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Cardio-facio-cutaneous syndrome: Does genotype predict phenotype?

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Abstract

Cardio-facio-cutaneous syndrome is a sporadic multiple congenital anomalies/mental retardation condition principally caused by mutations in *BRAF*, *MEK1*, and *MEK2*. Mutations in *KRAS* and *SHOC2* lead to a phenotype with overlapping features. In approximately 10–30% of individuals with a clinical diagnosis of cardio-facio-cutaneous, a mutation in one of these causative genes is not found. Cardinal features of cardio-facio-cutaneous include congenital heart defects, a characteristic facial appearance, and ectodermal abnormalities. Additional features include failure to thrive with severe feeding problems, moderate to severe intellectual disability and short stature with relative macrocephaly. First described in 1986, more than 100 affected individuals are reported. Following the discovery of the causative genes, more information has emerged on the breadth of clinical features. Little, however, has been published on genotype-phenotype correlations.

This clinical study of 186 children and young adults with mutation-proven cardio-facio-cutaneous syndrome is the largest reported to date. *BRAF* mutations are documented in 140 individuals (~75%), while 46 (~25%) have a mutation in *MEK 1* or *MEK 2*. The age range is 6 months to 32 years, the oldest individual being a female from the original report [Reynolds et al., 1986]. While some clinical data on 136 are in the literature, fifty are not previously published. We provide new details of the breadth of phenotype and discuss the frequency of particular features in each genotypic group. Pulmonary stenosis is the only anomaly that demonstrates a statistically significant genotype-phenotype correlation, being more common in individuals with a *BRAF* mutation.

Keywords

Cardio-facio-cutaneous syndrome; CFC; Noonan; Costello; genotype-phenotype

INTRODUCTION

Cardio-facio-cutaneous (CFC) syndrome is a relatively rare sporadic multiple congenital anomalies/mental retardation condition with characteristic features that include congenital heart defects, a characteristic facial appearance, ectodermal abnormalities, gastrointestinal dysmotility that includes failure to thrive with severe feeding problems, moderate-to-severe intellectual disability, and short stature with relative macrocephaly. First described by Reynolds et al. [1986] in 8 patients, the syndrome has been the subject of many reports. The discovery of several causative genes (see below), has allowed a greater understanding of the breadth of clinical features. Little, however, has been published on genotype-phenotype correlations.

CFC shows considerable phenotypic overlap with Noonan and Costello syndromes, making clinical diagnosis challenging, especially in the young child. Over the past decade, it has been demonstrated that all 3 syndromes are caused by mutations in genes in the Ras-ERK signalling pathway; CFC by mutations in *BRAF*, *MEK1*, and *MEK2*; Noonan syndrome by mutations in *PTPN11*, *SOS1*, *KRAS*, *RAF1*, *SHOC2*, *NRAS*, and, occasionally, *BRAF* or *MEK1*; and Costello syndrome by *HRAS* mutations [Tartaglia et al., 2001; Aoki et al., 2005; Niihori et al., 2006; Rodriguez-Viciana et al., 2006; Nava et al., 2007; Pandit et al., 2007; Razzaque et al., 2007; Roberts et al., 2007; Tartaglia et al., 2007; Nystrom et al., 2008; Cordeddu et al., 2009; Cirstea et al., 2010]. Mutations in *KRAS* cause considerable phenotypic heterogeneity, and, in many individuals, the features are intermediate between those of Noonan and CFC syndromes [Zenker et al., 2007]. While individuals with mutations in *SHOC2* have, in general, a distinct phenotype that represents a sub-type of Noonan syndrome and is easily recognized, several young children have presented with

features quite characteristic of CFC [authors' experience]. In up to a third of individuals with a clinical diagnosis of CFC, a mutation in one of the causative genes is not found [Rodriguez-Viciana et al., 2006; Nava et al., 2007; Narumi et al., 2007].

This clinical study of a cohort of 186 children and young adults with mutation-proven CFC is the largest to date and is focussed on the principal genes known to cause CFC, *BRAF*, *MEK1* and *MEK2*. *BRAF* mutations are documented in 140 individuals (~75%), while 46 (~25%) have a mutation in *MEK1* or *MEK2*. The age range is 6 months to 32 years, the oldest individual being a female from the original group reported in the seminal paper [Reynolds et al., 1986]. Fifty of the cohort are not previously published, but limited data on 136 are previously reported [Niihori er al., 2006; Narumi et al., 2007; Cave et al., 2007; Gripp et al., 2007; Armour and Allanson, 2008; Nystrom et al., 2008; Schultz et al., 2008]. While the methods of ascertainment vary from research group to research group, a core set of data have been gathered systematically, which provide new details of the breadth of phenotype and the frequency of particular features in each genotypic group.

METHODS

A core data set was established by a sub-group of authors (JA, BK and MZ). All international research consortia with an interest in CFC were approached and agreed to collaborate in assembling a large cohort of individuals with mutation-proven CFC. Each research consortium provided as complete a data set as possible for each patient. In many instances, the data provided exceeded information previously published. Ethics approval was obtained from the Research Ethics Boards of all collaborating institutions.

Individuals with a *BRAF* mutation were compared to individuals with a *MEK* mutation. Since the latter group was relatively small, aggregate data were chosen over separate *MEK1* and *MEK2* data. Results were expressed as a percentage: the number with a given feature compared to the total number for whom we had an informative answer (yes or no). Where no data were available, the individual was not included in the denominator.

Genotype-phenotype differences were evaluated using Fisher's exact test with two-tailed significance. Bonferroni correction was used. Statistical significance was defined as a p-value less than 0.05

RESULTS

Perinatal period

Table I shows the genotype-phenotype comparison of features noted in the prenatal and postnatal periods. None of these comparisons reached statistical significance. Polyhydramnios was a complication in about two-thirds. Prematurity (defined as birth before 37 weeks gestation) was also common and reported in almost half. Macrosomia was noted in a third.

Growth parameters

Short stature, with either relative or absolute macrocephaly, was typical of CFC. Table II shows the genotype-phenotype comparison. There were no differences of statistical significance. Two-thirds of individuals had stature below the 3rdcentile at the time of evaluation. Relative macrocephaly was much more common than absolute macrocephaly.

Cardiac

Heart disease is a cardinal feature of CFC. The most common anomalies reported in this study were pulmonary valve stenosis, hypertrophic cardiomyopathy, and atrial and ventricular septal defect defects. Table III provides details of the genotype-phenotype comparison. Pulmonary valve stenosis was statistically significantly more likely in association with a *BRAF* mutation. Hypertrophic cardiomyopathy was reported in up to a third of affected individuals. Atrial septal defects were more common than ventricular septal defects, and the latter defect was the only one more likely to be found in persons with a *MEK* mutation.

Skin and hair

Sparse, curly hair with absent or sparse eyebrows (ulerythema ophryogenes) were among the most common hair findings. The cardinal ectodermal features of CFC, keratosis pilaris and hyperkeratosis, were present in about half of all affected persons. However, nevi and deep palmar creases were as frequently reported. Details are in Table IV.

Central nervous system, development and behavior

Neurological issues in this cohort included hypotonia, seizures, tactile defensiveness and hydrocephalus. The details of genotype-phenotype comparison are found in Table V. Brain-imaging data on the entire cohort were not available. Data on the sub-group previously reported by Armour and Allanson [2008], collected in a non-systematic fashion, documented numerous anatomical differences, each present in a small number only, including: hydrocephaly, ventriculomegaly or increased extra axial space, reduced white matter, thin corpus callosum, cerebral atrophy/small volume, delayed myelination, Chiari I malformation, arachnoid cyst, pachygyria, nodular heterotopia, migration abnormality and cerebellar calcification.

Intellectual disability was universal in those with a *BRAF* mutation, but two individuals with a *MEK* mutation were reported to have normal intelligence. Unfortunately, formal psychometric testing had only rarely been carried out. Formal results from such a sub-group of 33 individuals are documented in Table VI. Most persons with a *BRAF* mutation had moderate intellectual disability but one had borderline intellectual functioning. While numbers are small, it appears that *MEK* mutations are associated with milder disabilities.

Gastrointestinal and genitourinary systems

The frequency of gastrointestinal problems was high, irrespective of genotype. Many symptoms were a consequence of dysmotility, including swallowing difficulties, frequent or forceful vomiting, gastro-esophageal reflux and failure to thrive (see Table VII).

There were sparse data on genitourinary features, but cryptorchidism was reported in up to two-thirds of males, and kidney or bladder abnormalities were present in up to one third of affected individuals.

Eyes

The common ocular findings are found in Table VIII. Refraction error or strabismus was noted in 30%-60%. The most distinctive finding, a hypoplastic or dysplastic optic nerve, was found in 44% of individuals with a *BRAF* mutation and 33% of those with a *MEK* mutation.

Musculoskeletal system

The combination of pectus excavatum and carinatum was the most common musculoskeletal feature, seen in up to two-thirds of individuals. Scoliosis and kyphosis were also noted frequently. The genotype-phenotype data are found in Table IX.

DISCUSSION

This is the largest study of CFC syndrome carried out to date, made possible by an international effort to share clinical and molecular data and collaborate on a number of research endeavors, including gene discovery and evaluation of genes in model organisms. Many of the individuals in this study have been previously reported [Niihori er al., 2006; Narumi et al., 2007; Cave et al., 2007; Gripp et al., 2007; Armour and Allanson, 2008; Nystrom et al., 2008; Schultz et al., 2008] but the systematic collection of clinical data for this study has, in many instances, increased what is known about those individuals. In addition, there are data on 50 unreported persons. The size of this cohort allows a robust genotype-phenotype comparison.

Few studies of genotype-phenotype correlation have been carried out to date. Nava et al. [2007], in a mixed cohort of children with CFC, Noonan and Costello syndromes, compared those with *BRAF* and *MEK* mutations, noting less frequent heart defects and milder motor delays in the latter group, two of whom had normal intelligence. The comparison with our study data is complicated, however, by the fact that 2 of the 3 children with a *MEK* mutation reported by Nava and colleagues carried a clinical diagnosis of Noonan syndrome. Schultz et al. [2008] reported *BRAF* and *MEK* mutations in 24 and 8 individuals with CFC, respectively, but failed to show phenotypic differences between the 2 mutation-specific groups. Dentici et al. [2009] reported 6 individuals with CFC and a *MEK* mutation and compared their features to individuals with *MEK* mutation in the literature. The 6 new cases did not differ with respect to phenotype.

Many of the clinical features described herein are in keeping with data from recently described series [Gripp et al., 2007; Narumi et al., 2007; Nava et al., 2007; Armour and Allanson, 2008] and the CFC index proposed by Kavamura et al. [2002]. Cardiac abnormalities were seen with similar frequency (see Table X). Arrhythmias were quite uncommon in this cohort with CFC: with 4 reports of supraventricular tachycardia, and one each of ventricular extrasystoles, AV block and Wolf-Parkinson-White syndrome, in contrast to the findings in Costello syndrome where they occur in almost half the affected individuals [Lin et al., 2011]. Intellectual disability was universal in 3 previous studies [Armour and Allanson, 2008; Nava et al., 2007; Narumi et al., 2007]. Our study had a small cohort which had undergone full psychometric testing, documenting normal intelligence in just one individual with a *MEK* mutation and borderline IQ in one with a *BRAF* mutation. Further details on specific aspects of cognition were not available. The structural central nervous system findings are similar in type and frequency to those in other studies. A recent review confirmed ventriculomegaly, hydrocephaly and cortical atrophy as the most frequent imaging findings [Papadopoulou et al., 2011]. It is difficult to compare skin findings between studies since the categories are presented differently. In large part, data seem comparable with prior studies, but a new study suggests that nevi and keratosis pilaris are more common than found in our cohort or previously reported (60% and 80% respectively) [Siegel et al., 2010]. The presence of normal or large birthweight with postnatal growth retardation and subsequent short stature is also fairly consistent across studies.

Previous studies report differences in the likelihood of polyhydramnios, hypotonia and failure to thrive (see Table X) [Armour and Allanson, 2008; Narumi et al., 2007; Nava et al., 2007; Gripp et al., 2007]. These are likely related, in part, to methods of ascertainment. Our

study data support the high likelihood of significant gastrointestinal dysmotility and optic nerve hypoplasia documented by Armour and Allanson [2008], but not described in previous series.

Despite the fact that *BRAF* is a proto-oncogene and somatic mutations of *BRAF* have been identified in 7% of cancers [Makita et al., 2007], there are few published reports of neoplasia in CFC. The only malignancy in this series has been previously published by Al-Rahawan et al. [2007]. This 3-year-old boy with a *MEK1* Y130C mutation had undergone a cardiac transplant at age 8 months for hypertrophic cardiomyopathy. He died shortly after an intra-cardiac mass was diagnosed as metastatic hepatoblastoma. It is unclear whether the post-transplant immune-suppressive therapy played a role in tumor development. There are 3 other individuals with molecularly confirmed CFC syndrome and malignancy. Acute lymphoblastic leukemia was diagnosed in 2 [van den Berghe and Hennekam, 1999; Niihori et al., 2006; Makita et al., 2007]. Both had *BRAF* mutations that have been reported in other individuals with CFC syndrome without accompanying malignancy. Non-Hodgkins lymphoma was reported in one [Ohtaki et al., 2010]. One boy with a *BRAF* mutation and a parasagittal meningioma is known to the support group CFC International. While multiple giant cell lesions are benign, they are tumor-like lesions probably driven by the proliferative effect of enhanced activity through the Ras-MAPK pathway, and are reported in association with a variety of pathway genes including *BRAF* [Neumann et al. 2009].

This study has limitations. Data are provided by 9 different research consortia, each of which has its own ascertainment method. While a standard set of clinical data on each subject has been sought, the quantity of data on each varies as it was not possible to re-evaluate everyone to ensure all details could be provided. In addition, a small subset of data published by Armour and Allanson [2008] was derived from parental questionnaire, introducing the possibility of recall bias. Those parents were members of CFC International. Medical records were not systematically collected for this study and some children had seen pediatric subspecialists while others had not. Parents who seek membership of such support groups may have children with greater needs or may be more inclined to seek out subspecialty resources. Lastly, the small size of the cohort with a *MEK* mutation does not allow meaningful comparison between *MEK1* and *MEK2* phenotypes. We are unable to assess differences between these 2 genotypes, between *BRAF* and *MEK1* or *BRAF* and *MEK2*. Our study of CFC continues and we hope to be able to address this deficiency in the future.

This study reports the most frequent medical issues in 186 individuals with mutation-proven CFC syndrome. Knowledge of the causative mutation allows confidence in the diagnosis and, more importantly, comparison of the 2 genotypic groups. While not reaching statistical significance, it appears a mutation in *MEK1* or *MEK2* is associated with a higher likelihood of prematurity, absolute macrocephaly, ventricular septal defect, keratosis pilaris, pectus deformity, cryptorchidism and a renal anomaly. Conversely, there is a lower likelihood of atrial septal defect and hypertrophic cardiomyopathy, curly or sparse hair, severe intellectual disability, serious and long-lasting gastrointestinal dysmotility leading to failure to thrive and the need for assisted feeding, optic nerve hypoplasia/dysplasia, and kyphosis. It is important to note that only the difference in frequency of pulmonary stenosis reached statistical significance. With time and the increasing availability of reasonably-priced molecular testing, children and adults with milder features will come to attention and these genotype-phenotype data will evolve.

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Biography

Judith E Allanson MD is a clinical geneticist in the Department of Genetics at Children's Hospital of Eastern Ontario and a Professor of Pediatrics at the University of Ottawa. She has a long-standing research interest in Noonan and Cardiofaciocutaneous syndromes and has published extensively on these conditions.

Yoko Aoki MD PhD is an Associate Professor of Medical Genetics, Tohoku University School of Medicine in Sendai, Japan. Her research interest is to identify new causative genes for inherited disorders and to explore the pathogenesis of disorders of the RAS/MAPK pathway.

Christine M Armour MD is a clinical geneticist at Kingston General Hospital and Assistant Professor of Pediatrics at Queen's University. She is interested in phenotypic and genotypic characterization of rare genetic disorders affecting both children and adults.

Hélène Cavé, PharmD, PhD, is a Professor of Biochemistry and Molecular Biology at Paris 7 Medicine University. As a Medical Biologist in the Genetics Department of the Robert Debré Hospital, she is responsible for the molecular diagnosis of Rasopathies in France (on the behalf of the French national network for rare diseases diagnostic). She is particularly interested in the risk of cancer and leukemia associated with Rasopathies.

Karen W Gripp MD is a Professor of Pediatrics at the T. Jefferson University in Philadelphia, PA., and Chief of the Division of Medical Genetics at the A. I. duPont Hospital for Children in Wilmington, DE., where she directs the program for patients with rasopathies. She has a long standing research interest in Costello syndrome and its genotype/phenotype correlation.

Dr Bronwyn Kerr is a consultant clinical geneticist in Genetic Medicine, based in Central Manchester NHS Foundation Trust in the UK. She has a longstanding interest in Costello syndrome, and other disorders of the RAS/MAPK pathway. She provides advice nationally and internationally on management of this group of disorders, and is developing a multi-disciplinary national management clinic.

Anna-Maja Nyström, PhD, is a clinical geneticist and is currently a postdoctoral research fellow at the Swedish University of Agricultural Science, Department of Animal Breeding and Genetics. Her doctoral studies and thesis, conducted at the Department of Immunology, Genetics and Pathology, Uppsala University, Sweden, were on “RAS-MAPK syndromes - a Clinical and Molecular Investigation”.

Katia Sol-Church PhD is a Research Assistant Professor of Pediatrics at the Thomas Jefferson College of Medicine in Philadelphia, PA., Senior Research Scientist at the A. I. duPont Hospital for Children in Wilmington, DE and Co-Director of the INBRE Centralized Research Instrumentation Core at the University of Delaware in Newark, DE. Her interest is primarily in pediatric disorders associated with skeletal dysplasia and cancer.

Dr Martin Zenker is a clinical and molecular geneticist and Head of the Institute of Human Genetics at the University Hospital Magdeburg, Germany. He has a long-standing research interest in the molecular basis of Noonan syndrome and related disorders and in genotype phenotype correlations. He is developing a multi-disciplinary national management clinic for Rasopathies.

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Table 1

Perinatal findings

	BRAF	%	MEK	%	Significance
Polyhydramnios	60/96	62	25/36	69	0.542
Prematurity	30/70	43	12/23	52	0.476
Macrosomia	15/44	34	7/20	35	1

Table 2

Growth characteristics

	BRAF	%	MEK	%	Significance
Height <3%	80/126	63	25/43	63	0.586
Absolute macrocephaly	13/64	20	6/17	35	0.210
Relative macrocephaly	63/91	69	14/21	67	0.799

Table 3

Cardiac findings

	BRAF	%	MEK	%	Significance
Hypertrophic cardiomyopathy	52/137	38	11/45	24	0.20
Pulmonary valve stenosis	64/127	50	18/48	37	0.000363*
ASD	36/126	28	7/39	18	0.310
VSD	10/87	11	4/21	19	0.466

ASD, atrial septal defect; VSD, ventricular septal defect.

Table 4

Ectodermal findings

	BRAF	%	MEK	%	Significance
Curly +/− sparse hair	121/130	93	31/40	77	0.014
Absent/sparse eyebrows	92/114	81	32/41	78	0.820
Keratosis pilaris	22/46	48	4/6	67	0.66
Hyperkeratosis	52/122	43	17/37	46	0.85
Nevi	44/105	42	12/33	36	0.685
Deep palmar creases	49/105	47	11/29	38	0.527

Table 5

Neurological findings

	BRAF	%	MEK	%	Significance
Hypotonia	89/112	79	32/37	86	0.46
Seizures	34/111	31	13/40	32	0.843
Tactile defensiveness	20/25	80	4/5	80	1
Hydrocephalus	7/26	27	0/6	0	0.296
Mental retardation	75/75	100	25/27	93	0.068

Table 6

IQ data

	BRAF	MEK	Significance
Normal		1	0.212
Borderline	1		1
Mild MR (50-69)	5	3	0.320
Moderate MR (35-49)	16	2	0.202
Severe MR (20-34)	4	1	1

Table 7

Gastrointestinal and genitourinary findings

	BRAF	%	MEK	%	Significance
Failure to thrive	97/117	83	32/41	78	0.489
Assisted feeding	35/65	54	6/15	40	0.397
Renal anomalies	5/29	17	2/6	33	0.516
Cryptorchidism	12/40	30	8/12	66	0.040

Table 8

Ophthalmological findings

	BRAF	%	MEK	%	Significance
Refraction errors	33/80	41	9/24	38	0.815
Strabismus	61/111	55	22/38	59	0.850
Optic nerve hypo- or dys-plasia	11/25	44	2/6	33	1

Table 9

Musculoskeletal findings

	BRAF	%	MEK	%	Significance
Pectus deformity	45/102	44	24/38	63	0.057
Scoliosis	10/29	34	3/6	33	0.648
Kyphosis	6/23	26	1/6	17	1

Table 10

Literature comparison (all numbers are %)

	This study	Armour and Allanson 2008	Narumi et al. 2007	Nava et al. 2007	Gripp et al. 2007
Cardiac defect	71	71	84	77	62
Hypotonia	81	94	56	78	77
Failure to thrive	82	67	n/a	81	100
Polyhydramnios	60	77	n/a	54	46

n/a: no data available