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Report

Delineation of Cohen Syndrome Following a Large-Scale Genotype-Phenotype Screen

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Cohen syndrome is an autosomal recessive condition associated with developmental delay, facial dysmorphism, pigmentary retinopathy, and neutropenia. The pleiotropic phenotype, combined with insufficient clinical data, often leads to an erroneous diagnosis and has led to confusion in the literature. Here, we report the results of a comprehensive genotype-phenotype study on the largest cohort of patients with Cohen syndrome assembled to date. We found 22 different *COH1* mutations, of which 19 are novel, in probands identified by our diagnostic criteria. In addition, we identified another three novel mutations in patients with incomplete clinical data. By contrast, no *COH1* mutations were found in patients with a provisional diagnosis of Cohen syndrome who did not fulfill the diagnostic criteria ("Cohen-like" syndrome). This study provides a molecular confirmation of the clinical phenotype associated with Cohen syndrome and provides a basis for laboratory screening that will be valuable in its diagnosis.

Cohen syndrome (COH1 [MIM 216550]) is an autosomal recessive condition associated with a complex phenotype that was described initially in a sib pair and an unrelated patient with hypotonia, obesity, prominent incisors, and mental deficiency (Cohen et al. 1973). Subsequently, >100 cases have been reported, 35 of them from Finland (Kivitie-Kallio and Norio 2001; present study), where Cohen syndrome is one of several overly represented autosomal recessive conditions (Norio 2003). The Cohen syndrome phenotype, described in a cohort of 29 Finnish patients, shows considerable clinical homogeneity, with five key features identified: (1) nonprogressive mental retardation, motor clumsiness, and microcephaly; (2) typical facial features; (3) childhood hypotonia/joint hyperextensibility; (4) retinochoroidal dystrophy and myopia; and (5) isolated neutropenia (Kivitie-Kallio and Norio 2001).

Kivitie-Kallio and Norio (2001) reviewed all the reported Cohen syndrome cases worldwide. They concluded that ~25% (27/110) had features consistent with those of the Finnish cases. However, the phenotype of most patients outside of Finland who are claimed to have Cohen syndrome is highly variable (Kivitie-Kallio and Norio 2001; Chandler and Clayton-Smith 2002). Indeed, a second subtype of Cohen syndrome, termed the "Jewish type" (Kondo et al. 1990), was reported following the description of 39 patients from 32 families in Israel (Sack and Friedman 1986). Although these patients had some general features of Cohen syndrome (e.g., developmental delay, hypotonia, and facial characteristics), they lacked the more specific features of the condition (e.g., neutropenia and retinochoroidal dystrophy) and also had additional features not associated nor-

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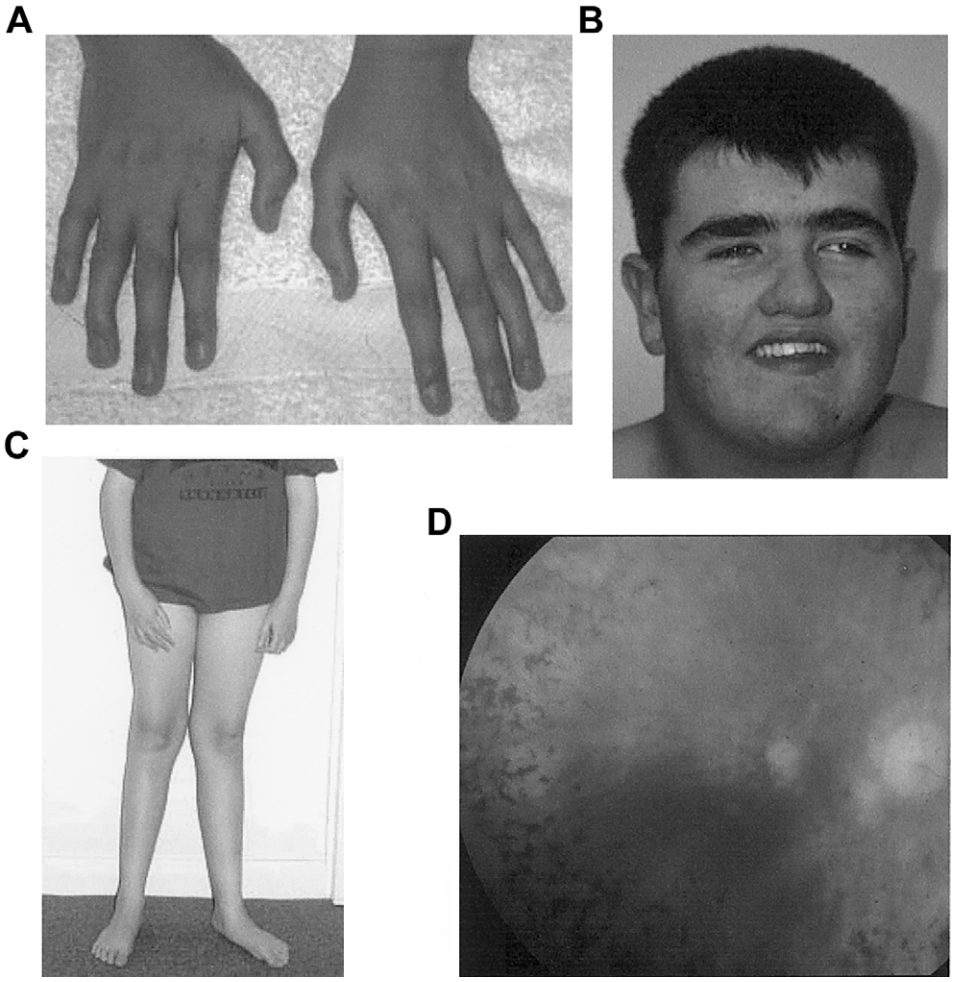

Figure 1 Phenotype of Cohen syndrome. *A,* Hands showing long tapering fingers. *B,* Characteristic facial appearance. *C,* Slender extremities with truncal obesity. *D,* Extensive retinal dystrophy with waxy disc pallor and retinal pigmentation.

mally with the disease (e.g., height >97th percentile and head circumference >97th percentile). Chandler and Clayton-Smith (2002) concluded that there was insufficient evidence to support the existence of a "Jewish type" of Cohen syndrome.

In an attempt to define the diagnostic criteria for Cohen syndrome in patients with a more heterogeneous genetic background, a study on U.K. patients with Cohen syndrome was conducted (Chandler et al. 2002, 2003). Although the above criteria are important diagnostic features, they would have identified only 24% of the U.K. cohort of patients with "true" Cohen syndrome, primarily because of a lack of thorough clinical investigation. In particular, it is difficult to confirm the diagnosis of Cohen syndrome in young children (age <5 years), with the use of very strict criteria, when the chorioretinal dystrophy has not yet become manifest or where there is inadequate information with regard to ophthalmic examination. These difficulties led to the publication of modified diagnostic criteria to distinguish between "true" Cohen and "Cohen-like" syndromes (Chandler et al. 2002, 2003). In addition to significant learning disabilities, a child with Cohen syndrome had to have at least two of the following features: facial gestalt, pigmentary retinopathy, or neutropenia ($<2 \times 10^{-9}/mm^3$) (Chandler et al. 2003) (fig. 1).

Elsewhere, we identified *COH1* as the gene responsible for Cohen syndrome (Kolehmainen et al. 2003). This novel widely expressed gene is of unknown function, although homology to the *Saccharomyces cerevisiae* VPS13 protein suggests a role in vesicle-mediated sorting and intracellular protein trafficking. The identification of the gene now allows a true evaluation of the clinical criteria for Cohen syndrome, through a molecular test for the condition.

We have, therefore, undertaken an extensive molecular assessment of a total of 76 patients from 59 families with a provisional diagnosis of Cohen syndrome and

have correlated it with clinical findings. The patients were assessed for the following eight clinical criteria: developmental delay, microcephaly, typical Cohen syndrome facial gestalt, truncal obesity with slender extremities, overly sociable behavior, joint hypermobility, high myopia and/or retinal dystrophy, and neutropenia. Those fulfilling six or more criteria were considered likely to have true Cohen syndrome. Those with lower scores ($\leqslant$5 of 8) were considered provisionally to have a Cohen-like syndrome. Ethical approval for this study was obtained from the relevant authorities in the United Kingdom and Finland.

Of 37 patients (19 male and 18 female; from 32 families) with Cohen syndrome, 20 met all eight criteria, 12 met seven, and 5 met six. Of the 32 families, 17 were from the United Kingdom, 9 were from Finland, 2 were from Belgium, 2 were from Denmark, 1 was of Arab ethnicity, and 1 was of Dutch extraction. All 37 patients had developmental delay and the typical facial appearance of Cohen syndrome, and 36 of them had chorioretinal dystrophy. Neutropenia was not confirmed in three patients who all had the typical facial gestalt and retinal dystrophy.

In the group of 39 patients with a Cohen-like–syndrome phenotype, full clinical data was available for 22 (from 14 families). Of these 22 patients, 2 met five diagnostic criteria, 1 met four, and the remainder met three or fewer. Specifically, none of these patients with Cohen-like syndrome had neutropenia, and only one out of seven patients with myopia and/or retinal dystrophy had the typical facial appearance of Cohen syndrome—and she did not fulfill sufficiently the other criteria for a diagnosis of true Cohen syndrome. The clinical data was incomplete for the remaining 17 patients (from 13 families) with Cohen-like syndrome. Of these patients, 16 fulfilled less than six criteria. The patient who did fulfill six criteria lacked both chorioretinal dystrophy and neutropenia and, therefore, did not meet the criteria for a diagnosis of true Cohen syndrome (Chandler et al. 2003). Chorioretinal dystrophy was present in four patients with facial features of Cohen syndrome, and the retinal status was missing for nine patients. Of those with a reported leukocyte count (10/17), only one had neutropenia.

The *COH1* gene in 35 of 37 patients with Cohen syndrome and in 8 patients with Cohen-like syndrome and incomplete clinical data was screened for sequence alterations by sequencing 27 overlapping cDNA fragments (Superscript, Invitrogen) with the use of Big Dye v2.1 (ABI) or by sequencing exon by exon from genomic DNA with the use of Big Dye v3.1 (ABI) and an ABI Prism 3730XL DNA Analyzer. Heterozygous frameshift mutations that could not be pinpointed by this method were further characterized by TA-cloning (Invitrogen) followed by sequencing of the insert. The rest of the patients were screened by SSCP from genomic DNA.

The sequence alterations in *COH1* associated with Cohen syndrome are listed in table 1. We found 22 different sequence alterations (19 of which were novel) in 28 (76%) of 37 patients. Of those patients, 17 had two sequence alterations (8 homozygous and 9 compound heterozygous), and 11 had one sequence alteration. The majority (19/22) of the identified changes are predicted to be truncating because of frameshift or nonsense sequence alterations. Three different and unknown heterozygous sequence alterations are predicted to exist in separate patients because of the deletion of one or two whole exons where no sequence alterations were detected in 300 bp of sequence from either side of the deleted exon(s). The deletion of exon 55 in patient CV1419 is predicted to be truncating. The deletion of exon 44 in patient CV1414 and the two-exon deletion (exons 20 and 21) in an affected sib pair (patients F5 and F6) are predicted to be nontruncating in-frame deletions, although it is unknown whether the transcripts are translated. A third nontruncating sequence alteration (p.Asn2993Ser) was found as a homozygous change in a Belgian affected sib pair. In the absence of a functional assay, it remains possible that this missense change represents a rare nonpathogenic variant.

Of 19 sequence alterations found by sequencing (exonic deletions not included), 17 were also identifiable by SSCP. None of the identified sequence alterations were found in a random panel of at least 192 control chromosomes (116 chromosomes for nonsense sequence alterations) screened by SSCP, sequencing, or restriction digestion of PCR-amplified genomic DNA. The heterozygous deletion of exons 20 and 21, exon 44, and exon 55 was not screened for in controls; however, for the latter two deletions, segregation of the mutant allele from a carrier parent was demonstrated for each of the probands. For three of the nine patients with Cohen syndrome in whom no sequence alteration was identified, there was no evidence of loss of heterozygosity, as determined with the use of five STR markers spaced throughout the *COH1* genomic region (data not shown).

In the group of patients with Cohen-like syndrome who had incomplete clinical data (17 patients), 1 Israeli patient (I1) and 1 patient from the United States (US1) had sequence alterations in *COH1* (table 1), increasing to 25 the total number of *COH1* sequence alterations identified (22 of which are novel). These additional three sequence alterations would be expected to result in functional null alleles, either through a frame shift or through altered splicing. Although both these patients were categorized initially as having Cohen-like syndrome because of the lack of full clinical data, patient US1 has developmental delay, the typical facial gestalt, and chorioretinal dystrophy and fulfils the diagnostic criteria for

Table 1

Sequence Alterations and the Presence/Absence of Clinical Features

	Gene Defect			Clinical Feature[a]							
Patient and Origin	DNA Alteration[b]	Protein Alteration	Exon/Intron	Developmental Delay	Microcephaly (Under 2 SD)	Typical Facial Gestalt	Obesity with Slender Extremities	Overly Sociable Behavior	Joint Hypermobility	High Myopia and/or Retinal Dystrophy	Intermittent Neutropenia
F1/ Finnish	[c.3348_3349delCT]+[c.5827C→T]	[p.Cys1117fsX8]+[p.Arg1943X]	23, 34	+	+	+	+	+	+	+	+
F2/ Finnish	[c.5827C→T]+[c.5827C→T]	[p.Arg1943X]+[p.Arg1943X]	34, 34	+	+	+	+	+	+	+	+
F3/ Finnish	[c.3348_3349delCT]+[c.5730_5731insA]	[p.Cys1117fsX8]+[p.Ile1913fsX6]	23, 34	+	+	+	+	+	+	+	+
F4/ Finnish	[c.3348_3349delCT]+[c.10838_10841delCTCT]	[p.Cys1117fsX8]+[p.Leu3614fsX36]	23, 56	+	+	+	−	−	+	+	+
F5/ Finnish	***[c.3348_3349delCT]+[EX20_21del]***	***[p.Cys1117fsX8]+[p.Gly942_Thr1027del]***	***23, 20, 21***	+	+	+	+	+	+	+	+
F6/ Finnish	***[c.3348_3349delCT]+[EX20_21del]***	***[p.Cys1117fsX8]+[p.Gly942_Thr1027del]***	***23, 20, 21***	+	+	+	+	+	+	+	+
F7/ Finnish	[c.3348_3349delCT]+[c.10838_10841delCTCT]	[p.Cys1117fsX8]+[p.Leu3614fsX36]	23, 56	+	+	+	−	−	+	+	+
F8/ Finnish	[c.3348_3349delCT]+[c.?]	[p.Cys1117fsX8]+[p.?]	23, ?	+	+	+	+	+	+	+	+
F9/ Finnish	[c.3348_3349delCT]+[c.?]	[p.Cys1117fsX8]+[p.?]	23, ?	+	+	+	+	+	+	+	+
F10/ Finnish	***[c.3348_3349delCT]+[c.?]***	***[p.Cys1117fsX8]+[p.?]***	***23, ?***	+	+	+	−	+	+	+	***ND***
F11/ Finnish	***[c.3348_3349delCT]+[c.?]***	***[p.Cys1117fsX8]+[p.?]***	***23, ?***	+	+	+	−	+	+	+	***ND***
CV1413/ British	[c.5750delC]+[c.9690-2A→G]	[p.Ser1917fsX19]+[p.Arg3230fsX20]	34, IVS52	+	+	+	+	+	+	+	+
CV1409/ British	[c.5613_5614insT]+[c.11169_11172dupGGAC]	[p.Ser1873fsX9]+[p.Arg3725fsX7]	34, 58	+	+	+	+	+	+	+	+
CV1325/ British	[c.11907dupC]+[c.?]	[p.Ser3970fsX22]+[p.?]	62, ?	+	+	+	−	−	+	+	+
CV1418/ British	[c.4334delA]+[c.?]	[p.Gln1445fsX7]+[p.?]	29, ?	+	+	+	−	+	+	+	+
CV1419/ British	[EX55del]+[c.?]	[p.Val3340fsX9]+[p.?]	55, ?	+	−	+	−	+	+	+	+
CV1414/ British	[EX44del]+[c.?]	[p.Leu2673_Gln2724del]+[p.?]	44, ?	+	+	+	−	+	+	+	+
CV1295/ Dutch	***[c.8697-2A→G]+[c.8697-2A→G]***	***[p.Glu2900fsX2]+[p.Glu2900fsX2]***	***IVS47, IVS47***	+	+	+	+	−	+	+	+
CV1294/ Dutch	***[c.8697-2A→G]+[c.8697-2A→G]***	***[p.Glu2900fsX2]+[p.Glu2900fsX2]***	***IVS47, IVS47***	+	−	+	+	+	+	+	+
CV1405/ British	[c.463_466delATAA]+[c.463_466delATAA]	[p.Asn156fsX4]+[p.Asn156fsX4]	5, 5	+	+	+	+	+	+	+	+
CV1258/ British	[c.8472G→A]+[c.?]	[p.Trp2824X]+[p.?]	46, ?	+	+	+	+	−	+	+	−
CV1422/ British	[c.2889G→A]+[c.?]	[p.Trp963X]+[p.?]	20, ?	+	+	+	+	+	−	+	+
CV1402/British	***[c.4471G→T]+[c.4471G→T]***	***[Glu1491X]+[Glu1491X]***	***29, 29***	+	+	+	+	−	+	***NC***	+
CV1424/ British	***[c.4471G→T]+[c.4471G→T]***	***[Glu1491X]+[Glu1491X]***	***29, 29***	+	+	+	+	−	+	+	+
D1/ Danish	[c.6420_6421delGA]+[c.8341delC]	[p.Gln2140fsX27]+[p.Leu2781X]	36, 45	+	+	+	+	+	−	+	+
D2/ Danish	[c.22_23delCCinsA]+[c.?]	[p.Pro8fsX3]+[p.?]	2, ?	+	+	+	+	+	−	+	+
B1/ Belgian	***[c.8978A→G]+[c.8978A→G]***	***[p.Asn2993Ser]+[p.Asn2993Ser]***	***49, 49***	+	+	+	+	+	+	+	+
B2/ Belgian	***[c.8978A→G]+[c.8978A→G]***	***[p.Asn2993Ser]+[p.Asn2993Ser]***	***49, 49***	+	+	+	+	+	+	+	+
U.S.1/ U.S.A.	[c.6733-2A→G]+[c.?]	[r.spl?;p.?]+[p.?]	IVS37, ?	+	+	+	ND	+	ND	+	ND
I1/ Israel	[c.11906_11915delCCAGCTGTTC]+[c.6732+1G→A]	[p.Pro3969fsX41]+[r.spl?;p.?]	62, IVS37	+	+	+	+	+	ND	ND	ND

Note.—Eight clinical features were used to diagnose 28 patients with true Cohen syndrome and 2 additional patients with incomplete clinical data. Sib pairs are in bold italics.

[a] + = presence; − = absence; NC = not confirmed; ND = no data.

[b] Mutations [c.3348_3349delCT], [c.8472G→A], and [c.6420_6421delGA] were described in Kolehmainen et al. (2003).

Cohen syndrome described by Chandler et al. (2003). Data for key diagnostic criteria is lacking for the Israeli patient I1, which makes an unequivocal clinical diagnosis of Cohen syndrome impossible. It is highly probable that both patients have Cohen syndrome. It is possible that some *COH1* mutations remain undetected in the group of patients with incomplete clinical data.

The 22 patients with Cohen-like syndrome and full clinical data were analyzed by SSCP. This technique detected 17 (89%) of the 19 mutations described here for patients with true Cohen syndrome. Only one patient from this group had a heterozygous change (p.Ala3753Thr) that was not identified in 192 CEPH control chromosomes. This patient lacked the facial gestalt typical of Cohen syndrome, was not neutropenic, had only mild learning difficulties, and had no visual difficulties apart from mild myopia (however, the patient did not have a full ophthalmological assessment). The patient is macrocephalic and has truncal obesity and a sociable personality. This patient does not meet the criteria for true Cohen syndrome. It remains possible that this sequence alteration is a rare nonpathogenic variant.

We conclude that there is a clear genetic demarcation between patients with true Cohen syndrome and those with a Cohen-like syndrome. The demonstration that all predicted pathogenic *COH1* sequence alterations were found in our patients with Cohen syndrome and that no such sequence alterations were found in patients with a Cohen-like syndrome validates our criteria for the accurate diagnosis of this syndrome. These criteria are detailed in Chandler et al. (2003) and include developmental delay, characteristic facial gestalt, chorioretinal dystrophy, and neutropenia. It should be noted that, as the neutropenia in Cohen syndrome is intermittent, it may be undetectable in patients unless repeated differential counts are made (Norio et al. 1984).

The patients with a Cohen-like syndrome were not phenotypically homogeneous, which suggests that they are unlikely to represent a single and separate clinical grouping. Although SSCP analysis alone cannot exclude small heterozygous genomic *COH1* deletions (in all but two patients), genetic analyses lend further support for a demarcation between true Cohen syndrome and Cohen-like syndromes. Microsatellite analysis using markers flanking *COH1* was undertaken on 12 families with Cohen-like syndrome. Linkage to the *COH1* locus was excluded in 4 of the 12 families and could be neither confirmed nor excluded in the remaining 8 families.

The majority (27/31) of *COH1* gene alterations detected in the patients with Cohen syndrome to date (Kolehmainen et al. 2003; present study) are predicted to result in a null allele, either through a nonsense change or through a frameshift resulting in a premature stop codon. Two mutations (in patients CV1414 and F5/6) are predicted to cause in-frame deletions. We have described two missense alterations: p.Leu2193Arg, reported elsewhere (Kolehmainen et al. 2003), and p.Asn2993Ser. In the absence of a functional assay, it remains possible that these missense changes represent rare nonpathogenic variants. Interestingly, the p.Asn2993Ser change creates an AG dinucleotide in the middle of exon 49, immediately upstream of a pyrimidine-rich region, creating the characteristic consensus of a splice acceptor site. If a new splice site were, indeed, created by this change, it would predict the deletion of the first 111 bp of exon 49 and an in-frame deletion of 37 aa in the conserved C-terminal VPS13 domain. Supportive evidence for the importance of the VPS13 domain can be obtained from the sequencing of RT-PCR products covering the 3′ end of *COH1* (c.9065-12097), which revealed that in normal lymphoblasts there are two mRNA forms, the longer of which includes the entire intron 60. This splice form has also been identified as a spliced EST (GenBank accession number BX648610). In this splice form, the ORF for exon 60 is extended by 1 bp into intron 60, before a truncating stop codon terminates the translation of the full VPS13 domain prematurely. In this study, we have shown that truncating sequence alterations in exon 62 cause Cohen syndrome (in patients CV1325 and I1, respectively). This demonstrates that the full-length splice form (exons 1–62) with the complete C-terminal VPS13 domain is essential for normal development and, when absent, results in classical Cohen syndrome.

This study represents the largest screen of patients with Cohen syndrome and Cohen-like syndrome to date. It has demonstrated clearly that predicted pathogenic sequence alterations in *COH1* are associated only with patients with Cohen syndrome, as defined by diagnostic criteria established elsewhere, and that within this group there is no apparent genotype-phenotype correlation. From a clinical perspective, this study has validated the precise diagnostic criteria necessary for the accurate diagnosis of Cohen syndrome and provides a basis for laboratory screening as part of a diagnostic service. The importance of the VPS13 domain in development has been highlighted also, and future work will need to be directed at elucidating its biological function.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Genbank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *COH1* [*Homo sapiens*] mRNA [accession number AY223814] and *COH1* [*H. sapiens*] spliced EST [accession number BX648610])

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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