially when evaluating specific system phenotypes separately, such as the ophthalmic and central nervous systems. We reviewed the available clinical data on CS cohorts of patients who share a founder effect and demonstrated that most features associated so far with CS are less than those always present in the patients who share a founder mutation thus representing clinical heterogeneity. Furthermore, there is a wide clinical variability of CS in the distinct founder mutation cohorts, the Finnish, Greek/Mediterranean, Amish and Irish travelers. The Greek/Mediterranean founder mutation is correlated to a CS phenotype characterized by specific and persistent skeletal features, corneal changes, periodontal disease, a distinct neurocognitive phenotype for the high recurrence of autism and non-verbal communication and inconstant microcephaly.

Conflict of interest

The authors do not report any conflict of interest.

Key words: clinical variability – *COH1* – Cohen syndrome – founder mutation – genetic isolate – mental retardation – migration

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Received 14 January 2011, revised and accepted for publication 15 March 2011

Cohen syndrome (CS) (OMIM#216550) is an uncommon autosomal recessive developmental disorder with a definite yet variable clinical phenotype. It has been attributed to mutations in the *COH1* gene in at least 200 patients of diverse ethnic background so far(1–10). The assessment of 29 Finnish patients with a highly homogeneous clinical picture led to the first design of the major features of CS, (i) mental retardation and microcephaly; (ii) typical facial features; (iii) neutropenia (neutrophil count $<1.5 \times 10^9$/l); (iv) pigmentary retinopathy and myopia and (v) hypotonia and joint hyperextensibility (11). Fifteen of the Finnish patients presented also an increased diameter of the body of the corpus callosum. The central nervous system phenotype in patients with CS was further enriched by the magnetic resonance imaging (MRI) finding of cerebellar hypoplasia, in patients of non-Finnish descent (5, 12, 13).

The demarcation of a homogeneous Finnish phenotype opposite to a wide clinical variability of extra-Finnish patients was followed by a lively debate on the diagnostic criteria of CS in ethnically diverse groups (1–4, 11, 14). This led to a revision of the diagnostic guidelines to formulate that significant learning difficulties should be accompanied with at least two of the following features: typical facial gestalt, pigmentary retinopathy or neutropenia (14).

The clinical heterogeneity of CS is evident when comparing patients of different ethnic backgrounds, especially on separate evaluation of specific system phenotypes, such as the ophthalmic

and central nervous systems (13, 15, 16). We review the available clinical data on CS patients who share a founder effect in an attempt to better define the syndrome's clinical variability and the Greek founder mutation phenotype.

Genetic isolates of CS

Cohen syndrome was part of the Finnish Disease Heritage, a group of rare hereditary diseases that are overrepresented in Finland, because of the distinguishing population structure in genetic isolates. The random inbreeding of distantly consanguineous couples clustered regionally the incidence of CS (17–20). The exceptional Finnish population structure provided the basis for linkage and haplotype analysis that permitted to map the *COH1* gene in the chromosomal region 8q22-8q23. The Finnish founder mutation was a 2-bp deletion (c.3348_3349delCT) resulting in a frameshift at codon 1117 and a stop that leads to protein truncation at codon 1124 (1).

In 2004, eight children with CS were reported, descendants of two extended Amish kindreds originating in northeast Ohio who were connected through marriage. The homogeneous clinical phenotype and, subsequently, the molecular analysis of the *COH1* gene confirmed the founder effect of the mutation in this population of known, increased coefficient of inbreeding. The two American Amish patients with CS among the kindreds were homozygous for the missense mutation c.8459T→C in exon 46 that is presumed to be a null mutation (15).

Cohen syndrome is also frequently observed among Irish travelers, a small minority group of <1% of the total Irish population. This nomadic population has remained isolated for many years, practicing consanguineous marriages, raising the prevalence of CS, among other autosomal recessive disorders, to an estimated 0.5 per 1000 children. The recurrent Irish traveler mutation is the presumably null mutation c.4471G>T in exon 29 of the *COH1* gene (21).

Bugiani et al. (6) reported 14 Greek patients with a homozygous intragenic *COH1* deletion. A 1-bp deletion (c.11564delA) results in a frameshift (p.Y3855fsX22) that leads to the deletion of exons 6–16. The patients originated from two small neighboring islands of the eastern Greek archipelago with a total population count of 1469, according to the 2001 Greek census. Most of the affected individuals descend from consanguineous marriages among the offspring of a common Cretan ancestor. Even younger generations follow local tradition that privileges inbreeding with a subsequent raise of CS's incidence in these islands to ~1/110.

The 'Greek deletion' was also identified in two families from Central Italy and one in Southern Italy. Haplotype analysis suggested that the recurrent deletion was probably due to an ancestral founder effect in the Mediterranean area (5, 10). In fact, Greek migration to Italy and especially, southern Italy, is a social phenomenon that has been described starting from the 8th and 7th centuries BC up to the 16th and 17th centuries, because of various reasons, including demographic crisis or commerce (22, 23).

Phenotypic comparison

We compared available clinical findings of Cohen patient cohorts of different ethnic backgrounds that share a homozygous mutation because of a founder effect enhanced by multiple consanguineous marriages (6, 15, 16, 21, 24). Although there are no available data concerning the 15 homozygous Finnish patients, given their clinical homogeneity, we utilized the data available from the 2001 study of Kivitie-Kallio and Norio (1, 11). The following data were extracted with the limitation that the CS patients among Amish and Irish travelers reported were of a younger, pre-pubertal age range, with respect to the more numerous, Finnish and Greek cohorts (Table 1).

Growth and head circumference

The most constant deficiencies in all cohorts are the short stature and the postnatal microcephaly. The first feature is neither specific for the Finnish that present it in less than half of the cases nor the Greeks, affected in a slightly higher percentage, but seems characteristic in the patients among Amish and Irish travelers who could however present a later stature recovery, given their younger age. The microcephaly is a specific feature in all cohorts except the Greeks, 7% of whom were normocephalic. Given that 75% of the Amish, 62% of the Finnish and one Greek patient out of the two with available prenatal history were born small for gestational age, this could suggest a prenatal onset of the growth deficiency. The truncal obesity, a characteristic feature of the first report of CS is not constant in any isolate, yet seems quite specific in the Irish travelers' childhood phenotype. It would be interesting to evaluate pubertal onset in the Amish and Irish patients given the discrepancy of its prevalence in the other two isolates.

Table 1. Comparison of Cohen syndrome phenotypes correlated to founder mutations

	Finnish (%)	Greek/Mediterranean (%)	Amish (%)	Irish travelers (%)
Mutation	c.3348_3349delCT	c.11564delA	c.8459T→C	c.4471G→T
Number of patients	$n = 15$[a]	$n = 15$[b]	$n = 8$[c]	$n = 5$[d]
Age range (years)	0.9–57	11–57	4–15	2–9
Sex	na	5F/10M	6F/2M	3F/2M
Growth				
Low birth weight	62	1/2 known	75	na
Feeding difficulties/failure to thrive	75/100	na	na/37.5	100/100
Truncal obesity	17	53	37.5	80
Delayed puberty	77	13	na	na
Short stature	41	60	100	100
Microcephaly, postnatal	100	93	100	100
Neurocognitive				
Reduced fetal activity	50	na	12.5	na
Hypotonia	100	na	100	na
Moderate-to-severe intellectual impairment	100	100	100	100
Nonverbal/speech delay	−/100	50/100	33/100	40/60
Friendly personality	100	13	75	100
Autistic features	–	93	25	50
Brisk reflexes	79	78.5	–	–
Seizures	–	–	13	–
Intracranial abnormalities	100	na	na	na
Motor and myoskeletal				
Motor delay	100	100	100	100
Poor motor coordination or clumsiness	100	–	–	100
Slender extremities and/or tapered fingers	97	100	100	60
Joint hypermobility	100	100	100	–
Sandal gap	82	100	–	–
Joint valgism (cubitus/genu/pes)	89	–	–	–
Kyphosis/scoliosis	69	100	–	–
Pectus carinatum	–	100	–	–
Ophthalmic				
Myopia	82	100	100	–
Progressive retinopathy	90	83	100	80
Corneal changes	–	100	–	–
Lens opacities/cataract/glaucoma	60	86	25	–
Blindness	–	20	–	–
Strabismus	77	60	25	–
Neutropenia	100	3/5 tested	2/2 tested	60
Periodontal disease/aphthous ulcers	100	100	25	–
Recurrent infections	–	na	50	80
Miscellaneous				
Neonatal complications	–	na	50	na
High-pitched voice	68	–	–	–
Cardiac murmur	24	–	–	–
Insulin-dependent diabetes mellitus	–	+	–	–
Cutaneous signs	–	–	Doughy skin	–
Premature aging	+	47	–	–
Tooth loss	–	100 over 30 years	–	–
Atypical facial findings	–	+	+	+

F, female; M, male; na, not available; +, present (unknown percentages); −, absent.
[a]Kivitie-Kallio et al. (24), Kivitie-Kallio and Norio (11) and Kolehmainen et al. (1).
[b]Bugiani et al. (6) and Douzgou et al. (16).
[c]Falk et al. (15).
[d]Murphy et al. (21).

Neurocognitive features

Moderate-to-severe intellectual impairment is the most constant feature and referral reason. In the Finnish CS patients it is associated with a similarly constant speech delay that, nonetheless, never leads to a complete absence of speech, and to a friendly personality. The Greeks present the constant association to speech delay too but half of the patients remain non-verbal. Moreover, they also present quite constant features of the autistic spectrum disorder. We observed this association in Greek patients who live under different conditions, both in and outside the islands, suggesting a non-environmental cause of this behavioral pattern. Only two Greek CS patients, male and female, presented a friendly disposition. The male patient has a mild mental retardation but manifested repetitive movements, speaks with short sentences and is hyperkinetic. The female patient, much older, is severely retarded and presents the autistic rocking. Autistic features are present, in decreasing frequencies, in the Irish travelers and also Amish children with CS. As a result, the diagnostic feature of mental retardation is associated, in each isolate, to an otherwise distinct neurocognitive and behavioral phenotype.

Motor and myoskeletal

Motor delay is the second diagnostic feature present in all patients of the four cohorts. The patients that belong to the Finnish and Greek cohorts present a richer skeletal phenotype, characterized by slender extremities and/or tapered fingers, joint hypermobility, sandal gap and spinal curvature anomalies that in the case of the Greeks are constant for all the features reported. Nevertheless, an Amish and Irish skeletal phenotype could develop with time, as an age-related consequence of the frequently present hypotonia. Pectus carinatum is a constant feature, of only the Greek cohort. Joint hypermobility is probably a constant feature but not at all reported in the patients among Irish travelers.

Ophthalmic

The comparison of the ophthalmic phenotype of the CS genetic isolates discloses that myopia and pigmentary retinopathy are the most represented features. They are not reported constantly in all groups, probably for their progressive, age-related nature. It would be interesting to investigate the presence of corneal changes, a constant feature of the Greek cohort as previously reported, in the Amish and Irish traveler cohorts too, as it is not present in the Finnish cohort (16, 24). Cataracts seem to recur among the Amish too, even at the young age range of the patients studied. Most importantly, 20% of the patients in Greek cohort develop blindness, a feature not noted in the other groups.

Neutropenia

Testing for the intermittent neutropenia observed in CS patients has proved a difficult task in the context of genetic isolates, for geographic or cultural limitations. Yet, the neutropenia's possible sequelae have been clinically observed in all populations. Most frequently, the oral region is affected, yet it is striking that one of the main referral reasons for the children with CS among the Irish travelers are the recurrent infections of the upper or lower respiratory tract (21).

Miscellaneous

Various separate findings have been described in each CS isolate. The Amish cohort neonatal phenotype is characterized, in 50% of the cases, by neonatal complications, such as respiratory distress syndrome, jaundice and acidosis (15). A high-pitched voice and an age-related decrease of the left ventricular function have been recurrently reported only in the Finnish (11). The insulin-dependent diabetes mellitus and the seizures reported in two and one patient of the Greek and Amish cohort, respectively, could represent a random association, given their high frequency in the general pediatric population. The tooth loss of all the Greek cohort patients after the age of 30 could be a consequence of the inappropriate dental follow-up to their constant periodontal disease. Premature aging is, on the other hand, a common finding in the Finnish and in quite the half Greek cohort patients and would be interesting to follow up in the other cohorts too.

Facial characteristics

Taking into consideration that the comparison of facial findings evaluated by distinct professionals, in the context of different ethnic backgrounds, is subject to bias of interpretation, the down-slanting palpebral fissures and a short philtrum that does not cover the front teeth, giving an open-mouth expression with prominent incisors, as reported in the initial Cohen's description (25) have been observed in all isolates. Differential facial findings have been described in all cohorts. Falk et al. report, in the Amish, synophrys and a low nasal

bridge with a pinched root and bulbous nasal tip, although there were no photos available (15). Two of the children with CS among Irish travelers did not present the gestalt (21). The CS patients in Greek cohort and the Italian patient with the founder mutation present a characteristic loss of the fronto-nasal angle (6, 10). In the Greek cohort, this feature was also noted in heterozygotes.

Discussion

Clinical heterogeneity and variability

Table 1 shows that most features associated so far with CS are less than those always present in the patients who share a founder mutation, demonstrating clinical heterogeneity. Furthermore, the clinical variability of CS in distinct founder mutation cohorts is evident, despite the differences in the population characteristics and in the availability of data. The Finnish phenotype is characterized by a constant, specific, neurocognitive, motor and behavioral profile in association with a less constant yet extended, skeletal phenotype, a quite constant, severe involvement of mainly the posterior eye segment and neutropenia with oral consequences. Diversely, the Greek/Mediterranean CS cohort phenotype is characterized by a similarly constant yet distinct neurocognitive phenotype for the high recurrence of autism, specific and persistent skeletal features, a severe ophthalmic phenotype that constantly involves both the anterior and posterior segment, and periodontal disease. The Amish founder mutation phenotype is characterized by more constant growth deficiencies, neurocognitive, motor, myoskeletal and ophthalmologic profiles that are more similar to the Greek one but for the lower prevalence of autism and is distinguished by the frequent, neonatal complications and infections. The Irish travelers' phenotype is the one characterized by the most constant growth deficiencies in association with a neurocognitive profile that comprises the non-verbal outcome and the autistic features of the Greek cohort along with the friendly personality observed in the Finnish cohort and is distinguished by the quite constant presentation of recurrent infections in a child with poor growth, developmental delay and neutropenia.

Clinical management and follow-up

The genetic heterogeneity observed implies that a differential management and follow-up of patients with CS should be adopted, on the basis of their ethnic background. The clinical strategy designed for the characteristics of the Finnish CS cohort would not have been feasible in the geographic and cultural background of the other founder mutation cohorts (11). Murphy et al. (21) consider *COH1* molecular analysis in any child from the Irish travelers' isolate with developmental delay and microcephaly.

In the case with a Mediterranean origin, we propose ophthalmologic evaluation, comprised of pachymetry measurement, for children who manifest psychomotor retardation with speech delay and autistic features, with the CS slender extremities and/or tapered fingers, joint hypermobility, sandal gap and typical gestalt. We recommend MLPA analysis of the *COH1* gene only when all of the above are positive given the distinct and quite constant founder mutation Mediterranean phenotype. In the case of adults, the same test could be provided to mentally retarded patients with the full-blown skeletal and ophthalmologic phenotype described in Table 1. MRI of the brain at all ages could evidence a central nervous system phenotype not investigated so far. The care for the patient of a founder Mediterranean origin with CS should include an early activation of measures for the autism, lack of speech, spinal curvature anomalies and ophthalmic problems.

Differential diagnosis

Bardet–Biedl (MIM 209900), Alstrom (MIM 203800), MORM (MIM 610156), Prader–Willi (MIM 176270) and monosomy 1p36 syndromes are frequently considered differentially with CS (26–28). The diagnosis could be especially difficult in very young children or neonates that have not yet manifested the full-blown CS phenotype. Bardet–Biedl syndrome can be excluded in a child of Mediterranean origin with psychomotor retardation, speech delay, obesity and vision problems in the absence of renal problems, hypogenitalism in males and if at a very young age, in the absence of radiographic evidence of polydactyly. Patients with Alstrom syndrome manifest nystagmus, not reported in those with CS. The absence of the CS gestalt or microcephaly could exclude MORM whereas the differential diagnosis with 1p36 monosomy syndrome relies on the absence of the CS gestalt. Prader–Willi syndrome could be excluded in the absence of ophthalmologic problems.

Genotype–phenotype correlation

No genotype–phenotype correlation has been proved so far in CS. The present study confirms this conclusion given the clinical heterogeneity noted among patients who share the same founder

mutation. The founder mutations comprised in the present study are all null mutations, two because of frameshifts (Finnish and Mediterranean) and two because of missense changes (Amish and Irish). All of them result in the truncation of the final protein probably causing non-functional protein or the transcript to be subjected to nonsense-mediated mRNA decay (1, 6, 15, 21). However, this study confirms a correlation of a specific CS phenotype characterized by the constant presence of specific skeletal features, corneal changes and periodontal disease, a high risk for autism and non-verbal communication and a lower risk for microcephaly, with the Mediterranean founder mutation.

Conclusions

This review has demonstrated the clinical heterogeneity and variability of CS in cohorts of patients distinguished by a common founder mutation and further delineated the Mediterranean ancestral mutation CS phenotype.

Acknowledgements

We would like to thank the families who agreed to take part in the study and the many colleagues from the Institute of Child Health who have participated in this work through the years.

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