COSTELLO SYNDROME AND THE RAS-EXTRACELLULAR SIGNAL REGULATED KINASE (ERK) PATHWAY

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Introduction

Costello syndrome is a multiple congenital malformation/mental retardation (MCA/MR) syndrome (OMIM # 218040) characterized by prenatally increased growth with subsequent (postnatal) growth retardation (usually as a result of severe postnatal feeding difficulties), distinctive coarse face (full lips, large mouth) with macrocephaly, loose skin resembling cutis laxa, diffuse hypotonia and laxity of the small joints with ulnar deviation of the wrists and fingers, tight Achilles tendons, non-progressive cardiomyopathy and/or congenital heart disease (usually valvar pulmonic stenosis), arrhythmia (usually supraventricular or paroxysmal tachycardia; most distinctively, chaotic atrial rhythm or multifocal atrial tachycardia) developmental delay and an outgoing friendly behaviour or hyperhemotionality (Galera et al. 2006; Hennekam 2003; Johnson et al. 1998; Rauen 2007a, b; Van Eeghen et al. 1999). Skin abnormalities include: (a) *cardinal manifestations* such as thick, loose skin on the dorsal aspects of the hands and feet and deep palmar and plantar creases; (b) *important manifestations* including benign tumours of ectodermal origin such as papillomas, calcified epitheliomas, dermoid cysts, mammary fibroadenosis, and syringomas appearing in the face and nasolabial regions or in other moist body surfaces; and (c) *other manifestations* such as diffuse hyperpigmentation, acanthosis nigricans and curly and sparse scalp hair (Johnson et al. 1998, Nguyen et al. 2007, Weiss et al. 2004). Patients may have a predisposition for malignancies (approximately 15% risk of malignant tumours), mainly abdominal and pelvic rhabdomyosarcoma and neuroblastoma in young children and transitional cell carcinoma of the bladder in adolescents and young adults (Gripp and Lin 2007).

Costello syndrome is inherited in an autosomal dominant manner and is caused by activating germline mutations in the HRAS proto-oncogene (OMIM # 190020) (Aoki et al. 2005; Estep et al. 2006; Gripp et al. 2006a, b; Kerr et al. 2006; Rauen 2007b). To date, most probands with Costello syndrome have the disorder as a result of a de novo mutation: parents of probands have not been proven to be affected (Gripp and Lin 2007).

Remarkable phenotypic overlaps exist between Costello syndrome and other syndromes encompassing MCA/MR and heart disease ("*neuro-cardio-faciocutaneous syndromes*") (Bentires-Alj et al. 2006), including *Noonan syndrome* (OMIM # 163950), *Cardio-facial-cutaneous (CFC) syndrome* (OMIM # 115150) (Noonan 2006, Rauen 2007), *LEOPARD syndrome* (OMIM # 151100) and *neurofibromatosis type1* (OMIM # 162200) (for reviews see also Allanson 2007, Bentires-Alj et al. 2006, Gripp and Lin 2007, Rauen 2007b). These overlaps are explained by the fact that the protein products of the causative genes of all these conditions interact in a common RAS/MAPK pathway (see below) (Rauen 2007a, Roberts et al. 2006). For these reasons the group of neuro-cardio-faciocutaneous syndrome have been tentatively renamed "*RAS/MAPK syndromes*" (Aoki et al. 2008). RAS is a critical signalling hub in the cell, which controls vital cellular functions including cell cycle progression, cell survival, motility, transcription, translation and membrane trafficking (Rauen 2007).

The pathogenesis of Costello syndrome is unclear, but there are many clues for a disturbed elastogenesis, possibly through a disturbed elastin-binding protein reuse by chondroitin sulphate-bearing proteoglycans accumulation (Hennekam 2003, Rauen 2007). It has been postulated that a chondroitin sulphate may induce shedding of EBP from Costello cells and prevent normal recycling of this reusable tropoelastin chaperone (Hinek et al. 2005). Subsequent accumulation of chondroitin 6-sulphate in cardiomyocytes contributes to the development of the hypertrophic cardiomyopathy of Costello syndrome (Hinek et al. 2005).

Historical perspective and eponyms

In 1971, and again (in more detail) in 1977, Costello described two children with psychomotor retardation, postnatal growth failure, macrocephaly, coarse facies, short neck, sparse and curly hair, dark skin colour and nasal papillomata (Costello 1971, 1977). A similar patient was described by Der Kaloustian et al. (1991): since this report, the disorder has been recognized as a distinct entity and given the name of Costello syndrome (OMIM 2006). After recognition of the disorder as Costello syndrome, a few patients were reported as "*facio-cutaneous-skeletal syndrome*" (Borochowitz et al. 1992), but the error was corrected in subsequent papers (Borochowith et al. 1993, Der Kaloustian 1993, Martin and Jones 1993) (notably, however, still the OMIM entry shows this eponym) (OMIM 2007). Early examples of Costello syndrome were also reported as *AMICABLE syndrome* (amicable personality, mental retardation, impaired swallowing, cardiomyopathy, aortic defects, bulk, large lips and lobules, ectodermal defects) (Hall et al. 1990).

Incidence and prevalence

About 115 patients having the clinical features of Costello syndrome have been reported until 2003, but only 103 patients were described in sufficient detail (the data on 12 patients were insufficiently for complete ascertainment) (Hennekam 2003). Following this literature review, a few isolated cases (Delrue et al. 2003) and large series (Kawame et al. 2003, Kerr et al. 2006) were described bringing the total number of reported cases to 200–300 affected individuals (Rauen 2007a). Our personal opinion is that Costello syndrome is under diagnosed, possibly because it is unknown to many paediatricians.

Clinical manifestations

Clinical manifestations include distinct facial appearance with large head, curly hair, nasal papillomata, hyper extensible fingers (small joints), loose integument of hands and feet, hyperpigmented and hyper elastic skin, acanthosis nigricans and cognitive delay.

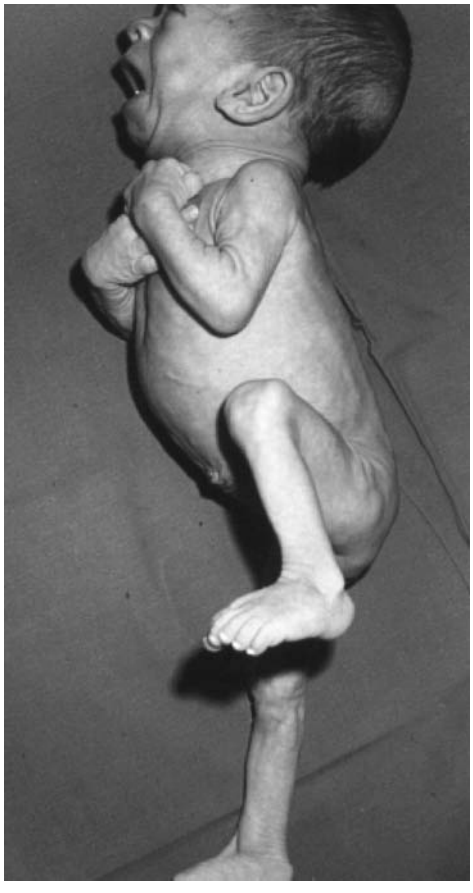


Fig. 1. A 4-month-old child with Costello syndrome shows generalized redundant skin and disproportion between the increased volume of the head and the thinness of the trunk and extremities.

Fig. 2. Redundant skin, deep palmar creases and persistent fetal pads.

Skin manifestations

Affected patients show a manifest disproportion between the excessive volume of the head and the thinness of the trunk and extremities (Fig. 1).

The most striking cutaneous sign of Costello syndrome is the redundant (loose) skin of the dorsal aspects of hands (Fig. 2) and feet (Fig. 3), face (Fig. 4) and trunk (Fig. 5), which is present since birth. This excessive skin causes deep palmar and plantar creases with or without ridges/hyperlinearity and may cause an unusual soft and velvety texture of the hands (Davies and Hughes 1994, Patton et al. 1987, Weiss et al. 2004). Nguyen et al. (2007) consider this feature a cardinal manifestation of the syndrome.

Other important skin abnormalities are tumours of ectodermal origin such as papillomas, calcified epitheliomas, dermoid cysts, mammary fibroadenosis, and syringomas (Nguyen et al. 2007). Papillomas (wart-like lesions) localized on the face, axillae, elbows, knees, vocal cords, anus, and abdomen are observed at variable ages (usually between age 2 to 6 years), and so their absence does not preclude the diagnosis of Costello syndrome: they are considered to result from friction or pressure (Siwik et al. 1998).

Acanthosis nigricans, as well as hyperkeratosis and increased skin pigmentation, are often seen

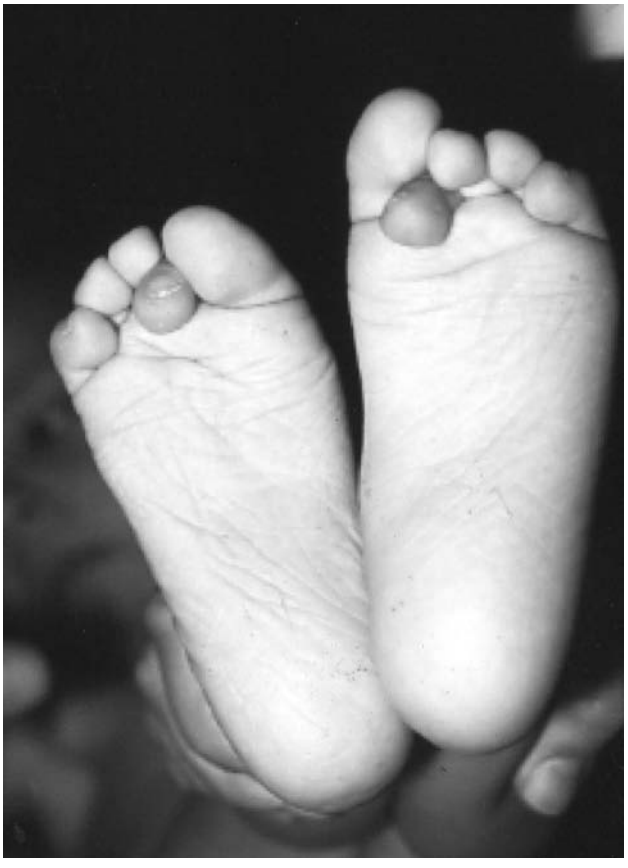


Fig. 3. Abundant and deep plantar creases and hyperextensibility of the second toes.

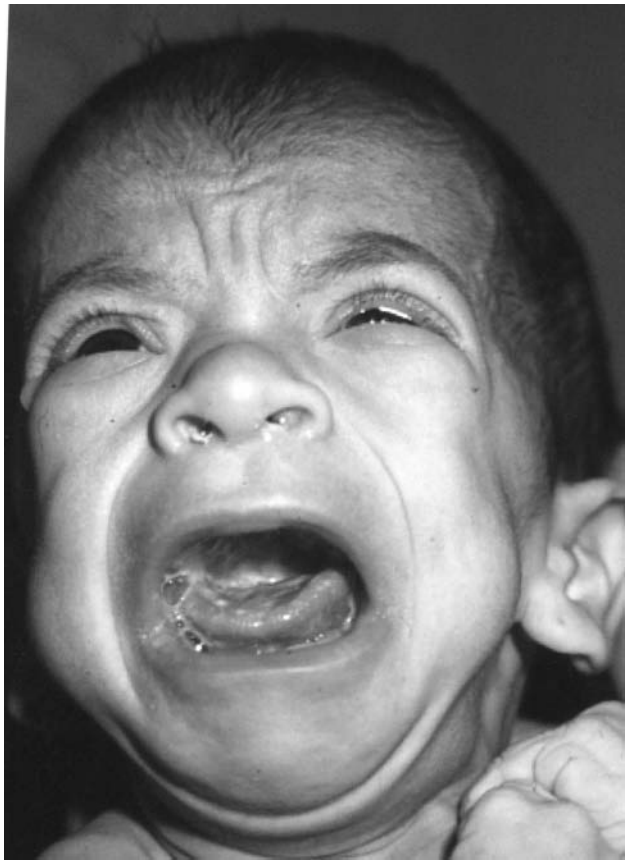


Fig. 4. Facial appearance of a child with Costello syndrome at age 2 months: note the redundant skin and low-set ears.

Fig. 5. A 2-year-old patient shows cutis laxa and pectus excavatum.

(Weiss et al. 2004). Scarce, short or thin hair is most frequently observed in Costello syndrome, but some patients show generalized hypertrichosis. Patients may show also dysplastic, thin, brittle, or deep-nails (Nguyen et al. 2007).

Other less common findings that have been reported are hyperhidrosis, multiple haemangiomas, hyperplastic nipples, supernumerary nipples, mammary fibroadenosis and unusual fat deposition (reviewed in Nguyen et al. 2007).

Systemic features

Polyhydramnios during pregnancy is noted in about 60%, and delivery is frequently ruled by caesarean section (Hennekam 2003). Prenatal overlap of feature of severe Noonan syndrome and Costello syndrome has been confirmed (Levaillant et al. 2006), with dysmorphologic similarities, due to oedema of foetal skin in face and extremities. Most common prenatal systemic abnormalities include increased nuchal translucency, polyhydramnios, bilateral pyelectasis and ventriculomegaly; prenatal foetal facial analysis found abnormal thickness of the skin in the prefrontal area, thick dysplastic ears, thick lips and deep-set creases in the hands and feet (Levellaint et al. 2006).

At birth, children frequently are macrosomic with increased birth weight and elevated head circumference percentiles, but they show decreased vitality with slow mobility. Poor suck is often times

noted. Postnatal growth retardation is significant and persists during life. Other systemic problems, such as failure to thrive, upper airway infections, joint hypermobility, hoarse voice, strabismus, and psychomotor and language acquisition delay are noted very early.

A review of the main clinical features in Costello syndrome, as described in the 103 patients reported in the literature until the year 2003, was provided by Hennekam (2003). These features included: developmental delay (100%), deep palmar/plantar creases (100%), loose skin of hands and feet (99%), poor neonatal feeding (97%), coarse facies (97%), thick lips (97%), postnatal growth retardation (96%), full cheeks (92%), depressed nasal bridge (90%), birth weight $>50^{th}$ percentile (89%), large, fleshy ear lobes (89%), short neck (88%), hyper extensible fingers (87%), macrocephaly (84%), curly, sparse hair (82%), low-set ears (83%), epicanthal folds (82%), short bulbous nose (77%), hyperpigmentation (78%), large mouth (75%), hypertrophic cardiomyopathy (61%) and cardiac dysrhythmia (53%). Other clinical features were reported in a lower number of patients, but were confirmed in most patients, such as hyperkeratosis, down slanting palpebral fissures, thick eyebrows, strabismus, macroglossia, apparently highly arched palate, gingival hyperplasia, teeth abnormalities, hoarse voice, broad distal phalanges, dysplastic/thin/deep-set nails, laxity of small joints, limited extension of elbow, hypotonia, increased anterior-posterior thorax diameter, umbilical or inguinal hernia, tight Achilles tendons, abnormal foot position, delayed bone age and outgoing personality. Endocrine abnormalities most frequently were manifested as growth hormone deficiency and hypoglycaemia. The hypoglycaemia is thought to be due to cortisol deficiency (Gregersen and Viljoen 2004) and patients with growth hormone deficiency have been successfully treated with biosynthetic growth hormone (Legault et al. 2001, Stein et al. 2004). It has been speculated that treatment of Costello patients with growth hormone may help to increase the stature and to reduce cardiac hypertrophy (Lin et al. 2002).

The anaesthesiology literature reports only moderate difficulties with intubations due to anatomic considerations, but no intraoperative deaths (Dearlove and Harper 1997).

Cardiovascular abnormalities

Siwik et al. (1998) in their series of 30 patients with Costello syndrome reported cardiac disease (of any type) in 60%, structural heart disease in 30%, hypertrophic cardiomyopathy in 20% and tachyarrhythmia in 18%. Lin et al. (2002) reviewed the incidence of hearth defects in 94 of the Costello patients in the literature and found abnormalities in 63% (including hypertrophic cardiomyopathy in 34% of patients and arrhythmias in 33%).

Many of the cardiologic abnormalities are related to the elastic tissue, which is also involved in the pathogenesis of several defects in this syndrome. The main congenital defects include: ventricular or atrial septal defects (13%), pulmonary valve stenosis (13%), patent ductus arteriosus (3%), bicuspid aortic valve, aortic stenosis, mitral valve stenosis or prolapse, and thickening of the ventricular septum. The hypertrophic cardiomyopathy may be already present at birth, or develops in the first year of life or at later ages. Several types of dysrhythmias including supraventricular tachycardia, atrial fibrillation, atrial ectopic tachycardia, and other forms of ventricular and/or atrial origin have been reported in patients with and without overt cardiac disease, which could have some impact on the patients' longevity (Fukao et al. 1996). The most common form of arrhythmia is however the atrial tachycardia, typically supraventricular or paroxysmal tachycardia. Most distinctive are chaotic atrial rhythm (also known as multifocal atrial tachycardia) and ectopic atrial tachycardia (Gripp and Lin 2007). Recently, Kawame et al. (2003) described severe cardiac abnormalities in 8 of the 10 patients of their series.

Post-mortem histological, histochemical and immunohistochemical studies of the hearts of three children with Costello syndrome revealed cardiomyocyte hypertrophy, massive pericellular and intracellular accumulation of chondroitin sulphate-bearing proteoglycans and a marked reduction of elastic fibres (Hinek et al. 2005). Normal stroma was replaced by multifocal collagenous fibrosis. Accumulation of chondroitin-6-sulphate was very high. In contrast, deposition of chondroitin-4-sulphate was below the level detected in normal hearts. This finding sug-

gests that an imbalance in sulphation of chondroitin sulphate molecules and subsequent accumulation of chondroitin-6-sulphate in cardiomyocytes contribute to the development of the hypertrophic cardiomyopathy of Costello syndrome (Hineck et al. 2005).

Neurological abnormalities

Developmental delay and mental retardation (ranging from mild to severe) are an almost constant finding (Axelrad et al. 2004, Kawame et al. 2003). There is a characteristic nonverbal cognitive malfunctioning with variability in receptive language (Axelrad et al. 2004). Apathy and nervous personality can be present aside a pleasant, happy and outgoing behaviour (see also below). Patients may show decreased physical activity and easy fatigability, which appear to be constitutional, but one must take into consideration that congenital heart defects may be contributory. Seizures have been also reported (Kawame et al. 2003). Costello patients have been reported to have a high prevalence of obstructive sleep-related respiratory disorders including respiratory events of obstructive type during sleep, fragmented sleep structure and increased number of awakenings associated to narrowing of the upper respiratory airways (Della Marca et al. 2006).

Behavioural and temperamental manifestations

A characteristic behaviour in infancy includes a happy and sociable personality with significant irritability, including hypersensitivity to sound and tactile stimuli, sleep disturbances (see above), and excess shyness with strangers (Axelrad et al. 2004, 2007; Kawame et al. 2003). Most affected patients have a warm and sociable personality, but they frequently are overprotected and show low frustration levels, maladaptive behaviours and poor emotional aspects (Axelrad et al. 2004). Hyperactivity with anxiety attacks and seldom self-mutilation, with an adverse reaction to psychotropic medication usually decrease or may disappear around age 2–4 years (Kawame et al. 2003).

Neuroimaging

Ventricular dilatation is observed in more than 40% of patients who may need shunting (Pratesi et al. 1999). The presence of Chiari I malformation and syringomyelia in a patient suggested to be a possible case of Costello syndrome has been reported (Gripp et al. 2002). Brain imaging in 28 of the 38 studied patients of Costello syndrome in the literature showed some type of congenital abnormality in the cerebral ventricles, cerebral hemispheres, cerebellum, brain and corpus callosum. These abnormalities mainly consisted of mild ventricular dilatation, cerebral atrophy, Chiari malformation, tonsillar malformations, hydrocephalus, syringomyelia and isolated anomalies that involved the optic nerves, brain stem and corpus callosum (Delrue et al. 2003). In addition to the congenital brain malformations patients may have dysmielinisation of the basal ganglia and white matter (Fig. 6). Similar white matter and structural brain abnormalities are seen in CFC (Roberts et al. 2006). These abnormalities may contribute to the delay in walking and psychomotor retardation. Moyamoya vasculopathy has been also described (Shiihara et al. 2005).

Neurophysiologic studies

Electrophysiological abnormalities have been described in nearly one third of the children of Costello syndrome, but only 20% had seizures. EEG abnormalities frequently are associated with brain imaging alterations, most often mild ventricular dilatation (Zampino et al. 1993). Different types of epilepsy have been noted such as West syndrome (Say et al. 1993), Lennox-Gastaut syndrome after a West syndrome in one patient and focalised epilepsy in another (Fujikawa et al. 2001) and tonico-clonic epilepsy (Costello 1977, Johnson et al. 1998). Patients with severe epilepsy also had brain parenchymal lesions and profound psychomotor retardation/regression (Fujikawa et al. 2001). Kawame et al. (2003) reported seizures in 50% of 10 patients with Costello syndrome without brain structural anomalies, but with behavioural and neurological features.

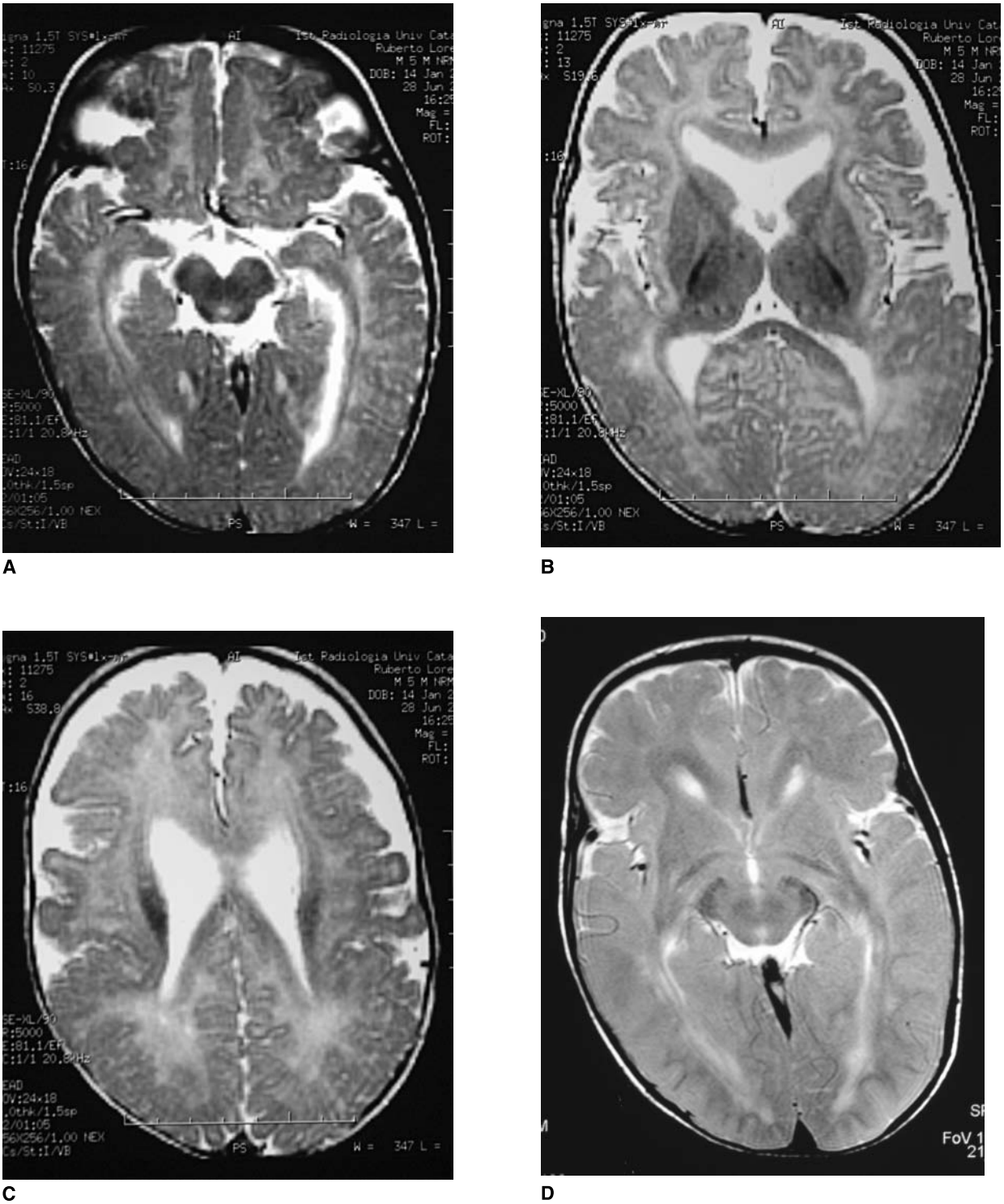
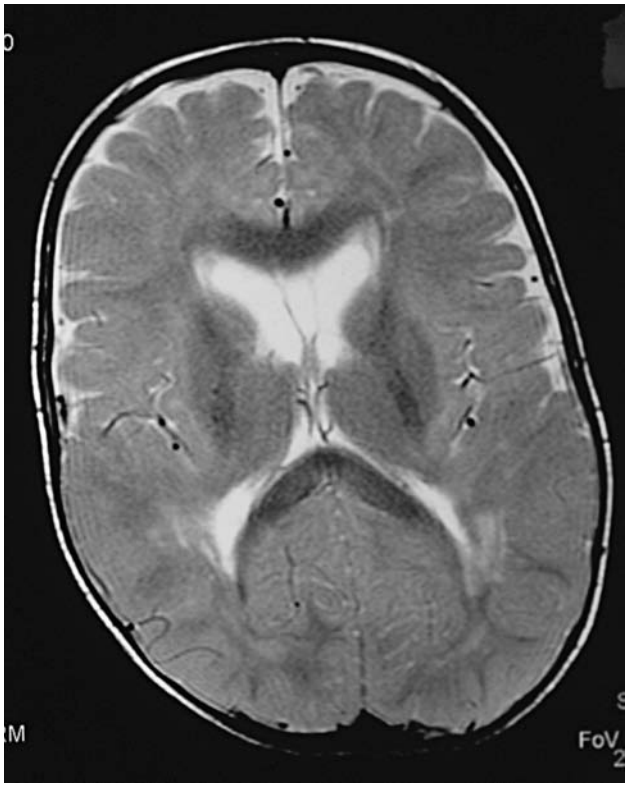


Fig. 6. Axial T2-weighted magnetic resonance (MR) images of the brain in a child with Costello syndrome showing at age 6 months (**A–C**) dilated ventricles and high signal lesions in the periventricular white matter and at age 2.5 years (**D–F**) partial regression of the ventricular enlargement with similar high signals in the periventricular white matter.



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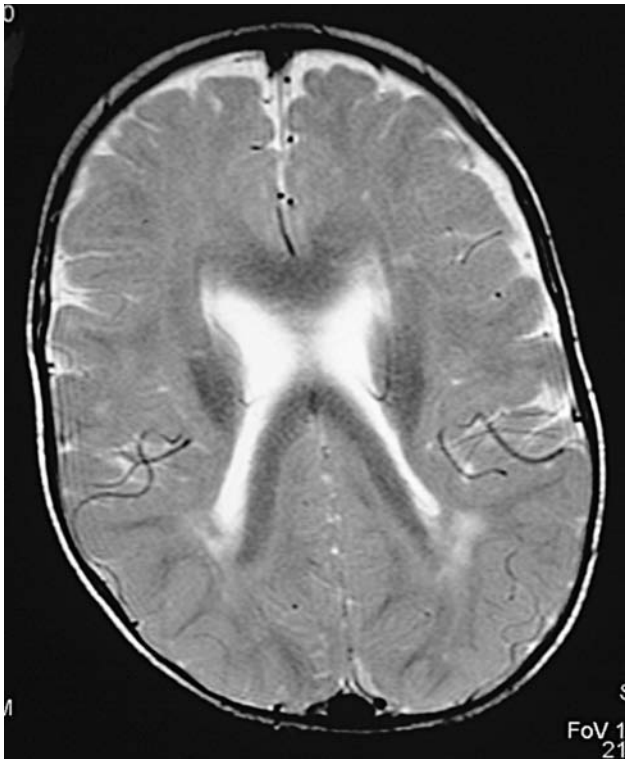

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Fig. 6. (Continued)

Genital abnormalities

Genital abnormalities such as undescended testes, a small penis, a hypoplastic scrotum, or large external genitalia have been observed. Libido usually is decreased.

Tumours and malignancies

Tumour occurrence and malignancies have an estimated frequency of 17% and have been recently reviewed (Gripp et al. 2002): recommendations for screening have been proposed (Gripp et al. 2002) but also criticised (De Baum 2002). The tumours reported by Gripp et al. (2002) were ganglioneuroblastoma, bladder carcinoma (Johnson et al. 1998), vestibular schwannoma (van Eeghen et al. 1999), epithelioma (van Eeghen et al. 1999), neuroblastoma (Lurie 1994) and 10 patients with embryonal rhabdomyosarcoma (Kerr et al. 1998, Sigaudy et al. 2000). Parameningeal rhabdomyosarcoma has been also reported (O'Neal et al. 2004). The increased incidence of tumours has been explained by the HRAS mediated RAS pathway activation (see below and also Kratz et al. 2007, Rauen 2007, Roberts et al. 2006).

The tumour screening protocol consists of abdominal and pelvic ultrasound examination every 3–6 months from birth until 8–10 years, urinary catecholamine excretion measurements every 6–12 months until 5 years, and annual screening for haematuria from 10 years on.

Natural history

Patients with Costello syndrome maintain macrocephaly throughout their lives, but weight gain and

growth are decreased and they most often show shortened height and low weight from youth to adulthood. The attained adult height has been reported to be between 116 cm and 161 cm (Hennekam 2003). Several causes have been suggested for the short height including hypothyroidism, ACTH deficiency, partial growth hormone deficiency or low response to stimulation test. A favourable response to growth hormone treatment has been reported (Gripp et al. 2006b, Legault et al. 2001).

All reported patients showed psychomotor retardation. The mean age for sitting is 23 months and for walking without help is 4 years; the first words are spoken at 4 years and 4 months, with delayed language development, and IQ test values range between 23 and 85 (mean 50) (Delrue et al. 2003). Most of these patients have a warm and sociable personality, but they frequently are overprotected and show low frustration levels, maladaptive behaviours and poor emotional aspects (Axelrad et al. 2004). Hyperactivity with anxiety attacks and seldom self-mutilation, with an adverse reaction to psychotropic medication has been reported (Van Eeghen et al. 1999). These symptoms usually decrease or may disappear around age 2–4 years (Kawame et al. 2003).

Prenatally, increased nuchal thickness, polyhydramnios (>90%), characteristic ulnar deviation of the wrists, and short humeri and femurs can be seen on prenatal ultrasonography. Because most features of the foetal **phenotype** are not unique and Costello syndrome is rare, the diagnosis is often not considered prenatally. Cardiac hypertrophy has not been reported, but foetal tachycardia (various forms of atrial tachycardia) has been detected in at least five foetuses subsequently diagnosed with Costello syndrome, which increases the index of suspicion of the diagnosis (Gripp and Lin 2007).

In the neonate, increased birth weight and head circumference (often >50th percentile) for gestational age can lead to the categorization of macrosomia. Hypoglycaemia is common. Failure to thrive and severe feeding difficulties are almost universal. Characteristic physical findings include a relatively high forehead, low nasal bridge, epicanthal folds, prominent lips and a wide mouth, ulnar deviation of wrists and fingers, loose-appearing skin with deep palmar and plantar creases, and cryptorchidism (Lo et al. 2008).

In infancy, severe feeding difficulties may lead to a marasmic appearance. Most infants display hypotonia, irritability, developmental delay, and nystagmus with delayed visual maturation improving with age. Cardiac abnormalities typically present in infancy or early childhood but may be recognized at any age. Approximately 75% of *HRAS* mutation-positive individuals with Costello syndrome (see below) have had some type of cardiac abnormality (Gripp et al. 2006a, b), compared to 60% of individuals with Costello syndrome diagnosed by clinical findings alone (Lin et al. 2002). In the more recent *HRAS* mutation-positive series, congenital heart defects (usually pulmonic stenosis) were noted in 25%, arrhythmia in 42%, and hypertrophic cardiomyopathy in 47%, compared to the earlier clinical series in which each of the above abnormalities was reported in about 30% of affected individuals.

In childhood, individuals are able to take oral feeds beginning between age two and four years. The first acceptable tastes are often strong (e.g., ketchup). The onset of speech often coincides with the willingness to feed orally. Short stature is universal, delayed bone age is common (Johnson et al. 1998), and testing may show partial or complete growth hormone deficiency. Atypically, cardiac hypertrophy detected in infancy as mild non-obstructive or non-progressive thickening may progress to severe lethal hypertrophy with "storage" (Hinek et al. 2005); most hypertrophic hearts remain stable or progress mildly. The complete natural history of cardiac hypertrophy in Costello syndrome has not been defined, but adult onset of hypertrophy has not been documented.

Adolescents often show delayed or disordered puberty, and may appear older than their chronologic age because of worsening kyphoscoliosis, sparse hair, and prematurely aged skin.

Adults. White et al. (2005) has tentatively delineated the adult phenotype in Costello syndrome reporting follow-up findings in 17 affected adults aged 16–40 years. Fourteen of these 17 adults had mild to moderate intellectual disability: 15 attained some reading and writing skills and 14 showed ongoing acquisition of new skills into adulthood. Two

patients had bladder carcinoma while benign tumours included multiple ductal papillomata (n = 2) and a 4th ventricle mass (plexus papilloma? n = 1). Endocrine problems in their series were osteoporosis, central hypogonadism, and delayed puberty (White et al. 2005). Other health problems were symptomatic Chiari malformation associated to adult-onset gastro-oesophageal reflux in three cases (White et al. 2005).

Life expectance. Life expectance in patients with Costello syndrome is often decreased. A recent review of the literature indicates that 14 children less than 6 years of age with Costello syndrome have died of several causes, particularly of cardiac anomalies, sudden death syndrome secondary to arrhythmias or tumours, or both (Gripp et al. 2002, Hennekam 2003, Lin et al. 2000, O'Neal et al. 2004). Few patients exceed 30 years of life. We have followed a patient since the age of 11 months, who was published when he was 35 years old (Pascual-Castroviejo and Pascual-Pascual 2005): he presently is 36 years of age and is in good health (Fig. 7). The longest survival known is in a woman published by Van Eeghen et al. (1999) when she was 33 years of age and who died at 37 years because of a perforated duodenal ulcer (Hennekam 2003). Suri and Garrett (1998) reported a 32-year-old patient who died with vestibular schwannoma suggesting a possible pathogenic relationship between Costello syndrome and neurofibromatosis type 2 (see molecular genetics).

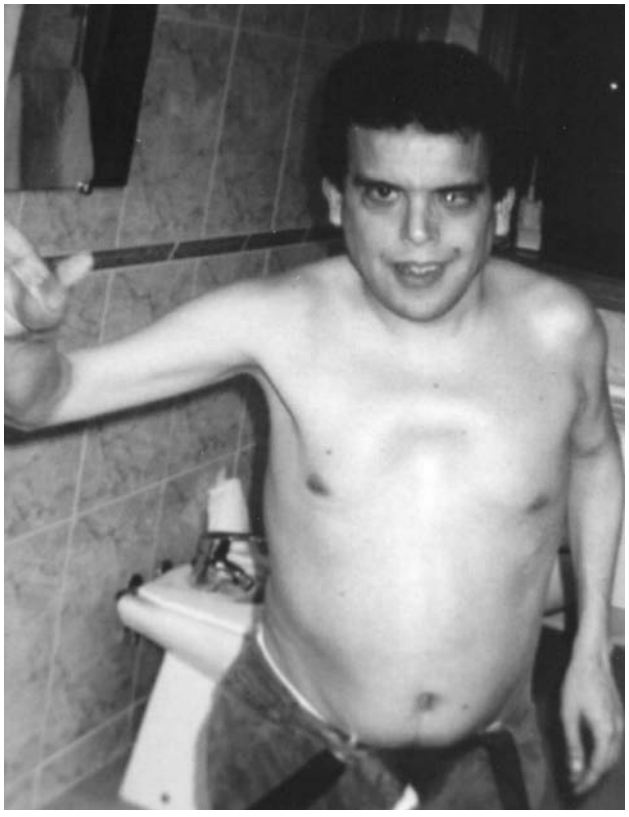

Fig. 7. Same patient as in Figs. 3 and 5 at age 35 years: he still shows pectus excavatum and deep palmar creases, and cataract in the left eye.

Molecular genetics and pathogenesis

Molecular genetics

Most of the reported patients have been isolated cases, sporadic and non familial. Consanguinity had seldom been reported (Borochowitz et al. 1992, Franceschini et al. 1999) and autosomal recessive inheritance had been postulated. Affected siblings have been published in few occasions (Berberich et al. 1999, Zampino et al. 1993, Johnson et al. 1998). Lurie (1994) reviewed 20 reported families and found that the 37 sibs of probands were all normal excluding an autosomal recessive inheritance pattern. A pair of monozygotic twins was reported by Van del Bosch et al. (2002). A single chromosomal translocation {46,XX,t (1;22) (q25;q11} associated with the condition was reported in the same patient in two distinct papers (Czeizel and Timár 1995, Maroti et al. 2002). The first to postulate autosomal dominant inheritance was van Eeghen et al. (1999) who reviewed previously reported patients and Ioan and Fryns (2002) who described Costello syndrome in a brother and sister, with minor manifestations in their mother.

Aoki et al. (2005) identified heterozygous *de novo* mutations in the *HRAS* gene (OMIM # 190020) in a cohort of 12 patients with the clinical diagnosis of Costello syndrome. Heterozygous missense mutations were found in codon 12 and codon 13 of the first coding exon, known mutation hotspots in RAS.

HRAS is a highly conserved gene located on 11p15.5 with variability of genetic sequence existing in the 3′ hypervariable region among other RAS family members (Midgley and Kerr 2002, Rauen 2007). The aminoacid substitutions in the protein product of *HRAS* caused by missense alteration found in codons 12 and 13 in Costello syndrome are well-known activating mutations in cancer (Rauen 2007).

Several studies have shown good correlation between the clinical diagnosis of Costello syndrome and the presence of heterozygous activating *HRAS* mutations (Aoki et al. 2005, Estep et al. 2006, Gripp et al. 2006b, Kerr et al. 2006, van Steensel et al. 2006, Zampino et al. 2007; reviewed in Rauen 2007a, b). The vast majority of mutations are Gly12Ser substitutions. HRAS is probably the only causal gene for Costello syndrome (Rauen 2007a). The origin of constitutional germline mutations causing Costello syndrome reflects a paternal bias (Rauen 2007a, b). Somatic mosaicism for a Gly12Ser substitution has been identified in one individual with Costello syndrome (Gripp et al. 2006a). No genotype-phenotype correlation have been noted. However, Kerr et al. (2006) suggested that the risk for malignant tumours may be higher in individuals with the G12A mutation (>55%) than in those with the G12S (<10%).

Costello, Noonan, CFC, LEOPARD and NF1 syndromes and the RAS-extracellular signal regulated kinase (ERK) pathway

Costello syndrome shows phenotypic overlaps with other MCA/MR syndromes ("*neuro-cardofaciocutaneous syndromes*" or "*RAS/MARK syndromes*") (Aoki et al. 2008, Bentires-Alj et al. 2006) including *Noonan syndrome* (OMIM # 163950), which is caused by mutations in the protein tyrosine phosphatase SHP-2 gene *PTPN11* (>50% of cases), in the *SOS1* gene (10% of cases) and in the *KRAS* gene (<5% of cases) (OMIM # 176876) and *Cardio-facio-cutaneous (CFC) syndrome* (OMIM # 115150) caused by mutations in the BRAF gene (>75–80% of cases), mitogen-activated protein/extracellular signal-regulated kinase *MEK1* and *MEK2* genes (10–15% of cases) and in the KRAS gene (<5% of cases) (Rauen 2007b). Clinical similarities are shared also with *LEOPARD syndrome* (OMIM # 151100) and *neurofibromatosis type1* (OMIM # 162200). The clinical overlaps between all these conditions are explained by the fact that the protein products of the CFC genes, the PTPN11 Noonan gene, the NF1 gene and those of HRAS involved in the causation of Costello syndrome, all have a role in the RAS-extracellular signal regulated kinase (ERK) pathway (Fig. 8) (Allanson 2007; Gripp and Lin 2007; Rauen 2007a, b; Roberts et al. 2006). RAS genes encode guanosine triphosphate-binding proteins that serve as molecular on-off switches that activate or inhibit downstream molecules. It is a signalling pathway that is important for vital cellular functions including cell cycle progression, cell survival, motility, transcription, translation and membrane trafficking (Rauen 2007a, b; Roberts et al. 2006). Specifically, Aoki et al. (2005) hypothesised that genes mutated in Costello syndrome and in PTPN11-negative Noonan syndrome encode molecules that function upstream or downstream of SHP2 in signal pathways. In 90% of individuals with Costello syndrome they found one or another of 4 heterozygous mutations in the HRAS gene (Aoki et al. 2005): these mutations had been previously identified somatically in various tumours. These observations suggested that germ-line mutations in HRAS perturb human development and increase susceptibility to solid tumours in patients with Costello syndrome (and of haematopoietic malignancies in those with Noona syndrome) (Roberts et al. 2006). The findings of Aoki et al. (2005) were confirmed by Gripp et al. (2006b) and Estep et al. (2005). Kerr et al. (2006) identified mutations of the HRAS gene in 86% of the 37 cases analysed.

At the moment, there are more questions than answers in trying to establish why pathogenetically related syndromes display major phenotypic differences. Yet, one can firmly state that the Costello, CFC and Noonan syndrome are genetically heterogeneous. As they are all caused by mutations in genes whose protein products are part of the RAS-ERK pathway, we also understand, at least partly, why they are phenotypically similar (Roberts et al. 2006).

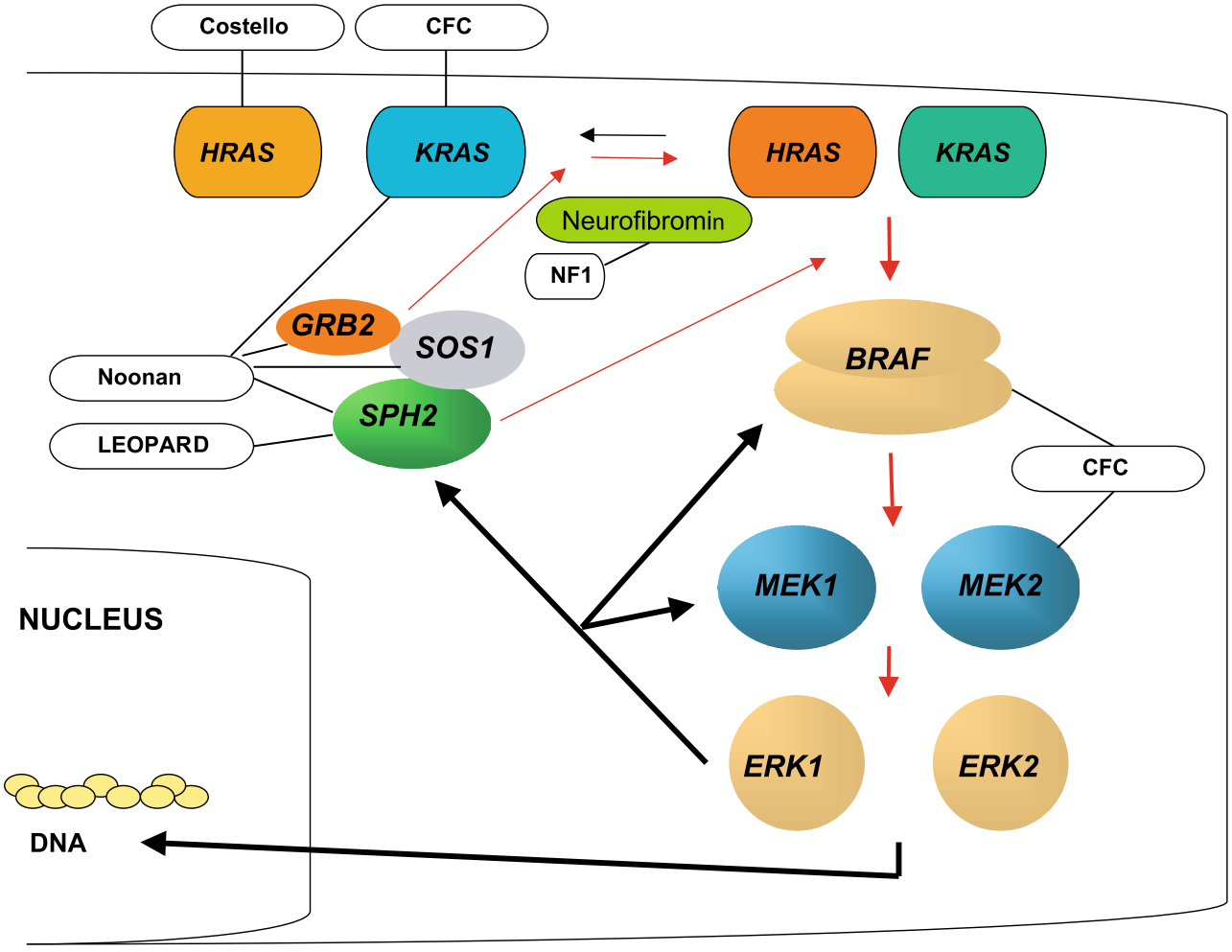

Fig. 8. RAS-extracellur signal-regulated kinase (ERK) signalling pathway connecting pathogenetically the Costello, Noonan, Cardiofaciocutaneous (CFC) and LEOPARD syndromes and neurofibromatosis type 1 (NF1). Inactivating HRAS and KRAS (orange and light green) are activated (dark orange and dark green) by neurofibromin (the protein product of the NF1 gene) and by SHP2, GRB2 and SOS1 (the protein products associated with the Noonan and LEOPARD genes). Red arrows and arrowhead = activation; black arrows and arrowheads = inhibition (see text for further explanation) (adapted and modified from Rauen 2007 and from Roberts et al. 2006).

Pathogenesis

The resemblance of Costello syndrome with other disorders associated with elastic fibre degeneration such as cutis laxa, Williams-Beuren syndrome and perhaps others, may indicate a common or close origin for all these entities (Mancini et al. 2003). Histological studies showed fine, disrupted, and loosely constructed elastic fibres in the skin, tongue, pharynx, larynx, and upper oesophagus, but not in bronchi, alveoli, aorta or coronary arteries (Mori et al. 1996), loss of anastomosing points in elastic tissue (Vila Torres et al. 1994), marked reduction of elastic fibres and replacement of normal stroma by multifocal collagen fibrosis, as well as accumulation of chondroitin-6-sulphate and decreased of chondroitin-4-sulphate (Hinek et al. 2005), all of which are in favour of a disturbed elastogenesis due to an anomaly in the elastin gene.

The human elastin gene is composed of 34 exons, and the major transcribed products are three distinct mRNAs of 3.5 Kb. These are produced by

alternative exon splicing, and the distribution and function of these spliced elastins are yet not completely understood (Indik et al. 1987). Elastin is the major component of extracellular elastic fibres of skin, arteries, lungs and possibly other structures, and its normal development is an essential determinant of arterial morphogenesis (Li et al. 1998a). Elastin is composed of cross-linked tropoelastin, and formed along a scaffold of microfibrils composed off different glycoproteins. Tropoelastin is guided intracellularly by elastin – binding protein (EBP), an enzymatically inactive variant of beta-galactosidase, which is also important in elastic fibre assembly (Hinek and Rabinovitch 1994). A decreased production of tropoelastin, inadequate intracellular trafficking or release from the cell surface through inadequate functioning of EBP, or disturbed extracellular assembly either of the tropoelastin chains themselves or along the scaffold of microfibrils, may disturb elastin fibre formation (Hennekam 2003). Hinek et al. (2000) showed that cultured fibroblasts from Costello syndrome patients produce normal levels of tropoelastin and properly deposit the microfibrillar scaffold, but do not assemble elastic fibres because of a deficiency of EBP.

A production defect of tropoelastin can be found in Williams-Beuren syndrome, an abnormal microfibrillar scaffold in Marfan syndrome, and a deficient functioning of EBP Hurler syndrome. Elastin may have a role in the function of the central nervous system (CNS), since patients with Williams-Beuren syndrome, who have deletions of the elastin gene, show mental retardation. It is possible that mental retardation in Costello and Williams-Beuren syndromes arises from a defect in elastin – mediated signal transduction in the CNS (Mori et al. 1996).

Differential diagnosis

Several diseases should be considered in the differential diagnosis of Costello syndrome (Kerr et al. 2008, Lin et al. 2008), particularly those which present cutis laxa such as leprechaunism (the diagnosis that we gave to our first patient in 1969 before Costello described his syndrome) (Davies and Hughes 1994, Martin and Jones 1991, Patton et al. 1987, Say et al. 1993, Weis et al. 2004).

In infants and young children, Costello syndrome is difficult to distinguish from cardiofaciocutaneous (CFC) syndrome or Noonan syndrome; in older children, the distinction between Costello syndrome and Noonan syndrome is clear. Feeding problems and failure to thrive are usually more severe in infants with Costello syndrome and CFC syndrome than in infants with Noonan syndrome. The distinctive combination of *pectus carinatum* and *pectus excavatum* typifies Noonan syndrome. Costello syndrome is distinguished by ulnar deviation of the hands, marked small-joint laxity, striking excess palmar skin, the presence of papillomata, and palmar calluses.

The cardiac abnormalities in Costello syndrome, CFC syndrome, and Noonan syndrome are similar. At least one of the three following main types of cardiac abnormality was noted in about 75% of individuals with mutation-positive Costello syndrome (Gripp et al. 2006b): congenital heart defects (25%), hypertrophic cardiomyopathy (47%), and arrhythmia (mostly atrial tachycardia) (42%) (Gripp and Lin 2007). Based on two series of individuals with mutation-positive CFC syndrome (Niihori et al. 2006, Rodriguez-Viciana et al. 2006), the frequency of cardiac anomalies in general and hypertrophic cardiomyopathy in particular in Costello syndrome and CFC syndrome is similar, but congenital heart defects are more common in CFC syndrome and arrhythmia is more common in Costello syndrome. Because of the overlap between Costello syndrome and CFC syndrome, the diagnosis of individuals with a phenotype considered borderline or atypical for Costello syndrome may be clarified by molecular genetic testing.

Noonan syndrome is characterized by short stature; congenital heart defect; broad or webbed neck; unusual chest shape with superior *pectus carinatum*, inferior *pectus excavatum*, and apparently low-set nipples; developmental delay of variable degree; cryptorchidism; and characteristic facies. Varied coagulation defects and lymphatic dysplasia are frequently observed. Congenital heart defects occur in 50% and 80% of individuals (Allanson 2007). Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20–50% of individuals.

Hypertrophic cardiomyopathy, found in 20–30% of individuals, may be present at birth or appear in infancy or childhood. Other frequent structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot; less common are incomplete atrioventricular canal (premium-type atrial septal defect) and coarctation. Length at birth is usually normal. Final adult height approaches the lower limit of normal. Most school-age children perform well in a normal educational setting; 10–15% require special education. Mild mental retardation is seen in up to one-third of individuals (Van Eeghen et al. 1999). Mutations in *PTPN11* have been identified in 50% of affected individuals and *KRAS* mutations have been reported in a small number (Schubbert et al. 2006).

Some newborns or very young infants with Williams-Beuren syndrome may show similar facies to Costello syndrome, but lack the additional features that affect the skin, head circumference, increased birth weight and several other signs of the Costello syndrome, except for the frequent presentation of cardiac disease in both syndromes, will easily allow differentiation, as it occurs with I-cell, Hurler syndrome, Weaver syndrome and other related entities (Van Eeghen et al. 1999).

Cardiofaciocutaneous (CFC) syndrome resembles Costello syndrome in young children. Hypotonia, nystagmus, mild to moderate mental retardation, and postnatal growth deficiency are typical. Feeding difficulties are common but may be less severe than in Costello syndrome. The dolichocephaly, high forehead, and slightly coarse facial features may resemble Costello syndrome, but the lips are not as thick and prominent. The hair is more consistently sparse or curly, and in contrast to Costello syndrome, the eyebrows are typically sparse or absent. Skin abnormalities include severe atopic dermatitis, keratosis pilaris, ichthyosis, and hyperkeratosis; the papillomata characteristic of Costello syndrome are not seen in CFC syndrome. As in Costello syndrome, pulmonic valve stenosis is common, as is atrial septal defect. Hypertrophic cardiomyopathy has been noted in about 40% of mutation-positive individuals, similar to Costello syndrome (Niihori et al. 2006, Rodriguez-Viciana et al. 2006). Atrial tachycardia had not been reported until recently; in the small number of reported cases, it has not been called chaotic atrial rhythm (Niihori et al. 2006). Malignant tumours have not been reported in CFC syndrome. The discovery of germline mutations in *BRAF*, and less commonly in *KRAS*, *MEK1*, or *MEK2*, allows for molecular confirmation of a clinical diagnosis of CFC syndrome (Gripp and Lin 2007, Niihori et al. 2006, Roberts et al. 2006, Rodriguez-Viciana et al. 2006).

Table 1. Initial diagnostic work-up for Costello syndrome

Complete general and neurological examination
Plotting of growth parameters
Nutritional assessment
Cardiologic evaluation with two-dimensional and Doppler echocardiography and baseline electrocardiography
Full ophthalmology evaluation
Clinical assessment of spine and extremities, range of motion
Multidisciplinary developmental evaluation (refer to dermatologists)
Abdominal and pelvic ultrasonography
MRI study of the brain
Genetics consultation

Adapted and modified from Gripp and Lin (2007) and Rauen et al. (2008).

Management

The suggested work-up at the time of initial diagnosis of Costello syndrome is listed in Table 1 (see also Rauen et al. 2008).

Treatment of Manifestations

Growth. Most infants require nasogastric or gastrostomy feeding. Because of gastroesophageal reflux and irritability, Nissen fundoplication is often performed. Anecdotally, **affected** children have very high caloric needs. Even after nutrition is improved through supplemental feeding, growth retardation persists.

Cardiac. Treatment of cardiac manifestations is generally the same as in the general population. All

individuals with Costello syndrome, especially those with an identified cardiac abnormality, should be followed by a cardiologist who is aware of the spectrum of cardiac disease and its natural history (Lin et al. 2002). Ongoing studies of the natural history will be needed to define the management for older individuals. Arrhythmias have been well documented but incompletely defined from a management point of view. Malignant rhythms may require aggressive anti-arrhythmic drugs and ablation. Pharmacologic and surgical treatment (myectomy) has been used to address cardiac hypertrophy. Individuals with Costello syndrome and severe cardiac problems may choose to wear a Medic Alert® bracelet.

Skeletal. Ulnar deviation of the wrists and fingers responds well to early bracing and occupational and/or physical therapy. Limited extension of large joints should be addressed early through physical therapy. Surgical tendon lengthening, usually of the Achilles tendon, is often required. Kyphoscoliosis may require surgical correction.

Central nervous system. When seizures occur, underlying causes including hydrocephalus, hypoglycaemia, and low serum cortisone concentration need to be considered (Gregersen and Viljoen 2004).

Cognitive. Developmental disability should be addressed by early-intervention programs and individualized learning strategies. Speech delay and expressive language limitations should be addressed early with appropriate therapy and later with an appropriate educational plan. Alternate means of communication should be considered if expressive language is significantly limited.

Respiratory. A high index of suspicion should be maintained for obstructive sleep apnea as the cause for sleep disturbance.

Dental. Dental abnormalities should be addressed by a pediatric dentist.

Papillomata. Papillomata usually appear in the peri-nasal region and less commonly in the perianal region, torso, and extremities. While they are mostly of cosmetic concern, papillomata may give rise to irritation or inflammation in hard-to-clean body regions and may be removed as appropriate. Recurrent facial papillomata have been successfully managed with regular dry ice removal.

Endocrinopathies. Neonatal hypoglycemia has frequently been reported and a high level of suspicion should be maintained. Rarely, hypoglycemia occurs in older individuals and may present with seizures. Under these circumstances, growth hormone (GH) deficiency needs to be excluded as the underlying cause (Gripp et al. 2000). Hypoglycaemic episodes unresponsive to GH therapy responded well to cortisone replacement in another individual (Gregersen and Viljoen 2004); thus, cortisol deficiency may also be considered.

Malignant tumours. Treatment of malignant tumours follows standard protocols.

Prevention of secondary complications

Cardiac. Certain **congenital** heart defects (notably valvar pulmonic stenosis) require antibiotic prophylaxis for subacute bacterial endocarditis (SBE), available by prescription from the cardiologist or other physician caregiver.

Sedation. Individuals with Costello syndrome may require relatively high doses of medication for sedation. No standardized information is available, but review of an individual's medical records documenting previously given dosages may provide guidance.

Anesthesia may pose a risk to individuals with some forms of unrecognised hypertrophic cardiomyopathy or those who have a predisposition to some types of atrial tachycardia.

Surveillance

Hypoglycemia. Neonatal hypoglycemia has frequently been reported and a high level of suspicion should be maintained. Monitoring of blood glucose concentration should follow typical protocols for neonates at risk for hypoglycemia.

Cardiac. While data regarding the natural history are insufficient to determine a schedule for repeating cardiac assessments if the initial evaluation is normal, it appears that the onset of new cardiovascular abnormalities declines after adolescence. The follow-up schedule must be customized based on

Table 2. Follow-up cardiac evaluation for Costello syndrome

If the newborn evaluation is normal, follow-up with echocardiogram at about age six to 12 month
For those without an apparent cardiac abnormality, follow-up approximately every one to three years until about age five to ten years and less frequently if the individual remains healthy
In an **affected** adolescent with a normal baseline cardiology evaluation who maintains normal blood pressure, echocardiogram at three- to five-year intervals
For any child with a cardiac abnormality, scheduled assessment as recommended by the treating cardiologist
Because tachycardia is an important cause of death with or without underlying structural defect or cardiac hypertrophy, health professionals and caregivers should be aware of the possibility of sudden cardiovascular collapse.

Adapted and modified from Gripp and Lin (2007).

the overall clinical situation and the treating cardiologist. The cardiologist should be aware of Costello syndrome-associated heart abnormalities and schedule tests as indicated.

As more information about the natural history of cardiac abnormalities (especially hypertrophic cardiomyopathy, hypertension, and aortic dilatation) becomes available, the following recommendations may change (Table 2).

Tumour screening consisting of abdominal and pelvic ultrasound and urine testing for catecholamine metabolites and haematuria was proposed by Gripp et al. (2002). However, a subsequent report (Gripp et al. 2004) on elevated catecholamine metabolites in individuals with Costello syndrome without an identifiable tumour concluded that **screening** for abnormal catecholamine metabolites is not helpful.

Serial abdominal and pelvic ultrasound **screening** for rhabdomyosarcoma and neuroblastoma was proposed every three to six months until age eight to ten years. Urinalysis for haematuria was suggested annually beginning at age ten years to **screen** for bladder cancer Gripp et al. 2002.

Neither of the above **screening** approaches has yet been shown to be beneficial; however, studies are ongoing. The most important factor for early tumour detection remains parental and physician awareness of the increased cancer risk.

Bone density. Osteoporosis is common in young adults with Costello syndrome (White et al. 2005), and bone density assessment is recommended as a baseline, with follow-up depending upon the initial result.

Therapies

Growth Hormone (GH) Treatment. If treatment with growth hormone is contemplated, its unproven benefit and potential risks should be thoroughly discussed in view of the established risks of cardiomyopathy and malignancy in individuals with Costello syndrome and the unknown effect of growth hormone on these risks.

Unproven benefit. Individuals with Costello syndrome frequently have low GH levels.

True growth hormone deficiency requires GH replacement. Three individuals with GH deficiency showed increased growth velocity without adverse effects after three to seven years of replacement therapy, but two continued to have short stature (Stein et al. 2004).

It is unclear from the literature if the use of GH is beneficial in individuals with Costello syndrome with partial growth hormone deficiency. An abnormal growth hormone response on testing and a good initial growth response was reported (Legault et al. 2001).

Cardiac hypertrophy. Whether the anabolic actions of growth hormone accelerate pre-existing cardiac hypertrophy is not known (Lin et al. 2002). In rare cases, cardiomyopathy has progressed after initiation of growth hormone treatment; whether the relationship was causal or coincidental is unknown (Kerr et al. 2003).

Malignancy. The effect of growth hormone on tumour predisposition has not been determined. Two reports have raised the possibility of an association:

Bladder carcinoma occurred in a 16-year-old treated with growth hormone (Gripp et al. 2000).

A rhabdomyosarcoma was diagnosed in a 26-month-old receiving growth hormone from age 12 months (Kerr et al. 2003).

References

Allanson JE (2007) Noona syndrome. Gene Reviews. http://www.genetests.org

Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, Filocamo M, Kato K, Suzuki Y, Kure S, Matsubara Y (2005) Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nature Genet 37: 1038–1040.

Aoki Y, Niihori T, Narumi Y, Kure S, Matsubara Y (2008) The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders. Hum Mutat May 9 [Epub ahead of print].

Axelrad ME, Glidden R, Nicholson L, Gripp KW (2004) Adaptive skills, cognitive, and behavioral characteristics of Costello syndrome. Am J Med Genet 128A: 396–400.

Axelrad ME, Nicholson L, Stabley DL, Sol-Church K, Gripp KW (2007) Longitudinal assessment of cognitive characteristics in Costello syndrome. Am J Med Genet A 143: 3185–3193.

Bentires-Alj M, Kontaridis MI, Neel BG (2006) Stops along the RAS pathway in human genetic disease. Nat Med 12: 283–285.

Berberich MS, Carey JC, Hall BD (1999) Resolution of the perinatal and infantile failure to thrive in a new autosomal recessive syndrome with the phenotype of a storage disorder and furrowing of palmar creases. (Abstract) Proc Greenwood Genet Center 10: 78.

Bertola DR, Pereira AC, Brasil AS, Albano LM, Kim CA, Krieger JE (2007) Further evidence of genetic heterogeneity in Costello syndrome: involvement of the KRAS gene. J Hum Genet 52: 521–526.

Borochowitz Z, Pavone L, Mazor G, Rizzo R, Dar H (1992) New multiple congenital anomalies (mental retardation syndrome (MCA/1MR), with facio-cutaneous-skeletal involvement. Am J Med Genet 43: 678–685.

Borochowitz Z, Pavone L, Mazor G, Rizzo R, Dar H (1993) Facio-cutaneous-skeletal syndrome: new nosological entity or Costello syndrome? Am J Med Genet 47: 173.

Costello JM (1971) A new syndrome. NZ Med J 74: 387.

Costello JM (1977) A new syndrome: mental subnormality and nasal papillomata. Aus Pediatr J 13: 114–118.

Czeizel AE, Tímar L (1995) Hungarian case with Costello syndrome and translocation t (1; 22). Am J Med Genet 57: 501–503.

Davies SJ, Hughes HE (1994) Costello syndrome: natural history and differential diagnosis of cutis laxa. J Med Genet 31: 486–489.

Dearlove O, Harper N (1997) Costello syndrome. Paediatr Anaesth 7: 476–477.

De Baun MR (2002) Screening for cancer in children with Costello syndrome. Am J Med Genet 108: 88–90.

Della Marca G, Vasta I, Scarano E, Rigante M, De Feo E, Mariotti P, Rubino M, Vollono C, Mennuni GF, Tonali P, Zampino G (2006) Obstructive sleep apnea in Costello syndrome. Am J Med Genet A 140: 257–262.

Delrue MA, Chateil JF, Arveiler B, Lacombe D (2003) Costello syndrome and neurological abnormalities. Am J Med Genet 123A: 301–305.

Der Kaloustian VM, Moroz B, Mc Intosh N, Watters AK, Blaichman S (1991) Costello syndrome. Am J Med Genet 41: 69–73.

Der Kaloustian VM (1993) Not a new MCA/MR syndrome but probably Costello syndrome? Am J Med Genet 47: 70–71.

Estep AL, Tidyman WE, Teitell MA, Cotts PD, Rauer KA (2006) HRAS mutation in Costello syndrome: detection of constitutional activating mutations in codon 12 ans 13 and loss of wild-type allele in malignancy. Am J Med Genet 140A: 8–16.

Franceschini P, Licata D, Di Cara G, Guala A, Bianchi M, Ingrosso G, Franceschini D (1999) Bladder carcinoma in Costello syndrome: report on a patient born to consanguineous parents and review. Am J Med Genet 86: 174–179.

Fujikawa Y, Sugai K, Fukumizu M, Hanaoko S, Sasaki M, Kaga M (2001) Three cases of Costello syndrome presenting with intractable epilepsy and profound psychomotor retardation/regression. Noto Hattatsu 33: 430–435.

Fukao T, Sakai S, Shimozawa N, Kuwahara T, Kano M, Goto E, Nakashima Y, Katagiri-Kawade M, Ichihashi H, Masuno M, Orii T, Kondo N (1996) Life-threatening cardiac involvement throughout life in a case of Costello syndrome. Clin Genet 50: 244–247.

Galera C, Delcrue MA, Goizet C, Etchegovhen K, Taupiac E, Sigaudy S, Arvelier B, Philip N, Bouvard M, Lacombe D (2006) Behavioural and temperamental features of children with Costello syndrome. Am J Med Genet A 140: 968–974.

Gelb BD, Tartaglia M (2006) Noonan syndrome and related disorders: dysregulated RAS-mitogen activated protein kinase signal transduction. Hum Mol Genet 15 (Spec No 2): R220–R226.

Gregerson N, Viljoen D (2004) Costello syndrome with growth hormone deficiency, and hypoglycemia: a new report and review of the endocrine associations. Am J Med Genet 129A: 171–175.

Gripp KW, Scott CI, Nicholson L, Mc Donald-Mc Ginn DM, Ozeran JD, Jones MC, Lin AE, Zackai EH (2002) Five additional Costello syndrome patients with rhabdomyosarcoma: proposal for a tumor screening protocol. Am J Med Genet 108: 80–87.

Gripp KW, Stabley DL, Nicholson L, Hoffman JD, Sol-Church K (2006a) Somatic mosaicism for an HRAS mutation causes Costello syndrome. Am J Med Genet A 140: 2163–2169.

Gripp KW, Lin AE, Stabley DL, Nicholson L, Scott CI, Doyle D, Aoki Y, Matsubara Y, Zackai EH, Lapunzina P, Gonzalez-Meneses A, Holbrook J, Agresta CA (2006b) HRAS mutation analysis in Costello syndrome: genotype and phenotype correlation. Am J Med Genet 140A: 1–7.

Gripp KW, Lin AE (2007) Costello syndrome. Gene Reviews. http://www.genetests.org.

Hall BD, Berbereich FR, Berbereich MS (1990) AMICABLE syndrome: a new unique disorder involving facial, cardiac, ectodermal, growth and intellectual abnormalities. Proc Greenwood Genet Center 9: 103A.

Hennekam RCM (2003) Costello syndrome: an overview. Am J Med Genet Part C (Semin Med Genet) 117C: 42–48.

Hinek A, Rabinovitch M (1994) 67 Kd elastin binding protein is a protective "companion" of extracellular insoluble elastin and intracellular tropoelastin. J Cell Biol 126: 563–574.

Hinek A, Smith AC, Cutiongeo EM, Callahan JW, Gripp KW, Weksberg R (2000) Decreased elastin deposition and high proliferation of fibroblasts from Costello syndrome are related to functional deficiency in the 67-kD_elastin-binding protein. Am J Hum Genet 66: 859–872.

Hinek A, Teitell MA, Schoyer L, Allen W, Gripp KW, Hamilton R, Weksberg R, Kluppel M, Lin AE (2005) Myocardial storage of chondroitin sulfate-containing moieties in Costello syndrome patients with severe hypertrophic cardiomyopathy. Am J Med Genet 133A: 1–12.

Indik Z, Yea H, Ornstein-Goldstein N, Sheppard P, Anderson N, Rosenblood JC, Peltonen L, Rosenbloom J (1987) Alternative splicing of human elastin mRNA indicated by sequence analysis of cloned genomic and complementary DNA. Proc Natl Acad Sci USA 84: 5680–5684.

Ioan DM, Fryns JP (2002) Costello syndrome in two siblings and minor manifestations in their mother: further evidence for autosomal dominant inheritance? Genet Counsel 13: 353–356.

Johnson JP, Golabi M, Norton ME, Rosenblatt RM, Feldman GM, Yang SM, Hall BD, Fries MH, Carey JC (1998) Costello syndrome: Phenotype, natural history, differential diagnosis, and possibly cause. J Pediatr 133: 441–448.

Kawame H, Matsui M, Kurosawa K, Matsuo M, Masuno M, Ohashi H, Fueki N, Aoyama K, Miyatsuka Y, Suzuki K, Akatsuka A, Ochiai Y, Fukushima Y (2003) Further delineation of the behavioral and neurologic features in Costello syndrome. Am J Med Genet 118A: 8–14.

Kerr B, Eden OB, Dandamudi R, Shannon N, Quarrell O, Emmerson A, Ladusans E, Gerrard M, Donnai D (1998) Costello syndrome: two cases with embryonal rhabdomyosarcoma. J Med Genet 35: 1036–1039.

Kerr B, Delrue MA, Sigaudy S, Perveen R, Marhe M, Burgelin I, Stef M, Tang B, Eden B, O'Sullivan J, De Sandre-Giovanoli A, Reardon W, Brewer C, Bennett C, Ouarell O, M'Cann E, Donnai D, Stewart F, Hennekam R, Cave H, Verloes A, Philip N, Lacombe D, Levy N, Arvelier B, Black G (2006) Genotype-phenotype correlation in Costello syndrome: HRAS mutations analysis in 43 cases. J Med Genet 43: 401–405.

Kerr B, Allanson J, Delrue MA, Gripp KW, Lacombe D, Lin AE, Rauen KA (2008) The diagnosis of Costello syndrome: nomenclature in Ras/MAPK pathway disorders. Am J Med Genet A 146: 1218–1220.

Kratz CP, Steinemann D, Niemeyer CM, Schlegelberger B, Koscielniak E, Kontny U, Zenker M (2007) Uniparental disomy at chromosome 11p15.5 followed by HRAS mutations in embryonal rhabdomyosarcoma: lessons from Costello syndrome. Hum Mol Genet 16: 374–379.

Legault L, Cagnon C, Lapointe N (2001) Growth hormone deficiency in Costello syndrome: a possible explanation for the short stature. J Pediatr 138: 151–152.

Levaillant JM, Gerard-Blanluet M, Holder-Espinasse M, Valat-Ricot AS, Devisme L, Cave H, Manouvrier-Hanu S (2006) Prenatal overlap of Costello syndrome and severe Noonan syndrome by tri-dimensional ultrasonography. Prenat Diagn 26: 340–344.

Li DY, Brooke B, Davis EC, Mechan RP, Sorensen LK, Boak BB, Eichwald E, Keating MT (1998a) Elastin is an essential determinant of arterial morphogenesis. Nature 393: 276–280.

Li DY, Faury G, Taylor DG, Davis EC, Boyle WA, Mecham RP, Stenzel P, Boak B, Keating MT (1998b) Novel arterial pathology in mice und human hemizygous for elastin. J Clin Invest 102: 1783–1787.

Lin AE, Grossfeld PD, Hamilton RM, Smoot L, Gripp KW, Proud V, Weksberg R, Wheeler P, Picker J, Irons M, Zackai E, Marino B, Scott CI Jr, Nicholson L (2002) Further delineation of cardiac abnormalities in Costello syndrome. Am J Med Genet 111: 115–129.

Lin AE, Rauen KA, Gripp KW, Carey JC (2008) Clarification of previously reported Costello syndrome patients. Am J Med Genet A 146: 940–943.

Lo IF, Brewer C, Shannon N, Shorto J, Tang B, Black G, Soo MT, Ng DK, Lam ST, Kerr B (2008) Severe

neonatal manifestations of Costello syndrome. J Med Genet 45: 167–171.

Lurie IW (1994) Genetics of the Costello syndrome. Am J Med Genet 52: 358–359.

Mancini GMS, van Diggelen OP, Kleijer WJ, Di Rocco M, Farina V, Yuksel-Apak M, Kayserili H, Halley DJJ (2003) Studies on the pathogenesis of Costello syndrome. J Med Genet 40: e37.

Maroti Z, Kutsche K, Sutajova M, Gal A, Northwang HG, Czeizel AE, Tímár L, Sólyom E (2002) Refinement and delineation of the breakpoint regions of a chromosome 1;22 translocation in a patient with Costello syndrome. Am J Med Genet 109: 234–237.

Martin RA, Jones KL (1991) Delineation of the Costello syndrome. Am J Med Genet 41: 346–349.

Midgley RS, Kerr DJ (2002) Ras as a target in cancer therapy. Crit Rev Oncol Hematol 44:109–120.

Mori M, Yamagata T, Mori Y, Nokubi M, Saito K, Fukushima Y, Momoi MY (1996) Elastic fiber degeneration in Costello syndrome. Am J Med Genet 61: 304–309.

Narumi Y, Aoki Y, Niihori T, Neri G, Cave 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 A 143: 799–807.

Nguyen V, Buka RL, Roberts BJ, Eichenfield LF (2007) Cutaneous manifestations of Costello syndrome. Int J Dermatol 46: 72–76.

Niihori T, Aoki Y, Narumi Y, Neri G, Cave 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.

Noonan JA (2006) Noonan syndrome and related disorders: Alterations in growth and puberty. Rev Endocr Metab Disord 7: 251–255.

OMIM (2007) Online Mendelian Inheritance in Man. Baltimore: Johns Hopkins University Press. http://www.ncbi.nlm.nih.gov/omim.

O'Neal JP, Ramdas J, Wood WE, Pellitteri PK (2004) Parameningeal rhabdomyosarcoma in a patient with Costello syndrome.

Pascual-Castroviejo I, Pascual-Pascual SI (2005) Síndrome de Costello. Presentación de un caso con seguimiento durante 35 años. Neurología 20: 144–148.

Patton MA, Tolmie J, Ruthnum P, Bamforth S, Baraitser M, Pembrey M (1987) Congenital cutis laxa with retardation of growth and development. J Med Genet 24: 556–561.

Pratesi R, Santos M, Ferrari I (1998) Costello syndrome in two Brazilian children. J Med Genet 35: 54–57.

Rauen KA (2007) HRAS and the Costello syndrome. Clin Genet 71: 101–108.

Rauen KA (2007a) HRAS and the Costello syndrome. Clin Genet 71: 101–108.

Rauen KA (2007b) cardiofaciocutaneous syndrome. Gene Reviews. http://www.genetests.org

Rauen KA, Hefner E, Carrillo K, Taylor J, Messier L, Aoki Y, Gripp KW, Matsubara Y, Proud VK, Hammond P, Allanson JE, Delrue MA, Axelrad ME, Lin AE, Doyle DA, Kerr B, Carey JC, McCormick F, Silva AJ, Kieran MW, Hinek A, Nguyen TT, Schoyer L (2008) Molecular aspects, clinical aspects and possible treatment modalities for Costello syndrome: proceedings from the 1st International Costello Syndrome Research Symposium 2007. Am J Med Genet A 146: 1205–1217.

Roberts A, Allanson J, Jadico SK, Kavamura MI, Noonan J, Opitz JM, Young T, Neri G (2006) The cardiofaciocutaneous syndrome. J Med Genet 43: 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.

Say B, Güçsavas M, Morgan H, York C (1993) The Costello syndrome. Am J Med Genet 47: 163–165.

Schubbert S, Zenker M, Rowe SL, Boll S, Klein C, Bollag G, van der Burgt I, Musante L, Kalscheuer V, Wehner LE, Nguyen H, West B, Zhang KY, Sistermans E, Rauch A, Niemeyer CM, Shannon K, Kratz CP (2006) Germline KRAS mutations cause Noonan syndrome. Nat Genet 38: 331–336.

Shiihara T, Kato M, Mitsuhashi Y, Hayakasa K (2005) Costello syndrome showing Moyamoya vasculopathy. Pediatr Neurol 32: 361–363.

Sigaudy S, Vittu G, David A, Vigneron J, Lacombe D, Moncla A, Flori E, Philip N (2000) Costello syndrome: report of six patients including one with an embryonal rhabdomyosarcoma. Eur J Pediatr 159: 139–142.

Siwik ES, Zahka KG, Wiesner GL (1998) Cardiac disease in Costello syndrome. Pediatrics 150: 706–708.

Stein RI, Legault L, Daneman D, Weksberg R, Hamilton J (2004) Growth hormone deficiency in Costello syndrome. Am J Med Genet 129A: 166–170.

Suri M, Garret C (1998) Costello syndrome with acoustic neuroma and cataract. Is the Costello locus linked to neurofibromatosis type 2 on 22q? Clin Dysmorphol 7: 149–151.

Tartaglia M, Cotter PD, Zampino G, Gelb BD, Rauen KA (2003) Exclusion of PTPN11 mutations in Costello syndrome: further evidence for distinct genetic etiologies for Noonan, cardio-facio-cutaneous and Costello syndromes. Clin Genet 63: 423–426.

Van Den Bosch T, Van Schoubroeck D, Fryuns JP, Naulaers G, Inion AM, Devriendt K (2002) Prenatal findings in a monozygotic twin pregnancy with Costello syndrome. Prenat Diagn 22: 415–417.

Van Eeghen AM, Van Gelderen I, Hennekam RCM (1999) Costello syndrome: Report and review. Am J Med Genet 82: 187–193.

van Steensel MA, Vreeburg M, Peels C, van Ravenswaaij-Arts CM, Bijlsma E, Schrander-Stumpel CT, van Geel M (2006) Recurring HRAS mutation G12S in Dutch patients with Costello syndrome. Exp Dermatol 15: 731–734.

Vila Torres J, Pineda Marfa M, Gonzalez Ensenat MA, Lloreta Trull J (1994) Pathology of the elastic tissue of the skin in Costello syndrome. An image analysis study using mathematical morphology. Anal Quant Cytol Histol 16: 421–429.

Weiss G, Confino Y, Shemor A, Trau H (2004) Cutaneous manifestation in the cardiofaciocutaneous syndrome, a variant of the classical Noonan syndrome. Report of a case and review of the literature. J Eur Acad Dermatol Venereol 18: 324–327.

White SM, Graham JM, Kerr B, Gripp K, Weksberg R, Cytrynbaum C, Reeder JL, Stewart FJ, Edwards M, Wilson M, Bankier A (2005) The adult phenotype in Costello syndrome. Am J Med Genet A 136: 128–135.

Zampino G, Mastroiacovo P, Ricci R, Zollino M, Segni G, Martini-Neri ME, Neri G (1993) Costello syndrome: Further clinical delineation, natural history, genetic definition, and nosology. Am J Med Genet 47: 176–183.

Zampino G, Pantaleoni F, Carta C, Cobellis G, Vasta I, Neri C, Pogna EA, De Feo E, Delogu A, Sarkozy A, Atzeri F, Selicorni A, Rauen KA, Cytrynbaum CS, Weksberg R, Dallapiccola B, Ballabio A, Gelb BD, Neri G, Tartaglia M (2007) Diversity, parental germline origin, and phenotypic spectrum of de novo HRAS missense changes in Costello syndrome. Hum Mutat 28: 265–272.