CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Clinical Report: Cognitive Decline in a Patient with Cardiofaciocutaneous Syndrome

Sergio Cabrera,[1] Chantal Morel,[2] and Maria Carmela Tartaglia[1,3]*

[1]University Health Network Memory Clinic, Toronto, Ontario, Canada

[2]Fred A. Litwin Family Centre in Genetic Medicine, University Health Network, Toronto, Ontario, Canada

[3]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada

Manuscript Received: 13 October 2014; Manuscript Accepted: 27 December 2015

Cardiofaciocutaneous Syndrome (CFCS) is a rare genetic syndrome caused by mutations in one of four genes: *BRAF*, *MAP2K1*, *MAP2K2*, and *KRAS*. There is tremendous phenotypic heterogeneity in patients with CFCS and so confirmation of diagnosis requires genetic testing. Neurologic and/or cognitive symptoms are present in almost all CFCS individuals. Little is known about cognitive function in older patients with CFCS. In this report, we present the cognitive, neuropsychiatric, and imaging findings of a patient diagnosed with CFCS who after having remained stable developed progressive cognitive/behavioral and motor decline. © 2016 Wiley Periodicals, Inc.

Key words: Cardiofaciocutaneous syndrome; RASopathies; cognitive decline

How to Cite this Article:
Cabrera S, Morel C, Tartaglia MC. 2016. Clinical Report: Cognitive decline in a patient with Cardiofaciocutaneous syndrome.
Am J Med Genet Part A 170A:1251–1256.

INTRODUCTION

Cardiofaciocutaneous Syndrome (CFCS) is a rare congenital anomaly syndrome characterized by distinctive facial appearance, heart defects, and intellectual disability [Reynolds et al., 1986; Allanson et al., 2011]. It is caused by mutations in one of four genes associated with the mitogen-activated protein kinase (MAPK) pathway: *BRAF*, *MAP2K1* and *MAP2K2*, and *KRAS*. Most cases represent de novo dominant mutations with men and women being equally affected [Roberts et al., 2006] but, transmission of an autosomal dominant germline mutation (*MAP2K2)* through multiple generations has been reported in one family [Rauen, 2012]. With an estimated prevalence of 1 in 810,000 [Abe et al., 2012] more than 100 cases have been reported in the literature [Rauen, 2012].

Over 80 clinical characteristics have been identified from all the reported CFCS cases; however, there are no specific criteria for CFCS [Kavamura et al., 2002]. There is tremendous heterogeneity in phenotype among the patients and so confirmation of the diagnosis requires genetic testing to identify the mutation in one of the genes involved in the disease (*B-RAF* 75%, *MAP2K1* or *MAP2K2* 25%, or *KRAS*<2%) [Niihori et al., 2006; Rodriguez et al., 2006; Tidyman and Rauen, 2009; Rauen, 2012]. Neurologic and cognitive symptoms accompanied by mild to severe developmental delay are present in nearly all CFCS individuals, although a few individuals may have IQs in the normal range [Manoukian et al., 1996; Armour and Allanson, 2008]. Since no longitudinal or natural history studies of CFCS have been performed, the cognitive function in older patients with this syndrome is unknown.

We present a case of a patient diagnosed with CFCS who after having remained stable developed progressive cognitive/behavioral and motor decline in his 30s.

CASE REPORT

A 39-year-old left-handed man with a Q262P mutation in the *BRAF* gene and clinical CFCS presented to the UHN Memory Clinic for progressive cognitive, behavioral, and motor impairment. He came accompanied by caregivers who have known him for approximately 10 years. Most of the history was obtained from them as our patient did not have very much insight into his deficits. They reported that in his early 30s he began to develop changes in behavior and a decline in his cognitive skills. He gradually became more dependent for his basic activities of daily living. He developed severe dysarthria wherein his speech became incomprehensible. In regard to his behavior, he became physically

Conflicts of interest: none.

*Correspondence to:
Carmela Tartaglia, M.D., Division of Neurology. UHN Toronto Western Hospital, Room 5WW 449. 399 Bathurst Street, Toronto, Ontario, Canada 6M5T 2S8.
E-mail: carmela.tartaglia@uhn.ca

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 3 February 2016
DOI 10.1002/ajmg.a.37552

and verbally aggressive displaying episodes of self-injurious behaviors such as biting his tongue, hitting his head against the wall, and destroying his personal possessions. He became apathetic, withdrawn, and quieter and in addition showed loss of empathy. He also became very disorganized.

He had a history of spastic quadriparesis, but had been able to walk and run without help. In his early 30s, his gait began to gradually decline and at the age of 37 he started using a walker and a wheelchair for long trips.

On examination, he was an alert, well-groomed gentleman who looked older than his stated-age of 39 and had dysmorphic features including macrocephaly with bitemporal narrowing, ocular hypertelorism, and bilateral eyelid ptosis. He also had prognathism and an elongated face. The forehead was prominent and the nasal tip bulbous. The ears were low set, but not posteriorly rotated. The neck was broad and the hairline low. He had down-turned corners of the mouth. His height and weight were 158 cm and 52 kg, respectively. His head circumference was 58.8 cm. He had pectus excavatum. Heart sounds and abdomen exam were normal. He had many moles on his ears, abdomen, and legs.

He had severe dysarthria and his speech consisted of very short and concrete answers. His thought form was coherent. He was inattentive and disinterested in the interview but was compliant with the neuropsychological evaluation. He had no comprehension deficits following oral commands. He did not exhibit any delusional thinking or perceptual abnormalities. Visual acuity in both eyes was 20/800 with correction. He had strabismus and constant nystagmus. He had spastic quadriparesis with bilateral pyramidal signs. He reported no sensory deficits.

The neuropsychological exam performed was a modified version of the Behavioral Neurological Assessment (BNA) [Darvesh et al., 2005] and is reported in Table I. The clinical dementia rating scale (CDR) [Morris, 1993] score was three (severe impairment in memory, judgment, problem solving, and managing of community and home affairs). The neuropsychiatric inventory [Cummings et al., 1994] revealed he had frequent mild agitation and irritability; and frequent moderate apathy and disinhibition. His brain CT scans did not reveal any diffuse or focal lesions. His CT scan was read by a neuroradiologist as subtle diffuse loss of cortical volume largely unchanged after a 7 year interval. His hippocampi were not atrophied and had not significantly changed over time. There was no significant vascular disease noted (Fig. 1).

Based on medical records from the pediatrician he saw in the 1970s, he was born at 38 weeks of normal delivery weighing nine pounds. He had significant delay in his motor milestones; sitting up by 13 months and walking at two-and-a-half years. He attended special education classes until the age of 21, and since the early 1990s he has been living in an assisted living facility. Detailed educational reports were obtained from the different schools he attended from the age of 3 until he was 21 years old when he finished high school. He was known for being a friendly and cooperative boy. In the Slosson Intelligence Test administered by his pediatric neurologist at the age of 4 years and 6 months his mental age was of 4 years and 2 months. His cognitive and language stage based on Piagetian concept of development at the age of 4 was considered at a 3-year-old level. At the same age, the patient was staged at IV (adequate for 35–40 months old) of the Brown's Stages of linguistic development [Brown, 1973] based on his syntactic and morphological language production. In addition, at the age of 4, his functional level as indicated by The Portage Guide to Early Education [Shearer and Shearer, 1972] was at three-and-a-half years for language, self-help skills, and cognitive function. From academic records his receptive and expressive language skills at 6 years and 10 months were reported as appropriate for his age in a Test for Auditory Comprehension of Language [Carrow-Woolfolk, 1973]. This test determined the patient́s understanding of the spoken language to be age equivalent to 6.4 years (24th percentile).

The educational reports indicated his speech was fluent, logical with good thought sequences. Until the age of 12, he displayed attention deficits, impulsivity, and some difficulty socializing. It was reported that these problems gradually improved and he became quite sociable and developed a great sense of humor. His memory was always reported as average, although no specific memory test was administered. He developed effective functional reading skills despite his visual acuity deficits (OD 8/400 and OS 2/400, both with correction) when he was 9. The Wide Range Achievement Test 2 (WRAT2) [Bijou and Jastak, 1941] was administered when he was 15 and he was rated at a grade 3 (out of 3) for reading, spelling, and mathematics. In his last years of high-school, he participated in the schoóĺs newspaper production class and was involved in the Job Entry program. Until his early 30s, he was actively involved in social activities at his residence. He worked there as a receptionist and had public speaking engagements to promote their programs. He managed all his basic activities of daily living, requiring only minimal supervision because of mobility. He managed some instrumental activities of daily living including meal preparation and scheduling his own appointments. He has been living in the same assisted living facility for over 20 years.

His past medical history included severe sleep apnea that is treated with continuous positive airway pressure and recent reassessment has shown adequate control. He has recurrent ear infections. He began having partial complex and generalized seizures at 4 days of age. Initially, the seizure frequency was very low so anticonvulsants were only started when he was 4 years old. He was on Phenobarbital and Valproic Acid but at age 32 the Valproic acid was discontinued because he developed hyperammonemia and he was started on Carbamazepine 1,200 mg/day. His hyperammonemia resolved with medication switch. Topiramate 150 mg a day was added when he was 38. His partial complex seizures have decreased to one per month comprising left or right extremity jerking that lasts less than 2 min. He has less than one generalized seizure per year. When he was having frequent partial complex and generalized seizures his electroencephalograms revealed frontotemporal epileptic activity with sharp wave discharges in both post-central regions. He has never been in status epilepticus. He has a cardiac arrhythmia which was treated with a pacemaker at the age of 29. At 36, his family doctor diagnosed him with depression and dementia and started him on Quetiapine 150 mg daily, Trazodone 100 mg daily, and Donepezil 10 mg daily. There has been no significant clinical changes with these medications. He is on Baclofen 30 mg per day with no change in the severity of the spasticity.

TABLE I. Neuropsychological Exam. Modified Version of the Behavioral Neurological Assessment (BNA-R)

BNA-R				Norms[a]
Orientation			6	N > 12 B 10–11 I < 10
Memory immediate recall[b] (Cerad word list)			12	N > 19
Learning:	Trial 1	Trial 2	Trial 3	B 16–18
#words learned	3/10	4/10	5/10	I
Intrusions/repetitions	0	0	0	
Memory delayed recall			0	N > 16
CERAD Word list			0/10	B 11–15
Intrusions/repetitions			0	I < 11
Benson figure delayed recall			0/17	
Memory delayed recognition			17	N > 20
CERAD delayed recognition			16/20	B 17–19
Benson figure delayed recognition recall[b]			1/1	I < 17
Visuospatial skills[b]			18	N > 28
Clock draw			1/15	B 24–27
Benson figure copy			17/17	I < 24
Executive functions			26	N > 108
Serial 7's			0/13	B 101–107
Serial 3's			2/13	I < 101
Digit span forward			4/9	
Digit span reverse			3/8	
Luria: Ramparts[b]			0/2	
Similarities			7/10	
Verbal fluency-lexical (F)			9	
TRAILS[b]:	Time (sec)	Errors	Lines	
A	90	0	10/24	
B	Could not do	–	0/24	
Language			70	N > 81
Verbal fluency-semantic (animals)			9	B 74–80
Naming (MINT)[b]			14/15	I < 74
Sentence repetition			10/10	
Single word comprehension[b]			4/8	
Single word reading comprehension[b]			2/2	
Sentence comprehension[b]			4/8	
Single word reading[b]			8/12	
Semantic knowledge[b]			10/10	

[a]Norms based on 180 healthy controls. University Health Network—Memory Clinic, Toronto Ages between 60–69 years. Non-published data.
[b]Tests with visual component.
N, Normal; B, Borderline; I, Impaired.

DISCUSSION

CFCS is a rare congenital condition characterized by multi-system anomalies including cognitive, cardiac, and motor symptoms. This case report features the oldest patient with genetically confirmed CFCS ever reported. Based on reliable information gathered from his caregivers, educational reports and medical records, this patient was able to manage his basic activities of daily living with only minimal supervision and had achieved verbal skills considered acceptable for age despite the mild impairment on syntactic and morphological language production. Social skills had also been considered normal for age. In his 30s, he began exhibiting cognitive, behavioral, and motor decline that progressed so that he now requires help for all basic activities of daily living. His behavioral changes including significant apathy and poor impulse control suggest frontal lobe dysfunction. Verbal and visual memory, as well as executive function, and both phonemic and semantic fluency were severely impaired while comprehension was moderately impaired. His visuospatial skills and other language functions such as naming, repetition, single word reading, and semantic knowledge were spared. His longstanding visual acuity deficits and nystagmus are largely unchanged and did not appear to interfere with cognitive testing since he performed very well in some tests such as semantic knowledge assessment, naming, and visuospatial skill that require visual processing. Although limited and not comparable to recent cognitive assessments, his performance on the neuropsychological tests and caregiver reports in the last 3 years demonstrate severe decline in cognition and behavior. It is unclear

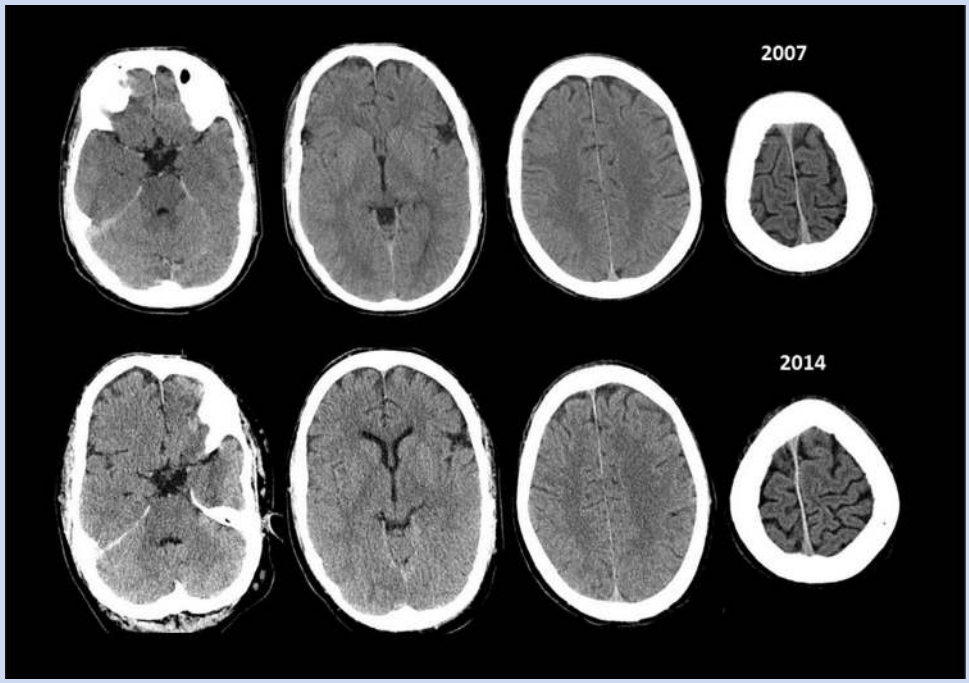

FIG. 1. Brain CT scans suggesting subtle change in the cortical volume after 7 years follow-up.

whether the CFCS itself is causing his progressive cognitive, behavioral, and motor decline or whether he has developed a concurrent neurodegenerative disorder.

There have been several publications describing the genotypic and the phenotypic spectrum of CFCS, but the natural history of the cognitive, behavioral, and motor deficits in older individuals with this diagnosis remains unknown. In a large cross-sectional study of patients with CFCS and Noonan Syndrome, both groups of patients had significant delays in adaptive behaviors relative to their peers; however, the authors reported improvement in these adaptive behaviors over time [Pierpont et al., 2010]. In other RASopathies, such as Costello Syndrome, patients have stable intellectual disability if it is present [Axelrad et al., 2009; Wingbermühle et al., 2009, 2012; Alfieri et al., 2014]. Since different mutations are associated with CFCS, it is unknown whether some mutations could to lead to progressive cognitive-behavioral and motor decline while other mutations could lead to stable deficits.

Developmental delay with moderate/severe intellectual disability has been reported in virtually all (96–100%) patients with CFCS [Narumi et al., 2007; Armour and Allanson, 2008; Abe et al., 2012], although a few reports have described patients with spared cognitive function [Manoukian et al., 1996; Armour and Allanson, 2008]. In a recent study examining the neuropsychiatric symptoms of patients with CFCS aged from 4 to 19, an increased incidence of psychopathology such as concomitant autism spectrum disorder was reported [Alfieri et al., 2014]. Although IQ was reported in this study, no neuropsychological assessment or follow-up of their cognitive function was available.

RAS–MAPK signaling pathways have been associated with several normal cellular processes in neurons including neuronal differentiation, plasticity, long-term potentiation, and memory formation [Orban et al., 1999; Davis and Laroche, 2006; Miyamoto, 2006]. In contrast, dysregulation in MAPK signaling pathways have been implicated in the pathogenesis of several disorders including cancer and neurodegenerative diseases, such as Alzheimeŕs disease (AD), Parkinsoń s disease and, Amyotrophic Lateral Sclerosis [Peel et al., 2004; Bendotti et al., 2005; Kim and Choi, 2010]. In AD, MAPK seems to play an important role in the phosphorylation of the tau protein at specific sites that are relevant to the pathophysiology of AD [Zhu et al., 2002; Peel et al., 2004]. There may exist an association between dysregulation of the RAS–MAPK signaling pathways and the development of AD pathology but this is unknown. The imaging in this patient with stable, mild, diffuse atrophy is atypical for AD.

RAS–MAPK signaling pathways are implicated in cell growth stimulation and oncogenic activities [Bos, 1988, 1989; Garnett and Marais, 2004]. However, there is some evidence for dual oncogenic/anti-oncogenic properties of the *ras* proto-oncogene family that may simultaneously activate the mitogenic MEK-ERK MAPK pathway and the MKK3/6-p38 pathway which triggers premature senescence [Wang et al., 2002; Deng et al., 2004]. This *ras* induced mechanism of senescence has been postulated as one of the possible causes of the accelerated aging seen in Werner Syndrome [Davis et al., 2005]. Accelerated-aging caused by dysregulation of RAS-MAPK pathways is a possible mechanism for the cognitive, behavioral, and motor decline seen in our patient.

Our case's neuroimaging, albeit a CT scan, did not show any significant structural brain abnormality and there was very little change in cortical volume or white matter characteristics over a

7 year interval. The atrophy pattern is not suggestive of a neurodegenerative disease, such as AD, frontotemporal dementia, or vascular disease. Furthermore, his CT scans did not show some of the typical findings reported in CFCS, such as ventriculomegaly and hydrocephalus [Yoon et al., 2007; Papadopoulou et al., 2011]. Since an MRI is contraindicated because of his pacemaker, we cannot easily investigate other brain abnormalities described in CFCS, such as cortical atrophy, prominent Virchow-Robin spaces and abnormal myelination [Yoon et al., 2007; Papadopoulou et al., 2011].

Accurate information from yearly educational reports until his 20s and the recent progressive cognitive, behavioral and motor decline reported by his caregivers, family members, and physicians who have been following him for many years suggest a progressive disease. His seizure disorder is stable and is not likely contributing to his cognitive impairment. Finally, in keeping with his congenital disorder, he has other neurological findings which have been previously described, such as motor and speech delay, learning disability, macrocephaly, ptosis, strabismus, nystagmus, pyramidal syndrome, and seizures [Yoon et al., 2007; Pierpont et al., 2014].

Longitudinal data is required to determine the long-term prognosis of patients with CFCS and investigate whether there are progressive neurological changes in the majority of these patients and are they due to the natural history of their primary disease, accelerated aging, or the development of a concomitant neurodegenerative process, such as AD [McKhann GM et al., 2011]. Future studies of this population will be required to better characterize prognosis and natural history of CFCS.

ACKNOWLEDGMENTS

We thank the patient, his caregivers, and his family for their invaluable collaboration.

REFERENCES

Abe Y, Aoki Y, Kuriyama S, Kawame H, Okamoto N, Kurosawa K, Ohashi H, Mizuno S, Ogata T, Kure S, Niihori T, Matsubara Y. Costello and CFC syndrome study group in Japan. 2012. Prevalence and clinical features of Costello syndrome and cardio-facio-cutaneous syndrome in Japan: Findings from a nationwide epidemiological survey. Am J Med Genet Part A 158A:1083–1094.

Alfieri P, Piccini G, Caciolo C, Perrino F, Gambardella ML, Mallardi M, Cesarini L, Leoni C, Leone D, Fossati C, Selicorni A, Digilio MC, Tartaglia M, Mercuri E, Zampino G, Vicari S. 2014. Behavioral profile in RASopathies. Am J Med Genet Part A 164A:934–942.

Allanson JE, Annerén G, Aoki Y, Armour CM, Bondeson ML, Cave H, Gripp KW, Kerr B, Nystrom AM, Sol-Church K, Verloes A, Zenker M. 2011. Cardio-facio-cutaneous syndrome: Does genotype predict phenotype. Am J Med Genet Part C Semin Med Genet 157C:129–135.

Armour CM, Allanson JE. 2008. Further delineation of cardio-facio-cutaneous syndrome: Clinical features of 38 individuals with proven mutations. J Med Genet 45:249–254.

Axelrad ME, Schwartz DD, Fehlis JE, Hopkins E, Stabley D, Sol-Church K, Gripp KW. 2009. Longitudinal course of cognitive, adaptive, and behavioral characteristics in Costello syndrome. Am J Med Genet Part A 149A:2666–2672.

Bendotti C, Bao Cutrona M, Cheroni C, Grignaschi G, Lo Coco D, Peviani M, Tortarolo M, Veglianese P, Zennaro E. 2005. Inter- and intracellular signaling in amyotrophic lateral sclerosis: Role of p38 mitogen-activated protein kinase. Neurodegener Dis 2:128–134.

Bijou SW, Jastak JF. 1941. Wide range achievement test. New York: Psychological Corporation.

Bos JL. 1988. The ras gene family and human carcinogenesis. Mutat Res 195:255–271.

Bos JL. 1989. Ras oncogenes in human cancer: A review. Cancer Res 49:4682–4689.

Brown R. 1973. A first language: The early stages. Cambridge: Harvard University Press.

Carrow-Woolfolk E. 1973. Test for auditory comprehension of language (English). United States: Teaching Resources.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. 1994. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. Neurology 44:2308–2314.

Darvesh S, Leach L, Black SE, Kaplan E, Freedman M. 2005. The behavioural neurology assessment. Can J Neurol Sci 32:167–177.

Davis T, Baird DM, Haughton MF, Jones CJ, Kipling D. 2005. Prevention of accelerated cell aging in Werner syndrome using a p38 mitogen-activated protein kinase inhibitor. J Gerontol A Biol Sci Med Sci 60:1386–1393.

Davis S, Laroche S. 2006. Mitogen-activated protein kinase/extracellular regulated kinase signalling and memory stabilization: A review. Genes Brain Behav 5:61–72.

Deng Q, Liao R, Wu BL, Sun P. 2004. High intensity ras signaling induces premature senescence by activating p38 pathway in primary human fibroblasts. J Biol Chem 279:1050–1059.

Garnett MJ, Marais R. 2004. Guilty as charged: B-RAF is a human oncogene. Cancer Cell 6:313–319.

Kavamura M, Peres C, Alchorne M, Brunoni D. 2002. CFC Index for the diagnosis of Cardiofaciocutaneous syndrome. Am J Med Genet 112:12–16.

Kim E, Choi E. 2010. Pathological roles of MAPK signaling pathways in human diseases. Biochim Biophys Acta 1802:396–405.

Manoukian S, Lalatta F, Selicorni A, Tadini G, Cavalli R, Neri G. 1996. Cardio-facio-cutaneous (CFC) syndrome: Report of an adult without mental retardation. Am J Med Genet 63:382–385.

Miyamoto E. 2006. Molecular mechanism of neuronal plasticity: Induction and maintenance of long-term potentiation in the hippocampus. J Pharmacol Sci 100:433–442.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. 2011. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:263–269.

Morris JC. 1993. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology 43:2412–2414.

Narumi Y, Aoki Y, Niihori T, Neri G, Cavé H, Verloes A, Nava C, Kavamura MI, Okamoto N, Kurosawa K, Hennekam RC, Wilson LC, Gillessen-Kaesbach G, Wieczorek D, Lapunzina P, Ohashi H, Makita Y, Kondo I, Tsuchiya S, Ito E, Sameshima K, Kato K, Kure S, Matsubara Y. 2007. Molecular and clinical characterization of cardio-facio-cutaneous (CFC) syndrome: Overlapping clinical manifestations with Costello syndrome. Am J Med Genet Part A 143A:799–807.

Niihori T, Aoki Y, Narumi Y, Neri G, Cavé H, Verloes A, Okamoto N, Hennekam RC, Gillessen-Kaesbach G, Wieczorek D, Kavamura MI, Kurosawa K, Ohashi H, Wilson L, Heron D, Bonneau D, Corona G, Kaname T, Naritomi K, Baumann C, Matsumoto N, Kato K, Kure S, Matsubara Y. 2006. Germline KRAS and BRAF mutations in cardio-facio-cutaneous syndrome. Nat Genet 38:294–296.

Orban P, Chapman P, Brambilla R. 1999. Is the Ras-MAPK signalling pathway necessary for long-term memory formation? Trends Neurosci 22:38–44.

Papadopoulou E, Sifakis S, Sol-Church K, Klein-Zighelboim E, Stabley DL, Raissaki M, Gripp KW, Kalmanti M. 2011. CNS imaging is a key diagnostic tool in the evaluation of patients with CFC syndrome: Two cases and literature review. Am J Med Genet Part A 155A:605–611.

Peel A, Sorscher N, Kim J, Galvan V, Chen S, Bredesen D. 2004. Tau phosphorylation in Alzheimer's disease: Potential involvement of an APP-MAP kinase complex. Neuromolecular Med 5:205–218.

Pierpont EI, Pierpont ME, Mendelsohn NJ, Roberts AE, Tworog-Dube E, Rauen KA, Seidenberg MS. 2010. Effects of germline mutations in the Ras/MAPK signaling pathway on adaptive behavior: Cardiofaciocutaneous syndrome and Noonan syndrome. Am J Med Genet Part A 152A:591–600.

Pierpont ME, Magoulas PL, Adi S, Kavamura MI, Neri G, Noonan J, Pierpont EI, Reinker K, Roberts AE, Shankar S, Sullivan J, Wolford M, Conger B, Santa Cruz M, Rauen KA. 2014. Cardio-facio-cutaneous syndrome: Clinical features, diagnosis, and management guidelines. Pediatrics 134:149–162.

Rauen KA. Cardiofaciocutaneous syndrome. 2007 Jan 18 [Updated 2012 Sep 6]. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Smith RJH, Stephens K, editors. GeneReviews^{TM} [Internet]. Seattle (WA): University of Washington, Seattle. pp 1993–2014.

Reynolds JF, Neri G, Herrmann JP, Blumberg B, Coldwell JG, Miles PV, Opitz JM. 1986. New multiple congenital anomalies/mental retardation syndrome with cardio-facio-cutaneous involvement—The CFC syndrome. Am J Med Genet 25:413–427.

Roberts A, Allanson J, Jadico SK, Kavamura MI, Noonan J, Opitz JM, Young T, Neri G. 2006. The Cardiofaciocutaneous syndrome. J Med Genet 11:833–842.

Rodriguez-Viciana P, Tetsu O, Tidyman WE, Estep AL, Conger BA, Cruz MS, McCormick F, Rauen KA. 2006. Germline mutations in genes within the MAPK pathway cause cardio-facio-cutaneous syndrome. Science 311:1287–1290.

Shearer MS, Shearer DE. 1972. The Portage project: A model for early childhood education. Except Child 39:210–217.

Tidyman W, Rauen K. 2009. The RASopathies: Developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev 19:230–236.

Wang W, Chen JX, Liao R, Deng Q, Zhou JJ, Huang S, Sun P. 2002. Sequential activation of the MEK-extracellular signal-regulated kinase and MKK3/6-p38 mitogen-activated protein kinase pathways mediates oncogenic ras-induced premature senescence. Mol Cell Biol 22:3389–3403.

Wingbermühle E, Egger J, van der Burgt I, Verhoeven W. 2009. Neuropsychological and behavioral aspects of Noonan syndrome. Horm Res 72:15–23.

Wingbermühle E, Roelofs RL, van der Burgt I, Souren PM, Verhoeven WM, Kessels RP, Egger JI. 2012. Cognitive functioning of adults with Noonan syndrome: A case-control study. Genes Brain Behav 11:785–793.

Yoon G, Rosemberg J, Blaser S, Rauen K. 2007. Neurological complications of cardio-facio-cutaneous syndrome. Dev Med Child Neurol 49:894–899.

Zhu X, Lee H, Raina A, Perry G, Smith M. 2002. The role of mitogen-activated protein kinase pathways in Alzheimer's disease. Neurosignals 11:270–281.