ORIGINAL ARTICLE

Diagnostic criteria, clinical characteristics, and natural history of Cohen syndrome

K E Chandler, A Kidd, L Al-Gazali, J Kolehmainen, A-E Lehesjoki, G C M Black, J Clayton-Smith

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Correspondence to:
Dr K E Chandler,
Academic Unit of Medical Genetics and Regional Genetics Service, St Mary's Hospital, Hathersage Road, Manchester, UK;
katec@central.cmht.nwest.nhs.uk

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Cohen syndrome is a rare, recessively inherited condition associated with facial dysmorphism, developmental delay, and visual disability. A delay in making the diagnosis commonly occurs, contributed to by the lack of a definitive molecular test and the clinical variability of published case reports. A specific clinical phenotype has been delineated in a homogeneous cohort of Finnish Cohen syndrome patients, but the applicability of their diagnostic criteria to non-Finnish patients has been debated. Detailed delineation of Cohen syndrome in patients from outside Finland is therefore warranted. We report on the clinical features of 33 non-Finnish Cohen syndrome patients. Variability within the clinical spectrum is identified and the natural history of Cohen syndrome described. Diagnostic guidelines for facilitating accurate and early diagnosis are discussed. Results from molecular genetic analysis using markers located within the previously mapped COH1 critical region support allelic but not genetic heterogeneity in this UK cohort.

Cohen syndrome was first described in 1973 by Cohen *et al*[1] when they reported three children with a characteristic facial appearance in association with mental retardation, hypotonia, joint laxity, obesity of mid-childhood onset, and ocular anomalies. Since then, over 100 cases have been reported world wide.[2–22]

In 1984, reporting on a small group of Finnish patients, Norio *et al*[23] extended the characterisation of Cohen syndrome to include microcephaly, neutropenia, and specific ophthalmic abnormalities, namely high myopia and retinal dystrophy. Consanguinity in the reported families provided support for an autosomal recessive pattern of inheritance. Subsequent delineation of a cohort of 29 Finnish patients showed a highly homogeneous clinical phenotype with consistent ophthalmological and haematological abnormalities.[24–29] In the same cohort, molecular genetic analysis identified a single major locus for the Cohen syndrome gene, COH1, on the long arm of chromosome 8.[30] Haplotype analysis indicated a strong founder effect with a common ancestral mutation accounting for the majority of Finnish patients.[31]

Greater clinical variability is observed in case reports of Cohen syndrome from outside Finland and it has been proposed that the Finnish patient phenotype may be particular to Finland.[12] To date, no other large cohort of Cohen syndrome patients has been well delineated. We therefore determined to ascertain a large group of patients with Cohen syndrome from across the UK and assess their dysmorphic, ophthalmological, haematological, behavioural, and cognitive features. Intra- and interfamilial variability within the clinical spectrum were investigated and the natural history of Cohen syndrome delineated. In addition, molecular genetic analysis was undertaken using genetic markers located within the COH1 critical region at 8q22-23 in 11 of the Cohen syndrome families.

MATERIALS AND METHODS

Clinical analysis

Over a two year period (1999-2001), 33 patients with Cohen syndrome were ascertained through clinical geneticists and via the Cohen syndrome support group. Careful clinical assessment was carried out on all patients by the author or one of the co-authors. This entailed a full clinical history, physical examination, and review of the medical records. Venous blood was collected to determine the patient's neutrophil count. Neutropenia was defined as a neutrophil count less than 1.50×10^{-9}/mm^3. Detailed ophthalmic assessment, including electrodiagnostic tests, was performed by the patient's local ophthalmologist and previous ophthalmic notes reviewed. Formal psychometric assessment of the patient was carried out by a trained clinical psychologist (MM). Three psychometric assessments, designed for use with children/adults with learning difficulties, were applied. Testing was performed in the home environment, so only families within a reasonable travelling distance were invited to take part. Of these, 16 Cohen syndrome patients (eight male, eight female) agreed to be assessed.

The diagnosis of Cohen syndrome was based on the presence of the following typical clinical features, as originally reported by Cohen *et al*[1] and further delineated by Norio *et al*[23]: mental retardation, microcephaly, characteristic facial appearance (downward slanting and wave shaped palpebral fissures, prominent nose and short and upturned philtrum with an open mouthed expression), slim, tapering extremities with relative truncal obesity in the mid-childhood years, hypotonia, joint laxity, neutropenia, ophthalmic abnormalities, namely myopia and/or pigmentary retinopathy.

In order that the full phenotypic spectrum of Cohen syndrome might be seen, clinical variability was allowed for within the patient cohort. Therefore, 75% of the features were deemed necessary for the diagnosis as some were age dependent (for example, truncal obesity, retinopathy) or intermittent (for example, neutropenia).

Molecular analysis

Molecular genetic analysis was undertaken in 18 study patients and members of their families on whom DNA was available. The 11 families investigated comprised one consanguineous family of three affected sibs and no unaffected sibs, three families of two affected children with no unaffected sibs (including one consanguineous family), two families of two affected children with unaffected sibs, and five families with one affected child and one or two unaffected sibs (fig 1).

Eight polymorphic genetic markers, spanning the COH1 critical region, were analysed. Five of them (D8S1778, D8S559,

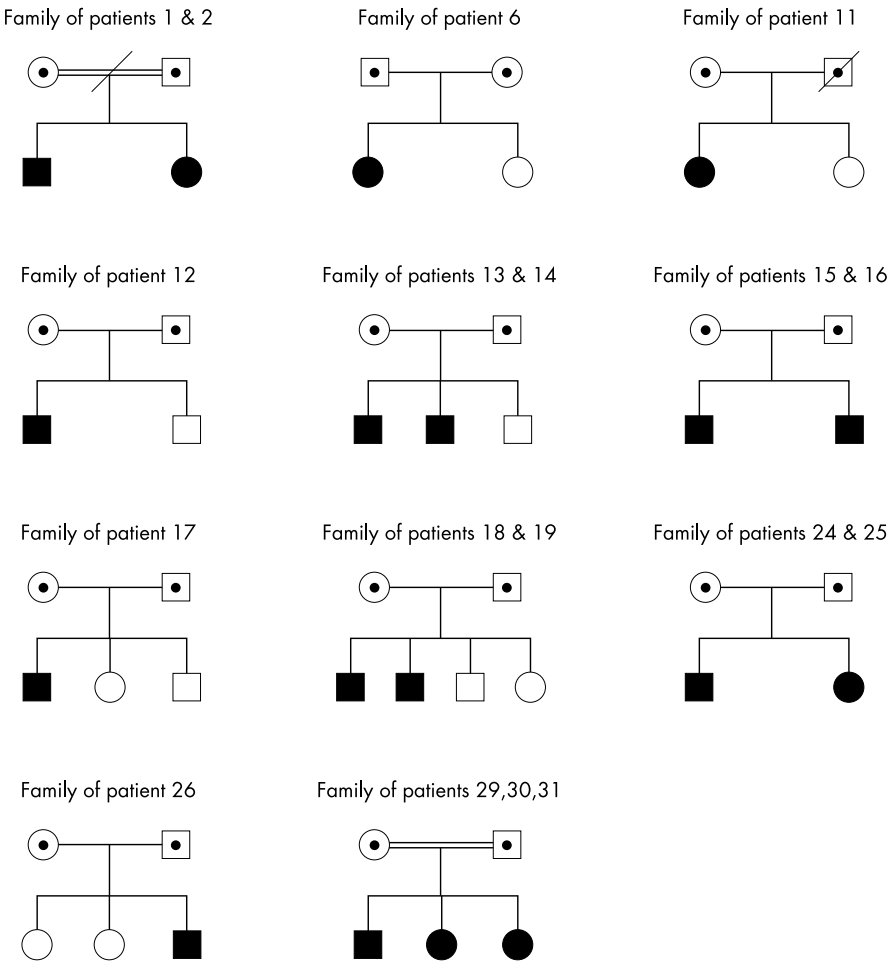

Figure 1 Family pedigrees of 11 Cohen syndrome families in whom molecular genetic investigations were possible.

Table 1 Primer pair sequences and PCR running conditions for genetic markers analysed

Locus	Primer ID	Primer sequence (5′-3′)	Primer annealing temperature (°C)
D8S1778	AFMb327yh1	F:ttttgcaggagggcgtcta R:ccactgagcccagcctatta	60
D8S559	AFM352td9	F:aattgaagtgaggtaggaggttg R:agctattgctcttacaggaggg	61.5
D8S1762	AFMb307xb5	F:gtgtaatccagttccccag R:ttgctgtaaacctttggc	55
	CA1	F:agagccaacctcccaaaact R:gctcatatttaaacaccactcgg	62
	CA2	F:cagtgtcctggctaccatgt R:atggcctaccctgtgattgt	59
	CA3	F:ccaagagaaacatactcattacca R:aagaaagagcaaaaagggca	59
D8S1714	AFMa1842zg5	F:cccttgccagagccat R:ccactgacgccctgat	60
D8S521	AFM078za9	F:tttgaaatcctacagagttcct R:ctgttaatgaatgcggtgtc	60

D8S1762, D8S521, D8S1714) were published microsatellite markers from Généthon. An additional three unpublished markers were designed and provided by the research group in Helsinki, (labelled CA1, CA2, and CA3). At the time of genetic investigations, the working order of the eight markers analysed was as shown in fig 2.

PCR amplification was performed with each marker using standardised methods. DNA (40 ng) was suspended in a 20 µl reaction containing 5 pmol of each forward and reverse primer, 0.75 mmol/l dATP, dGTP, dCTP, dTTP, 67 mmol/l Tris-HCl (pH 8.0), 3.7 mmol/l $MgCl_2$, 6.7 µmol/l EDTA, 16 mmol/l $(NH_4)_2SO_4$, 0.085 mg/ml BSA, and 0.1 units of *Taq* DNA polymerase. Samples were processed through 30 cycles of amplification consisting of 45 seconds at 94°C (denaturation), 45 seconds at optimum annealing temperature (table 1), and one minute at 72°C (extension). The final extension step was

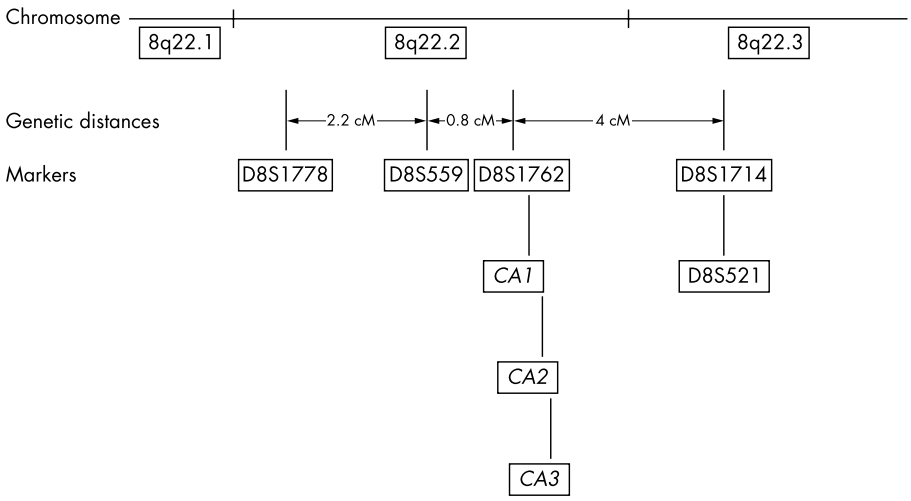

Figure 2 Map of chromosome 8q22 markers and genetic distances.

Table 2 Clinical features of a cohort of 33 patients with Cohen syndrome

Patient	Age at assessment (y)	Sex	Ethnic origin	OFC centile	Height centile	Weight centile	Body Mass Index centile	Neutrophil count ($\times 10^{-9}$/mm^3)	Myopia	Retinopathy
*1	16	F	Arabic	<<0.4	<<0.4	<0.4	25	2.2	Low	Y
*2	15	M	Arabic	0.4	0.4	25	75	1.7	Low	Y
3	15	M	UK	<<0.4	0.4	25	91	1.1	High	Y
4	7	M	UK	<<0.4	25	25	>25	2.0	High	Y
5	7	F	UK	0.4	25	75	>91	1.2	High	Y
6	16	F	UK	<<0.4	<<0.4	5	>50	0.7	Low	Y
7	7	F	UK	<<0.4	<0.4	3	75	0.6	Low	Y
8	4	F	UK	10	10	75	>91	0.3	High	Y
9	21	F	UK	<3	0.4	>90	>98	0.5	High	Y
10	3	F	UK	<<0.4	<3	<3	25	0.7	High	Y
11	46	F	UK	<3	10	90	>91	0.6	High	Y
12	17	M	UK	<3	<<0.4	0.4	–	<1.5	Y	Y
13	7	M	UK	<<0.4	3	10	>50	0.9	High	Y
14	6	M	UK	<<0.4	10	25	>91	0.6	High	Y
15	9	M	UK	0.4	25	75	75	–	Y	Y
16	15	M	UK	3	25	75	>91	0.7	High	Y
17	18	M	UK	<0.4	25	>90	>91	1.1	High	Y
18	26	M	Dutch	<3	<3	10	50	0.7	High	Y
19	32	M	Dutch	25	10	>90	>98	0.9	High	Y
20	5	M	UK	0.4	0.4	25	>91	0.6	Low	Y
*21	28	F	UK	0.4	0.4	98	>98	1.1	Y	–
*22	15	F	UK	0.4	10	75	91	1.8	High	–
*23	22	F	UK	0.4	0.4	25	50	1.4	Y	–
24	3	M	UK	<0.4	0.4	10	>75	<1.5	Y	Y
25	4	F	UK	0.4	0.4	50	>98	<1.5	High	Y
26	15	M	UK	3	0.4	10	>75	0.8	High	Y
27	15	F	UK	<3	0.4	25	>75	0.9	Low	Y
28	8	F	UK	<3	0.4	25	>75	0.5	N	Y
*29	6	F	Arabic	–	<3	50	>91	Normal	High	Y
*30	10	F	Arabic	–	10	50	>75	Normal	High	Y
*31	12	M	Arabic	10	10	75	>75	Normal	High	Y
32	42	M	UK	<3	<0.4	75	>98	0.7	High	Y
33	34	M	UK	0.4	<<0.4	50	>98	0.6	Y	Y

*Patients are from a known consanguineous family.

lengthened to 10 minutes. After PCR amplification, products were extracted with one volume of phenol/chloroform and mixed with one volume of sucrose loading dye before loading on 8% non-denaturing acrylamide/bisacrylamide gels. Gels were subjected to electrophoresis at 400 volts for two to three hours in 1 × TBE running buffer at room temperature. Following electrophoresis, gels were silver stained using standard methodology.[32]

RESULTS

The cohort of Cohen syndrome patients consisted of 33 patients from 22 families. These comprised two consanguineous families of three affected children, seven sets of sib pairs (one consanguineous), nine singly affected from within a family, and four only children. The male to female ratio was 17:16. The patients' ages ranged from 3 to 46 years. The median age at diagnosis of Cohen syndrome was 8 years, (range 2-34 years). Salient clinical features are summarised in table 2.

Pregnancy and the neonatal period

A normal pregnancy was reported in most cases, (23/33, 70%). Two pregnancies were investigated because of raised alpha-fetoprotein on serum screening but no abnormalities were

Table 3 Developmental progress in a cohort of 33 patients with Cohen syndrome

Patient	Age at assessment	Age sat unsupported	Age first walked	Age of first words	Age spoke in sentences	Degree of learning difficulties
1	16 y	12 mth	3 y	2 y	6 y	Severe
2	15 y	–	3 y	2 y	6 y	Severe
3	15 y	18 mth	2.5 y	2.5 y	4 y	Severe
4	7 y	12 mth	2 y	No speech	No speech	Severe
5	7 y	10 mth	1.5 y	2 y	6 y	Severe
6	16 y	18 mth	2.5 y	3 y	5 y	Severe
7	7 y	18 mth	4.5 y	3.5 y	7.5 y	Moderate
8	4 y	12 mth	3 y	3 y	Not yet (4 y)	Moderate
9	21 y	7 mth	1 y	2 y	2.5 y	Moderate
10	3 y	12 mth	3 y	3 y	Not yet (3 y)	Severe
11	46 y	9 mth	2.5 y	>8 y	Single words only	Profound
12	17 y	8 mth	1.5 y	1 y	8 y	Severe
13	7 y	10 mth	3 y	4 y	6 y	Severe
14	6 y	9 mth	1.5 y	2.5 y	Not yet (6 y)	Severe
15	9 y	9 mth	2 y	2 y	Single words only (9 y)	Profound
16	15 y	18 mth	4.5 y	1.5 y	2.5 y	Moderate
17	18 y	18 mth	3.5 y	4.5 y	5 y	Severe
18	26 y	6 y	8 y	No speech	No speech	Profound
19	32 y	18 mth	4.5 y	5 y	8 y	Severe
20	5 y	18 mth	2.5 y	3 y	Not yet (5 y)	Severe
21	28 y	4 y	7 y	No speech	No speech	Profound
22	15 y	7 mth	2 y	1.5 y	7 y	Severe
23	22 y	2 y	>5 y	15 y	Single words only	Profound
24	3 y	12 mth	3 y	No speech	No speech	Moderate
25	4 y	12 mth	3.5 y	2.5 y	4 y	Moderate
26	15 y	12 mth	3 y	3 y	4 y	Moderate
27	15 y	14 mth	3 y	3 y	4 y	Severe
28	8 y	10 mth	2 y	No speech	No speech	Profound
29	6 y	6 mth	1.5 y	2 y	Single words only (6 y)	Severe
30	10 y	8 mth	2.5 y	2 y	Single words only (10 y)	Severe
31	12 y	8 mth	2.5 y	1.5 y	Single words only	Severe
32	42 y	10 mth	2.5 y	3 y	5 y	Severe
33	34 y	10 mth	2.5 y	No speech	No speech	Severe

found. Six pregnancies were monitored because of poor fetal growth, three had oligohydramnios, and in three reduced fetal movements were noted. The majority, (30/33, 91%), of babies were born at term (range 38-42 weeks' gestation). Congenital abnormalities were uncommon and minor. They included tongue tie (1/33), cryptorchidism (3/33), and single palmar crease (1/33).

Significant feeding difficulties were a common perinatal problem (27/33, 82%). Two patients required assisted feeding by nasogastric tube and percutaneous gastrostomy for the first 18 months of life. Neonatal hypotonia was reported in 56%. Stridor, usually secondary to laryngomalacia, was described in 21% of patients. Usually it resolved spontaneously, although in two sibs it continued until the age of 18 months but required no medical intervention. Another child had a respiratory arrest aged 4 months and laryngeal stenosis was confirmed on laryngoscopy. She required insertion of a tracheostomy until the age of 18 months. A different child had moderate stridor with O_2 dependency and laryngoscopy at 3 months of age showed vocal cord paresis. She was dependent on a tracheostomy until the age of 4.

Developmental delay and learning difficulties

All patients had global developmental delay. The median age of sitting unsupported was 12 months (range 6 months-6 years) and of first walking 2.5 years (range 12 months-8 years). The median age given for first spoken words was 2.5 years (range 12 months-15 years) and for speaking in short sentences was 5 years, (range 2.5-8 years). Of the 22 patients aged 8 years and over at the time of the study, 13 (59%) had achieved reasonable verbal communication, although their speech content tended to be immature and repetitive. Of the other nine patients, which included five adults, five were using single words only and four were non-verbal. A summary of the study patients' developmental history is shown in table 3.

The five youngest patients were in mainstream nursery or reception classes with special educational needs assistance. Four patients (12%) were at schools for those with moderate learning difficulties. Twenty-four patients (73%) attended schools for those with severe learning difficulties and, of this group, five patients were described as having profound learning difficulties (15%).

Growth and puberty

The mean birth weight was 2800 g (range 2000-3700 g), corresponding to the 3rd centile for gestation. Most parents described an exaggerated weight gain, particularly in the truncal region, in mid-childhood. At the time of clinical assessment, all patients aged 8 years or over were truncally obese with comparatively slim limbs (fig 3). Six patients were classified as obese and a further seven as overweight, with a body mass index above the 98th and 91st centiles, respectively. Measurements of head circumference at birth were poorly recorded. Where available, they were normal, ranging from the 10th to 75th centile. At the time of assessment, 28/31 (90%) patients had an occipital frontal circumference (OFC) below the 3rd centile for age. Of these, 21 patients (64%), were severely microcephalic, with OFC at or below the 0.4th centile. At the time of the study assessment, the patients' heights ranged from <0.4th to 25th centile for age. Short stature (at or below the 3rd centile) was identified in 64% of patients, with the majority measuring less than or on the 0.4th centile.

Pubertal histories were taken on 17 patients (eight female, nine male), aged over 12 years at the time of assessment. The median age of onset of pubertal development for boys was 15 years (range 13-18 years) and of menarche in girls was 15 years (range 14-16 years). Delayed onset of menarche and of

Figure 3 A 12 year old patient showing the characteristic body shape in Cohen syndrome in which there is a truncal distribution of body fat with comparatively slender limbs.

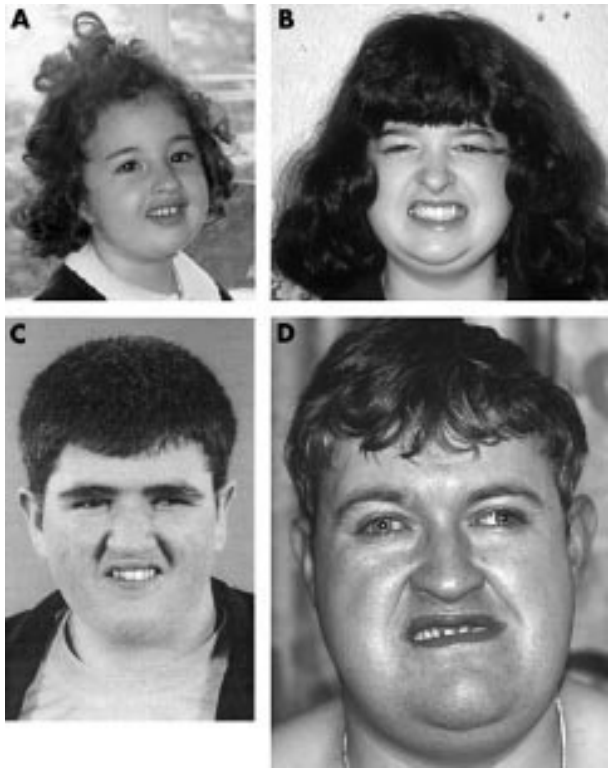

Figure 4 Four patients with Cohen syndrome showing the characteristic facial appearance at age (A) 6 years, (B) 15 years, (C) 18 years, and (D) 46 years. Note the thick head of hair, heavy eyebrows, and prominent, beak shaped nose and typical grimacing facial expression.

pubertal development (over 16 years <0.4th centile) was recorded in 40% of patients.

Facial dysmorphism

In the older child or adolescent the facial gestalt is specific (fig 4A-D.). Typically, patients with Cohen syndrome have a thick head of hair, bushy eyebrows, and luxuriant eyelashes. They have a high nasal bridge and a beak shaped nose. The prominence of their nose is exaggerated by malar hypoplasia. The palpebral fissures are downward slanting and have a characteristic wave shaped outline (fig 5A, B). The appearance around the mouth is distinctive with a short, upturned philtrum (fig 6). When asked to smile, the patient with Cohen syndrome grimaces, screwing up their nose and eyes and further shortening their philtrum. The upper lip is thin and does not cover the front teeth giving an open mouthed expression and the appearance of prominent central incisors. The facial appearance of the infant and young child with Cohen syndrome differs somewhat but still has distinctive features (fig 7A-D). A hypotonic facial expression with an open mouth is characteristic. The mouth typically has downturned corners and the lower lip is often thick and pouting. The philtrum is not always so obviously short. The eyes are a striking feature and lend an almost "china doll" appearance to the infant. They are downward slanting and wave shaped with thick eyebrows and eyelashes. The child's nose is less prominent and beak shaped.

Appearance of the hands and feet

Cohen syndrome patients' hands are typically narrow with slender fingers that taper after the proximal interphalangeal joint (fig 8A, B). Joint hyperextensibility and camptodactyly are frequent. The feet are also narrow with marked joint laxity. An exaggerated sandal gap is a common finding (fig 8C, D).

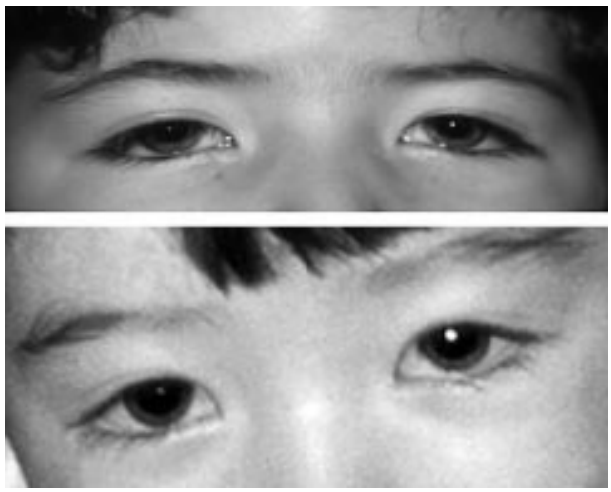

Figure 5 The palpebral fissures are downward slanting and have a distinctive wave shaped outline as shown in these two patients.

Joint hyperextensibilty

Generalised joint hyperextensibility is observed and especially affects the hands, feet, ankles, and knees (table 4). After puberty, kyphoscoliosis often develops and may be progressive through adult life.

Ophthalmic abnormalities

All of the Cohen syndrome patients had visual abnormalities, which are reported in detail elsewhere.[33] Consistent findings were of an early onset myopia and a progressive pigmentary retinopathy. The myopia usually started under the age of 5 and progressed to high myopia (>–7 dioptres) by the second decade.

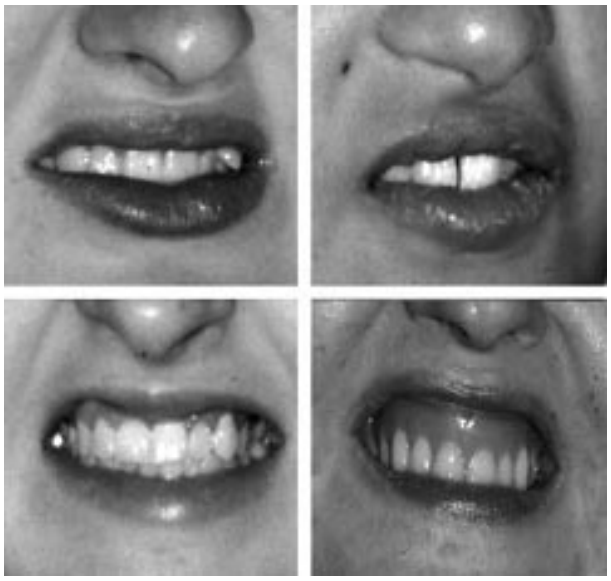

Figure 6 The philtrum is short and upturned.

Retinal pigmentary changes produced a "bull's eye maculopathy" in the young child. By the age of 10, patients had a generalised and symptomatic pigmentary retinopathy confirmed by attenuated or extinguished responses on electrodiagnostic testing. Visual handicap was progressive and significant with 35% of patients registered partially sighted or blind.

Neutropenia and infections

Twenty-five of 32 patients tested were neutropenic (78%), with documented neutrophil counts less than $1.50 \times 10^{-9}/mm^3$. A further three study patients had neutrophil counts at the lower end of the normal range ($1.5\text{-}2.0 \times 10^{-9}/mm^3$). The earliest recorded neutropenia was 3 years of age. Severe infections were rarely reported in association with the neutropenia. However, one patient was recorded in her medical notes as having a neutrophil count of $0.04 \times 10^{-9}/mm^3$ which coincided with severe oral ulceration infected with *Pseudomonas aeruginosa*. Sixty percent of patients (20/33) were described as having frequent but minor skin and/or dental infections.

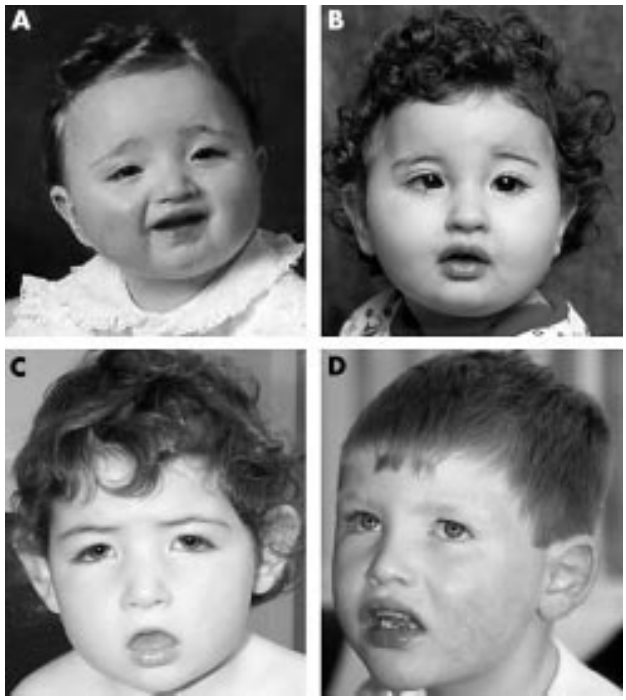

Figure 7 Four patients aged (A) 1 year, (B) 2 years, (C) 4 years, and (D) 5 years, showing the facial appearance of the infant and young child with Cohen syndrome. Note the hypotonic facial expression with an open mouth and thick and pouting lower lip. The eyes are downward slanting and wave shaped with thick eyebrows and eyelashes. The child's nose is less prominent and the philtrum not so obviously short.

Behaviour and cognitive function

Patients with Cohen syndrome were often described by their parents as placid babies, affectionate children, and

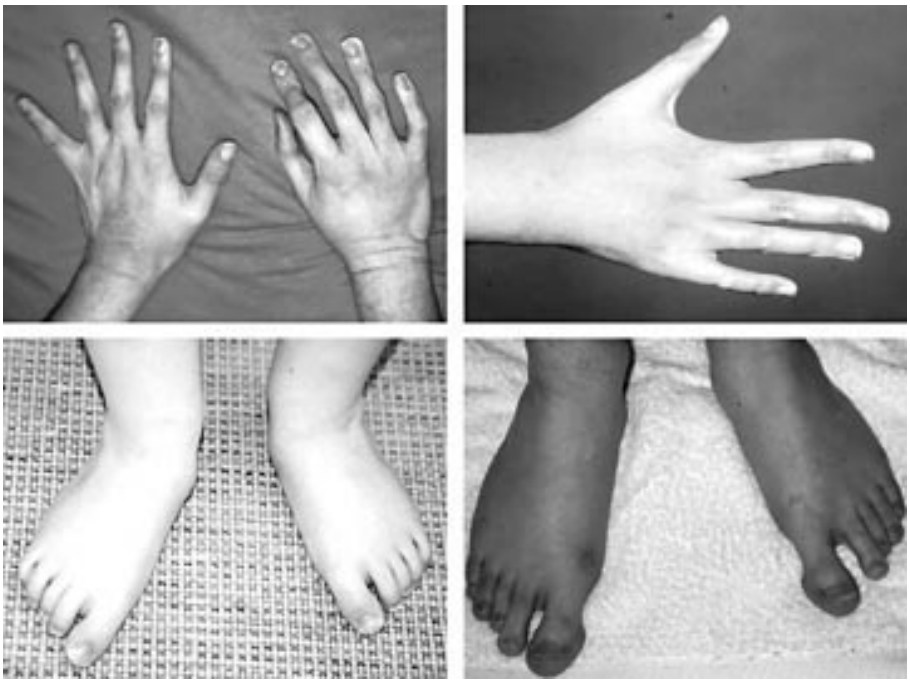

Figure 8 The typical appearance of the hands and feet in Cohen syndrome. The fingers are slender and taper from the proximal interphalangeal joint. There is an exaggerated gap between the first and second toes and occasionally a bulbous big toe.

Table 4 Joint abnormalities in a cohort of 33 Cohen syndrome patients

Joint abnormality	% of patients reported
Pes planus	97
Hyperextensible finger joints	91
Genu valgum	66
Kyphoscoliosis	31
Dislocating patella	9

cooperative, socially interactive adults. Behavioural mannerisms included overfamiliarity with strangers, overexcitability, and hand flapping. Formal psychometric assessments identified mild maladaptive behaviour in the majority of patients (62.5%).[34] Significant maladaptive behaviour and non-maladaptive behaviour were less common, each occurring in only 19% of patients. Neuropsychological testing indicated that 62.5% (10/16) of patients had significant intellectual impairment. In a further 25% (4/16), the level of mental retardation was too profound to permit formal assessment.

Results of molecular genetic studies

In all 11 families investigated, the segregation pattern of the eight polymorphic markers analysed was consistent with linkage to the COH1 locus at 8q22. Allele sharing was seen among affected sibs and was not observed in the unaffected sibs or parents.

Haplotypes constructed for the eight linked markers for each of the 18 patients showed at least six different haplotypes across the refined region. Interestingly, homozygosity across all eight markers was seen in one apparently non-consanguineous family from an isolated region in the UK as well as the two known consanguineous families. The haplotypes for 19 COH1 chromosomes are shown in table 5.

DISCUSSION

Cohen syndrome remains a difficult diagnostic problem, in particular in the young child.[19] The clinical variability of published case reports is misleading and may confound accurate diagnosis.[3–11 14–16] While detailed studies from Finland have delineated a specific phenotype in Finnish patients, the suggestion that the majority of these patients share a common mutation lessens the impact of the observed clinical homogeneity.[24–29 31] Detailed delineation of a cohort of Cohen syndrome patients from outside Finland is therefore useful in determining the applicability of their clinical phenotypic criteria to non-Finnish patients. The group of patients described here represents a valuable resource for assessing diagnostic criteria and determining the variability of the clinical phenotype in Cohen syndrome.

Diagnostic criteria

Based on findings in their cohort of Finnish patients, Kivitie-Kallio and Norio[29] proposed the following features as essential for the diagnosis of Cohen syndrome: (1) non-progressive mental retardation, motor clumsiness, and microcephaly; (2) typical facial features including wave shaped eyelids, short philtrum, thick hair, and low hairline; (3) childhood hypotonia and joint hyperextensibility; (4) retinochoroidal dystrophy and myopia by 5 years of age; (5) periods of isolated neutropenia.

We agree that these features are all important for the diagnosis of Cohen syndrome but suggest that they are not obligatory. Indeed, our study shows that such restrictive criteria would have led to the correct diagnosis in only eight of the 33 patients (24%). This is predominantly as a result of a lack of full ophthalmic investigations at a young age in many of the study patients. In our experience, the retinopathy, while likely to be present at a young age, was seldom confirmed before the age of 5 years when many of the families were unaware of their child's visual problem. Further variability was also observed with regard to microcephaly and neutropenia, which were not identified in all UK Cohen syndrome patients.

We suggest that for all patients in whom a diagnosis of Cohen syndrome is considered, investigations should include a differential white cell count as well as referral to an experienced paediatric ophthalmologist for formal ophthalmic assessment and electrodiagnostic tests, even in the young child. Once fully investigated, we propose as a more comprehensive aid to diagnosing Cohen syndrome the presence of at least two of the following major criteria in a child with significant learning difficulties: (1) facial gestalt, characterised by thick hair, eyebrows and eyelashes, wave shaped, downward slanting palpebral fissures, prominent, beaked shaped nose, short, upturned philtrum with grimacing expression on smiling; (2) pigmentary retinopathy; (3) neutropenia (defined as $<2 \times 10^{-9}/mm^3$).

Table 5 Haplotypes associated with 19 COH1 chromosomes

Pt ID	D8S1778	D8S559	D8S1762	CA1	CA2	CA3	D8S1714	D8S521
24/25†	5	6	2	2	1	6	5	3
17	6	6	2	2	1	6	2	6
17	6	6	2	2	1	2	3	1
26	6	6	2	2	1	4	5	4
12	6	6	2	2	3	2	5	3
12	6	5	2	2	2	4	6	4
15/16	6	5	2	1	2	4	5	4
13/14	5	5	4	2	2	4	5	4
1/2*	6	2	2	1	2	4	4	5
15/16	5	5	2	1	2	4	4	4
6	3	(5)	2	1	2	4	3	3
29/30/31*	7	6	1	1	2	4	4	3
6	5	(4)	2	3	2	4	4	4
11	(7)	5	4	2	1	5	4	4
11	(6)	5	4	2	1	5	6	4
18/19	5	3	2	2	1	3	3	3
18/19	5	3	2	2	1	3	4	4
13/14	6	6	3	1	1	2	5	4
26	1	6	4	1	3	1	5	4

*Known consanguinity.
†Haplotype suggests consanguinity.
( )Non-informative marker.

In addition, there are a number of less specific but supportive criteria which we believe are very common in Cohen syndrome, namely: (1) early onset, progressive myopia, (2) microcephaly, (3) truncal obesity with slender extremities, (4) joint hyperextensibility.

Clinical heterogeneity in Cohen syndrome

Our study has identified several areas of clinical variability in Cohen syndrome. Microcephaly, often marked, is a characteristic but not universal finding. Short stature occurs in two-thirds of patients and in a third is severe. The association of obesity with Cohen syndrome has been overstated in published reports and generalised obesity is in fact uncommon. Half of the patients are overweight but only 1/5 are obese and this is predominantly truncal obesity. An isolated and variable neutropenia is common, but its intermittent nature means that it may not be present at the time of testing. Psychometric assessment affirms that Cohen syndrome patients typically have severe learning difficulties although more moderate retardation may occur in a proportion of patients. Profound learning disability associated with autistic spectrum behaviour is seen in up to a fifth of patients. A mildly maladaptive behavioural pattern is more commonly observed.

Certain new clinical features associated with Cohen syndrome have been identified in this study. Stridor secondary to laryngomalacia was common in infancy but more significant laryngeal abnormalities were also reported, namely laryngeal stenosis and vocal cord paralysis. A high pitched voice was a consistent finding, even in those patients who have not had previous laryngeal problems. While raising the question of whether such abnormalities reflect an intrinsic difference in laryngeal function, our observations also highlight the association in Cohen syndrome of upper airway problems which may be severe and even life threatening.

Molecular genetic analysis

Segregation analysis within 11 of these Cohen syndrome families showed allele sharing across the COH1 critical region in affected sibs that is not identified among unaffected sibs. Haplotype analysis confirmed the presence of several haplotypes in these families suggesting the presence of allelic heterogeneity. Our results support the COH1 locus as the major locus of the Cohen syndrome gene in patients outside Finland. Moreover, they indicate that the clinical homogeneity seen in the Finnish patient population is not purely a reflection of a founder effect and that several different mutations may be causative of a similar clinical phenotype. No correlations between clinical features and the different haplotypes have been identified and significant intrafamilial variation was observed. Specific genotype-phenotype comparisons must therefore await identification of the Cohen syndrome gene. Once available, our patient cohort will represent an invaluable resource owing to its proven clinical and genetic heterogeneity.

The natural history of Cohen syndrome

Assessment of this large group of Cohen syndrome patients shows a common natural history. Most patients are born of low birth weight, following a normal pregnancy. Neonatally, significant feeding difficulties and hypotonia are frequent problems. Most parents have concerns about their child during the first year of life. Global developmental delay is seen in all patients. Delayed motor milestones and clumsiness are compounded by hypotonia and joint laxity. Speech delay is universal and often severe, but many patients achieve reasonable communication by the age of 8 years. All patients with Cohen syndrome have special educational needs and most attend schools for children with severe learning difficulties. Progressive visual disability is a significant problem for Cohen syndrome patients. An early onset progressive myopia and pigmentary retinopathy are evident in the majority of patients. A truncal distribution of fat is consistently seen in the over 8 year olds but true obesity is uncommon. Pubertal development is often delayed. Generalised and marked joint laxity is frequent in Cohen syndrome, affecting particularly the hands, feet, and knees. In adult life, progressive kyphoscoliosis may occur. The patients' general health is usually good and, despite being neutropenic, severe infections and hospitalisation are rare. Patients continue to live at home or in residential care in their adult life and require supervision for many daily living skills. There is no evidence to suggest a shortened lifespan in adult life.

Differential diagnosis

The diagnosis of Cohen syndrome is often considered within the differential diagnoses of inherited conditions where mental retardation is associated with retinopathy and obesity, for example, Bardet-Biedl and Alström syndromes.[35] However, the clinical phenotype is quite distinct for these conditions and very different from that of Cohen syndrome. Deafness, diabetes mellitus, and a cardiomyopathy are characteristic of Alström syndrome and the patients are usually of normal intellect.[36] Postaxial polydactyly and renal dysplasia are diagnostic features of Bardet-Biedl syndrome.[37] An important difference concerns the pigmentary retinopathy which typically causes early loss of central vision in Alström and Bardet-Biedl syndromes as opposed to the peripheral visual field loss seen initially in Cohen syndrome. In addition, the pattern of obesity is quite different and tends to be generalised rather than the specific truncal obesity of Cohen syndrome. Truncal obesity of mid childhood onset may be seen in patients with chromosomal abnormalities associated with significant mental retardation and microcephaly. Detailed karyotyping including FISH studies for subtelomeric deletions is therefore recommended as part of the investigations in a patient suspected of having Cohen syndrome. Carbohydrate deficient glycoprotein syndrome type 1 can present with developmental delay, hypotonia, and microcephaly as well as truncal obesity and a pigmentary retinopathy.[38] However, neuroimaging may identify olivopontocerebellar atrophy and transferrin isoelectric focusing or phosphomannomutase assay should establish a defect of glycoprotein metabolism. The facial appearance in Cohen syndrome is striking and not easily confused with other syndromic gestalts. However, the beaked nose with overhanging columnella is reminiscent of the nasal configuration of Rubenstein-Taybi syndrome in which microcephaly and severe learning disability are also seen.[39] More recently, a specific facial phenotype in older patients with Mowat-Wilson syndrome and mutations in the *SIP1* gene has been recognised. Notably, patients have a short and upturned philtrum similar to that seen in Cohen syndrome patients.[40]

CONCLUSIONS

Through this large group of Cohen syndrome patients, we have confirmed that Cohen syndrome has a distinctive clinical phenotype identifiable not only in Finnish patients but also in other genetically diverse patient groups, as represented by this UK cohort. Despite the specificity of abnormalities seen in Cohen syndrome, there is nonetheless variability within its clinical spectrum. Most parents report concerns about their child in the first year of life and yet diagnosis is unusual under the age of 5 years. The diagnostic guidelines we have proposed encompass the observed phenotypic heterogeneity and stress the need for thorough investigation at an early age in order to facilitate earlier diagnosis. This is important not only for the patient, who will benefit from the appropriate intervention by a multidisciplinary team, but also for the families who can be accurately counselled regarding cause, prognosis, and recurrence risks.

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Authors' affiliations

K E Chandler, G C M Black, J Clayton-Smith, Academic Unit of Medical Genetics and Regional Genetics Service, Manchester, UK
A Kidd, North of Scotland Regional Genetic Service, Aberdeen, UK
L Al-Gazali Faculty of Medicine and Health Sciences, United Arab Emirates University, UAE
J Kolehmainen, A-E Lehesjoki, Folkhälsan Institute of Genetics and Department of Medical Genetics, University of Helsinki, Finland

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