ELECTRONIC LETTER

Mutational spectrum of *COH1* and clinical heterogeneity in Cohen syndrome

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Cohen syndrome (CS) is an autosomal recessive disorder with variability in the clinical manifestations, characterised by mental retardation, postnatal microcephaly, facial dysmorphism, pigmentary retinopathy, myopia, and intermittent neutropenia. Mutations in the gene *COH1* have been found in an ethnically diverse series of patients. Brief clinical descriptions of 24 patients with CS are provided. The patients were from 16 families of different ethnic backgrounds and between 2.5 and 60 years of age at assessment. DNA samples from all patients were analysed for mutations in *COH1* by direct sequencing. Splice site mutations were characterised using reverse transcriptase PCR analysis from total RNA samples. In this series, we detected 25 different *COH1* mutations; 19 of these were novel, including 9 nonsense mutations, 8 frameshift mutations, 4 verified splice site mutations, 3 larger in frame deletions, and 1 missense mutation. We observed marked variability of developmental and growth parameters. The typical facial gestalt was seen in 23/24 patients. Early onset progressive myopia was present in all the patients older than 5 years. Widespread pigmentary retinopathy was found in 12/14 patients assessed over 5 years of age. We present evidence for extended allelic heterogeneity of CS, with the vast majority of mutations leading to premature termination codons in *COH1*. Our data confirm the broad clinical spectrum of CS with some patients lacking even the characteristic facial gestalt and pigmentary retinopathy at school age.

Cohen syndrome (CS; MIM #216550) is an uncommon autosomal recessive disorder with variability in the clinical manifestations including psychomotor retardation, microcephaly, typical facial dysmorphism, progressive pigmentary retinopathy appearing at mid-childhood, early onset and severe myopia, and intermittent neutropenia.¹⁻⁴ The characteristic craniofacial appearance includes downwards slanting and wave shaped palpebral fissures, short philtrum, heavy eyebrows, thick hair, and prominent nasal base. Finnish patients present with a homogeneous phenotype as result of a specific allele. However, a broad clinical spectrum in non-Finnish cases and the age dependent appearance of some clinical signs may contribute to a delay in making the diagnosis.

Recently, the CS phenotype was found to be associated with mutations in the gene *COH1* in different populations.⁵⁻⁸ *COH1* maps to chromosome 8q22 and codes for various splice forms. It comprises up to 62 exons and its longest transcript is 14 093 nucleotides in length with an open reading frame of 4022 codons.⁵ *COH1* encodes a potential transmembrane protein presumably involved in vesicle mediated sorting and

intracellular protein transport.^{5-9,10} The mouse homologue of *COH1* is widely expressed in neurones of the postnatal and adult brain suggesting a role in neuronal differentiation.⁸ This suggests that *COH1* primarily has a function in postmitotic cells, which may be the reason for the postnatal microcephaly seen in CS.⁸

Overall, more than 50 *COH1* mutations have been reported in association with CS. Most are termination mutations and predicted to result in a null allele, while missense mutations and larger deletions are less common.

To determine the variability of the clinical manifestations and the spectrum of mutations associated with this condition we investigated 24 patients with CS from 16 families, with a wide range of geographical and ethnic origins.

METHODS

Patients

This study included 24 patients from 16 families (17 male and 7 female patients, ranging in age from 2.5 to 60 years). The diagnosis of CS was based on clinical manifestations including developmental delay/mental retardation and at least two of three criteria: typical facial gestalt (fig 1), pigmentary retinopathy or myopia, and neutropenia (table 1). There were 12 non-consanguineous families, comprising three French families (one with two affected children and two with one affected child each), three German families (two with one affected child and one with five affected male members), one Turkish family (one affected child), one Belgian family (one affected child), one family of English and German origin (one affected child), one Canadian family from English/Scottish descent (one affected child), and two Polish families (with one and two affected children, respectively). The four consanguineous families reported were all Turkish (two with affected sibling pairs and two with one affected child each).

Clinical assessments were carried out on all patients by at least one of us. Blood samples were collected from the parents and from affected and unaffected siblings. Signed informed consents were obtained from the parents of the affected and unaffected children.

Mutation analysis

Genomic DNA was isolated from peripheral blood using standard techniques. For mutation screening, 62 exons and five potential alternative exons including their flanking splice sites, and the predicted promoter region of *COH1* were analysed. Primer pairs for genomic amplification were generated on the basis of the sequence of a chromosome 8 genomic contig (GenBank accession number NT_008046.15).⁷ All primer sequences are available on

Abbreviations: CS, Cohen syndrome

Figure 1 Typical facial features of patients with CS. Shown are patients 8-1 (A), 8-2 (B), 11 (C), 7 (D), 9 (E), 15-1 (F), 2-5 (G), and 2-4 (H). Signed informed consents were obtained from the parents of the affected children and guardians of affected adults for publication of the images.

request. PCR products were purified using exonuclease I and shrimp alkaline phosphatase, and then sequenced directly with a commercial kit (BigDye Terminator cycle sequencing kit, version 1.1, Applied Biosystems) and analysed on an automated DNA analyser (model 3730; Applied Biosystems).

RT analysis

Total RNA was extracted from peripheral blood, and reverse transcription (RT) performed using commercial kits (PAXgene blood RNA validation kit, PreAnalytiX and Omniscript RT kit, Qiagen). Primer pairs for cDNA amplification were designed from the sequence of the full length *COH1* transcript (GenBank accession number NM_017890.3). Analysis of PCR products was performed by purifying single bands from agarose gel using a gel extraction kit (QIAquick; Qiagen), and sequenced directly as described above.

RESULTS

Clinical data

In our series of 24 patients with CS from 16 families, we observed marked variability of developmental and growth parameters (table 1). At the time of assessment, short stature (height at or below the third centile) was present in 16 of 24 cases. Postnatal microcephaly was found in 20 of 24 patients. Truncal obesity was documented in the majority of patients analysed (17/24). Mental retardation and intellectual impairment varied from moderate to severe. All but one of the patients (patient 2-2) learned to walk independently. The majority of patients achieved verbal communication skills and most used short sentences at mid-childhood. However, two adult patients (2-2 and 2-3) and two 5 year old patients (14-1 and 15-2) were non-verbal. Stereotypic movements were seen in patients 5 and 15-2.

Typical craniofacial features were seen in 23/24 patients (fig 1). Patient 6, who presented with everted lips, bulbous nasal tip, and normal appearing philtrum, lacked the facial gestalt characteristic of CS (fig 2). The affected siblings of

family 2 were 44 and 60 years old at assessment and both had the characteristic facial features of CS including short philtrum and downwards slanting palpebral fissure.

Progressive visual disability was a consistent finding. An early onset of progressive myopia with refractive errors ranging from -0.3 to -8 dioptres was evident in all the patients older than 5 years. Patient 8-2 was too young to assess this clinical sign. Retinal examination had been performed on all study patients. All but two of the patients older than 5 years had widespread pigmentary retinopathy with vessel attenuation and optic pallor. Two siblings (13-1 and 13-2) had normal retinal examinations at the ages of 16.5 and 14.5 years. Electrodiagnostic tests have not been carried out on these two patients but functional impairment such as nyctalopia was not recorded. Six patients between 3.5 and 5 years of age had normal retinas on ophthalmological examination. The adult patients assessed by us showed progressive ophthalmological changes. Severe retinochoroidal atrophy, generalised bone spiculae-like pigment accumulations, cataracts, and optic nerve pallor were found in two affected brothers aged 53 and 44 years (2-4 and 2-5, respectively). The ophthalmological abnormalities led to total blindness in mid-adulthood in patients 2-1 and 2-5.

Narrow hands and feet were found in all patients. Progressive kyphoscoliosis developed after the age of 40 years in patients 2-4 and 2-5 but was also present in an affected teenager (patient 6). Neutropenia defined as a neutrophil count $<1.5 \times 10^9/l$ was shown in the majority of patients analysed for that clinical sign (14/16 patients).

Hypogonadotropic hypogonadism, severe and complete growth hormone deficiency, insulin resistance, and compensatory hyperinsulinemia were found in patient 10.

Molecular analysis

We analysed all 24 patients by direct genomic sequencing of the whole coding region including the exon splice sites and the promoter region. In the full length transcript of *COH1*, we

Table 1 Summary of the clinical findings in 24 patients with CS from 16 families

Patient	Origin	Consanguinity	Sex	Age at assessment (years)	Microcephaly	Short stature	Truncal obesity	Age first walked	Speech development	Typical facies	Myopia (dioptries)	PR	Narrow hands /feet	Neutropenia	Miscellaneous
1	German/English	—	M	5	+	—	—	3 years	Sentences	+	−0.3	—	+	+	
2-1	German	—	M	60	—	—	+	Childhood	Sentences	+	+	+	+	NA	Total blindness
2-2	German	—	M	44*	—	—	—	No walking	No speech	+	NA	NA	+	NA	
2-3	German	—	M	56	—	+	—	Childhood	No speech	+	NA	NA	+	NA	
2-4	German	—	M	53	+	+	+	Childhood	Single words	+	+(−7)	+	+	+	Cataracts, kyphoscoliosis
2-5	German	—	M	44	+	+	—	Childhood	Sentences	+	+(−7)	+	+	+	Cataracts, total blindness, kyphoscoliosis
3	English/Scottish	—	F	9	+	+	—	2.5 years	Sentences	+	+	+	+	+	Juvenile rheumatoid arthritis, inflammatory bowel disease
4	Turkish	—	M	5.5	+	+	—	2 years	Sentences	+	−5	+	+	+	Stereotypic movements
5	Polish	—	F	5	+	—	+	2 years	Single words	+	−3	+	+	+	Scoliosis
6	French	—	M	17	+	+	+	22 months	Sentences	—	−4	+	+	—	Autistic features
7	Belgian	—	F	15	+	+	+	Delayed	Delayed	+	+	+	+	+	
8-1	French	—	M	7	+	+	+	Delayed	Delayed	+	+	+	+	+	
8-2	French	—	M	3.5	+	+	+	Delayed	Delayed	+	—	—	+	+	
9	French	—	F	16.5	+	+	+	Delayed	Delayed	+	+	+	+	+	Hypogonadism, growth hormone deficiency
10	German	—	M	15.5	+	+	+	5.5 years	Single words	+	+	+	+	+	Stereotypic movements
11	German	—	M	11.5	+	+	+	Delayed	Sentences	+	−8	+	+	+	
12	Turkish	+	M	28	+	+	+	12 months	Sentences	+	−10/−7	+	+	—	
13-1	Turkish	+	F	16.5	+	+	+	16 months	Single words	+	−5	—	+	NA	
13-2	Turkish	+	M	14.5	+	+	+	13 months	Single words	+	−4	—	+	NA	
14-1†	Polish	—	M	5	+	—	+	20 months	No speech	+	−3.5/−2.5	—	+	+	
14-2†	Polish	—	M	3	+	—	+	3 years	Single words	+	−6.5/−4.0	—	+	+	
15-1	Turkish	+	F	8	—	+	+	2 years	Sentences	+	+	−‡	+	+	Unilateral ptosis, stereotypic movements
15-2	Turkish	+	F	5	+	—	—	2 years	No speech	+	−6	—	+	NA	
16	Turkish	+	M	2.5	+	—	—	2.5 years	Single words at 2.5 years	+	NA	NA	+	NA	

*Died due to ileus at age of 44 years; †these patients were reported as family 8 by Hennies *et al*† but only one mutation had been identified at that time; ‡last retinal examination at age of 4 years. PR, pigmentary retinopathy; NA, not available.

Figure 2 Facial dysmorphism differs in patient 6 by the presence of everted lips, bulbous nasal tip, and a normal philtrum. Signed informed consent was obtained from the parents of the patient for publication of the image.

identified 25 different mutations; 19 of these were novel, including 9 nonsense mutations, 8 frameshift mutations, 4 verified splice site mutations, 3 larger in frame deletions, and 1 missense mutation identified in two unrelated families. The mutations identified are summarised in table 2. Each mutation cosegregated in the respective family in all cases and was not seen in 150 chromosomes from control subjects.

Heterozygous mutation c.1563G→A identified in family 1 affected the last base pair of exon 11 (table 2). To analyse whether the mutation caused an altered splicing of *COH1*, we performed RT-PCR on a total RNA sample from peripheral

blood of patient 1. Amplified cDNA with primers located in exons 8 and 16 showed the regularly processed product in a very low level. Amplification with primers placed in exon 8 and intron 11 resulted in a mutant cDNA fragment. Sequencing demonstrated an abnormal transcript including more than 177 bp of the intron 11, resulting in a new reading frame of 19 codons followed by a stop codon in intron 11.

In family 9, we identified a heterozygous mutation, c.7322_7322+1delGGinsATGGAGC (table 2), at the splice donor site. RNA analysis with primers located in exons 39 and 45 and in exon 39 and intron 40, respectively, showed lack of splicing with an altered codon 2441, followed by 35 novel codons and a stop codon. A heterozygous splice donor site mutation c.2934+1_2934+2delGT was identified in family 11 (table 2). We identified complete skipping of exon 20 with primers located in exons 19 and 24. Consequently, the altered transcript lacked 110 nucleotides. Mutation c.6732+1G→A, first reported by Kohlemainen *et al.*,⁶ changed the splice donor site of intron 37 (family 3; table 2). Total RNA from the affected individual analysed with primers located in exons 35 and 39 revealed a cryptic splice site in intron 37. The defective splicing leads to an addition of four bases into the *COH1* transcript. The sequence of the cryptic splice site (GTGGGT) is consistent with the consensus motif (GURAGU) at five of six positions, including the highly conserved dinucleotide GT at the beginning.

DISCUSSION

In this paper, we report the clinical and molecular data on 24 individuals with CS, from 16 families, caused by mutations in *COH1*. Overall, 11 compound heterozygous cases, 4 homozygous cases with known consanguinity, and 1 homozygous case with unknown consanguinity were observed. In one patient (family 10), only one heterozygous mutation was detected. This patient was also assumed to be compound heterozygous. The lack of a second pathogenic mutation points to the existence of further alternative exons and/or other transcripts of *COH1*.^{5,7,11} Alternatively, further mutations could reside within intronic sequences, which were

Table 2 Summary of mutations in *COH1* identified in this study

Nucleotide exchange	Exon	Amino acid change/ predicted consequence	Genotype	Family
c.1504C→T	11*	p.Arg502X	Heterozygous	3
c.1563G→A	11	p.Lys521fsX20	Heterozygous	1
c.2074C→T	15†	p.Arg692X	Heterozygous	8
c.2516_4299del	18–28	p.Gly839fsX19	Heterozygous	14
c.2727_2730dupGCTC	19*	p.Asn911fsX3	Heterozygous	14
c.2934+1_2934+2delGT	20	p.Gly942fsX14	Heterozygous	11
c.2516_3083del	18–21	p.Gly839_Thr1027del	Heterozygous	11
c.4877_4879dupAAT	31	p.Tyr1627X	Homozygous	12
c.4923G→A	31	p.Trp1641X	Heterozygous	2
c.4955C→G	31	p.Ser1652X	Heterozygous	2
c.5152_5295del	33	p.Glu1718_Glu1765del	Heterozygous	5
c.5215_5232delAGTGTGGCTCAAGTCAA	33	p.Ser1739_Gln1744del	Heterozygous	10
c.5426_5427dupAG	34†	p.Gln1810fsX21	Heterozygous	8
c.5461_5462insC	34	p.Arg1821fsX18	Heterozygous	6
c.5920C→T	34	p.Arg1974X	Heterozygous	5
c.6732+1G→A	37‡	p.Val2245fsX17	Heterozygous	3
c.7322_7322+1delGGinsATGGAGC	40	p.Ser2441fsX37	Heterozygous	9
c.7153G→T	40	p.Glu2384X	Heterozygous	9
c.8292C→A	45	p.Cys2764X	Homozygous	13
c.8318C→T	45	p.Ser2773Leu	Homozygous	15, 16
c.10456_10457delAG	56	p.Leu3487fsX25	Homozygous	7
c.11245G→T	58	p.Glu3749X	Heterozygous	4
c.11564_11565delAT	60	p.Tyr3855fsX30	Heterozygous	4
c.11780delC + c.11783TG→AA	61	p.Thr3927fsX15	Heterozygous	1
c.11907dupC	62‡	p.Ser3970fsX22	Heterozygous	6

*Mutation reported by Hennies *et al.*;⁷ †Mutation reported by Kohlemainen *et al.*;⁶ ‡Mutation reported by Kohlemainen *et al.*⁶

analysed only at the conserved splice sites, or could represent larger deletions.

In total, we identified 25 different mutations, of which 19 were novel (table 2). Most of the patients described here carried mutations resulting in premature termination codons. This is consistent with previously reported cases. In total, 61 of the 73 mutations in *COH1* published to date resulted in premature termination through frameshift or nonsense mutations,^{5–8 12 13} and six mutations are larger in frame deletions. Thus, the pathogenic implications of missense mutations associated with CS (6 of 73), identified only in two of our cases, have still to be clarified. Several coding SNPs found indicate that the *COH1* product appears to have some tolerance to such variations (table 3).

Nearly all mutations except for those found in Finnish patients^{5 6} were seen only once or in a few families. Four novel splice site mutations (families 1, 3, 9, and 11) were confirmed on RNA analysis. The splice site mutation c.1563G→A (family 1) resulted in intron retention and an aberrant stop codon. The second splice site mutation, c.7322_7322+1delGGinsATGGAGC (family 9), led to intron retention with an aberrant stop after 2477 residues. The splice site mutation found in family 11 (c.2934+1_2934+2delGT) resulted in exon skipping. The fourth splice mutation, c.6732+1G→A (family 3), resulted in activation of a cryptic 5' splice site within the intronic sequence and a subsequent frameshift.

Our data help in defining the phenotypic spectrum of CS. Consistent with previously reported cases of CS,^{7 8 12 13} the patients reported by us demonstrate an obviously broad phenotypic variability, in contrast to the patients with apparent founder mutations, who have a fairly homogeneous phenotype. Thus, *COH1* mutations may be present in patients with CS lacking either microcephaly or truncal obesity. The majority of patients in our study showed short stature. Most patients reported by us (21/24) had moderate mental retardation. Three patients were classified as having profound mental retardation with complete lack of speech, and one adult patient could not walk.

Table 3 Overview of all single nucleotide polymorphisms and CS associated missense mutations in the coding region of *COH1*

Exon	Nucleotide exchange	Alternative residues	Source
Synonymous polymorphisms			
25	c.3855A→G	p.Leu1248Leu	rs1697391
39	c.7038A→G	p.Val2346Val	This study
40	c.7227G→A	p.Pro2409Pro	This study
52	c.9566T→C	p.Ser3189Ser	This study
56	c.10140G→T	p.Ala3380Ala	This study
57	c.10980T→C	p.Pro3660Pro	This study
61	c.11640A→G	p.Ser3880Ser	rs7844645
Non-synonymous polymorphisms			
17	c.2485G→A	p.Ala829Thr	This study
18	c.2596G→A	p.Val866Ile	This study
34	c.5980A→G	p.Ile1994Val	This study
42	c.7751T→C	p.Val2548Ala	rs7833870
46	c.8465A→G	p.Tyr2822Cys	This study
50	c.9098C→A	p.Ala3033Glu	rs6992059
52	c.9424A→G	p.Ser3142Arg	This study
56	c.10294G→A	p.Gly3432Arg	rs6468694
Potentially pathogenic missense mutations			
37	c.6578T→G	p.Leu2193Arg	Kolehmainen <i>et al.</i> ⁵
39	c.7022A→G	p.Tyr2341Cys	Hennies <i>et al.</i> ⁷
43	c.7934G→A	p.Gly2645Asp	Mochida <i>et al.</i> ⁸
45	c.8318C→T	p.Ser2773Leu	This study
46	c.8459T→C	p.Ile2820Thr	Falk <i>et al.</i> ¹²
49	c.8978A→G	p.Asn2993Ser	Kolehmainen <i>et al.</i> ⁵

In previous studies early onset of high myopia and pigmentary retinopathy have been a hallmark of CS.^{14 15} In all our patients older than 5 years, the severity of myopia was comparable to that reported earlier.^{14 15} Pigmentary retinopathy was not confirmed by retinal examination in two patients who were teenagers at the time of assessments although these patients did not undergo electrodiagnostic testing. Thus, retinopathy present at school age may not to be obligatory for the diagnosis of CS.

Despite some variability in the facial appearance in CS, craniofacial abnormalities including wave shaped palpebral fissures and short philtrum were seen in almost all patients and in different ethnic backgrounds.^{5–7 12} However, the facial dysmorphism may be subtle, which can lead to delay in diagnosis.¹² In our opinion, despite mild hypertelorism, the facial appearance of one patient reported by Falk *et al.*¹² (given as sketch drawing in that report) is consistent with the typical facial features of CS. One patient in this study (patient 6) had facial features not typical of CS, including everted lips, bulbous nasal tip, and normal philtrum (fig 2). Therefore, the diagnosis of CS cannot be ruled out in the absence of characteristic facial features.

Although no significant endocrinal abnormalities were found in Finnish patients on the examination of pituitary function,⁴ one of our patients, of German origin, showed growth hormone deficiency and hypogonadotropic hypogonadism.

Long term follow up and clinical information on patients older than 40 years are rare in the literature.³ Our patients between 44 and 60 years of age show that the features characteristic of CS remain in older patients, and can be used in making the diagnosis even at that age. Total blindness found in two adult patients reported here contrasts with the Finnish group of CS patients, in whom marked deterioration of visual function occurred over the age of 50 years, but no patient was reported to be completely blind.³ However, one third of CS patients from Britain were registered with severe visual impairment or blindness.¹⁶

Kyphoscoliosis was seen in three of our patients as teenagers or adults and this tends to be progressive through adult life. As CS patients do not have life threatening disorders and are generally in good health, their life span does not seem to be markedly reduced.

The detailed clinical information and the results of the molecular analysis of *COH1* on patients with CS presented here enabled us to provide evidence of extended allelic heterogeneity as well as to obtain further information regarding the clinical findings, particularly the facial features, in patients of different ethnic backgrounds.

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