Understanding Costello syndrome; a journey

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Costello syndrome

- Costello 1971, 1977
- Moderate MR
- Poor postnatal growth
- Distinctive facies
- Loose skin hands, feet
- Nasolabial warts
1991-1998 clinical features

- Striking natural history
- Severe feeding difficulty invariable
- “Marasmic” phase
- Most NG feeding/ gastrostomy/ fundoplication
Key features

- Development; mild to moderate ID
- Pleasant sociable personality
- Distinctive face and hands
- Relative macrocephaly
- Short stature (Some GH)
- Warts at moist surfaces
- Cardiac abnormalities
Hands and Feet

- Excess skin
- Hyperkeratosis
- Hyperextensible
- Square tips
- Ulnar deviation
- Flexion at wrists
1998

- Embryonal rhabdomyosarcoma in two children with CS from the north of England
- A cancer predisposing syndrome
Cancer risk 2002

- Published cancers; 21/127, 17%
- Embryonal rhabdomyosarcoma 11 of 21
- Mostly less than age 6
- Neuroblastoma/ ganglioneuroblastoma childhood
- Bladder carcinoma; adolescence and adult life
- Gastric polyps/leiomyoma/ breast fibroadenosis
- Benign bladder tumours
Families

- International Costello syndrome support groups 1996
- Web based
- Colin Stone
- Tammy Moore

Alabama 1999
International meetings

• 2001 Toronto
• 2003 Wilmington
• 2005 St Louis
• 2007 Portland
• 2009 San Francisco
• 2011 Chicago
• 2013 Orlando

French Costello Syndrome Association 2001
International Costello Family Forums

• Natural history growth, milestones, development, “the phenotype”
• International collaboration, The adult phenotype, Sue White
• Powerful parent and professional partnership
• Strong research emphasis
HRAS mutations cause CS
Aoki et al 2005

- HRAS mutations in >80% CS patients
- Mostly residues 12/13
- Activating
- Mostly paternal allele
- Somatic mosaicism reported
RAS-RAF-ERK-MAP kinase cascade

- Cancer pathogenesis
- Downstream of growth factor, cell adhesion and cytokine receptors
- Outcome: cell fate (proliferation, differentiation, cell death)
- Cognition: learning, memory, synaptic plasticity
- Immune modulation; vascular development
Genomic structure of \textit{HRAS} with mutations

Residues associated with mutations in Costello syndrome

Residues associated with oncogenic mutations

Aoki et al 2005
activation leads to transcription of genes influencing cell proliferation, growth and other processes in both nucleus and cytosol
“Rasopathies”

- Collectively common
- A single gene causes CS, multiple genes CFC, Noonan and NSML syndrome
- Collectively “neuro-cardio-facio-cutaneous” syndromes (NCFCs)
- Overlapping clinical features
- Few genotype/phenotype correlations
- Precise clinical diagnosis often difficult
RAS/MAPK 1/1000
HRAS testing and the CS phenotype

Relatively homogenous. UK prevalence 2000-9;1/381,914 LB
CS is due to HRAS mutations Aoki 2005

- Heterozygous \textit{HRAS} mutations identified in 15 out of 16 UK patients

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Heterozygous mutation</th>
<th>Amino acid change</th>
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<tbody>
<tr>
<td>11</td>
<td>34 G &gt; A</td>
<td>G12S</td>
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<tr>
<td>2</td>
<td>35 G &gt; C</td>
<td>G12A</td>
</tr>
<tr>
<td>1</td>
<td>34 G &gt; T</td>
<td>G12C</td>
</tr>
<tr>
<td>1</td>
<td>35 GC &gt; AA</td>
<td>G12E</td>
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</tbody>
</table>

Activating
Predominantly paternal
Somatic mosaicism reported
Germline mosaicism reported

![Graphical representation of DNA sequencing](image)
CS versus CFC

Face evolves with time, 3-D studies; overlap NS/CFC, CS/CFC, not CS/NS.

Peter Hammond
Diagnostic clues; prenatal

- Polyhydramnios 90%
- Macrocephaly
- Macrosomia
- Nuchal thickening
- Ascites
- Ventriculomegaly
- Hand posture
- Arrhythmia
- CS: G12D, G13C

- Prematurity 50%
- Advanced paternal age 50%

Smith, Padraza and Proud 2009,
Kuniba et al Am J Med Genet; 2009:
Lin et al, Prenat Diag; 2009
Lee et al; Clin Genet;2009
CS; malignancy risk

- Prospective study 15% (Karen Gripp)
- Rhabdomyosarcoma 60%
- Incomplete age dependence
- Neuroblastoma 15%
- Bladder carcinoma 15%
Accurate clinical studies

- Cardiac manifestations
- Orthopaedic manifestations
- Eye
- Neurological manifestations
- Musculoskeletal manifestations
- Growth charts
- All underpinned by accurate molecular diagnosis
- Mutation specific
Neurodevelopmental evaluation

- Stable IQ
- Severe to average range
- Mean mild ID
- Adaptive behaviour scales show 70% in ID range
- Girls higher function
- Late childhood burst in non-verbal fluid reasoning
- Socialisation a strength
- Activities of daily living difficult
- Boys more behaviour difficulty

Longitudinal Course of Cognitive, Adaptive, and Behavioral Characteristics in Costello Syndrome
Milder phenotypes

- G13C
- Absent MAT, ulnar deviation, papillomata
- Less neurosurgical procedures
- Taller
- Loose anagen hair, very long eyelashes
- Gripp et al, 2011

- C.173C>T
- 3 patients, one father-son
- No papillomata or malignancy
- One with significant cognitive impairment
- Gripp et al, 2012

Mutation specific counselling, when is Costello syndrome the right name?
Severe neonatal phenotypes

- Congenital myopathy with excess muscle spindles (CMEMS)
- Some Noonan like features
- Hypotonia, variable contractures, absence of spontaneous movement, areflexia, cardiomyopathy.
- G12S, G12V, E63K, Q22K

Van der Burght et al, J Med Genet; 2007
• Polyhydramnios, macrosomia
• Flexion contractures at wrist
• Septal/biventricular cardiac failure
• Severe jaundice
• Hypoglycaemia
• PAT; ASD, thickened septum
• Tracheomalacia/bronchomalacia
• Chylothorax
• Pulmonary lymphangectasia
PM
G12C

- Pleural and pericardial effusions
- W, HC 98th
- Small lungs
- CPAP dependent
- Atrial tachyarryhythmia
Severe neonatal phenotype

- Early lethality unrelated to tumour (UK 9/35, 6 multi-organ failure)
- Hypoglycaemia, Cardiomyopathy (G12V)
- Respiratory failure (aponea, airway, lung)
- Pleural and pericardial effusion
- Chylous ascites
- Severity scoring supports increased severity G12A and G12C (McCormack et al 2013)
Where are we now?

- Mutations in HRAS cause Costello syndrome
- Accurate description of phenotype
- A recognisable prenatal phenotype
- A core homogenous phenotype, milder and more severe variants (neonatal)
- Spectrum of mutation severity
- Differentiating from CFC may be difficult
H-ras G12V homozygotes vs wild type

Mouse models: H-ras

- H-ras G12V mice generated at CNIO
- In homozygosity,
  - Noted to have unusual appearance
  - Some behavioural/cognitive differences
  - Hypertrophic cardiomyopathy and angiotensin-mediated hypertension

A Rasopathy

Altered clinical understanding
Increased research capability
Expanded international collaboration
Biannual research meeting

Denayer and Legius Eur J Paed;2007
A Rasopathy

- A clinical continuum
- Few truly specific or distinguishing features
- Research into one disorder may benefit all, cellular studies, animal models

- Treatment trials Novartis
Considering treatments

• Diagnostic test, major advances in natural history as a necessary baseline
• Treatment goals? Cardiomyopathy, adaptive behaviour or learning, muscular strength or endurance, skin manifestations, severe feeding difficulty and irritability of early life
• Improved understanding of mutation specific cellular biology
Acknowledgements

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• Costello Syndrome Family Network
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