Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of \textit{IDH1} and \textit{IDH2}

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\textsuperscript{1}Nature Genetics 2011 Nov 6;43(12):1262-5. doi: 10.1038/ng.994.
**IDH 1 / IDH2 - missense and heterozygous mutations**

Isocitrate

\[ \text{Isocitrate} \rightarrow \text{NADP}^+ \rightarrow \text{Isocitrate} \]

\[ \text{NADP}^+ \rightarrow \text{IDH1} \rightarrow \text{Mut IDH1} \]

\[ \text{Mut IDH1} \rightarrow \text{2-hydroxiglutamate} \rightarrow \text{Oncometabolite} \]

\[ \text{2-hydroxiglutamate} \rightarrow \text{NADPH} \rightarrow \alpha\text{-ketoglutarate} \rightarrow \alpha\text{-KG} \]

\[ \alpha\text{-ketoglutarate} (\alpha\text{-KG}) \rightarrow \text{gain of function} \]
*IDH1* mutations in CS is associated with a hypermethylation profile and increased 2HG

Nature Communications í *Paul Guilhamon et al.*
Differential diagnosis

Biomarker for detection of relapse

Therapeutic option
IDH1 inhibitors
Circulating tumour DNA from a patient with chondrosarcoma: *IDH1*

Acknowledgment: Tim Forshew, Alice Gutteridge, Victoria Rathbone, Manu Gupta, Adrienne M Flanagan
Chondrosarcoma ctDNA increases with grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>% Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>LG (Ollier's)</td>
<td>20 (1/5)</td>
</tr>
<tr>
<td>G1</td>
<td>0 (0/3)</td>
</tr>
<tr>
<td>G1/2</td>
<td>0 (0/1)</td>
</tr>
<tr>
<td>G2</td>
<td>33 (4/12)</td>
</tr>
<tr>
<td>G2/3</td>
<td>100 (3/3)</td>
</tr>
<tr>
<td>G3</td>
<td>100 (2/2)</td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>100 (4/4)</td>
</tr>
</tbody>
</table>

Digital PCR Analysis of Circulating Tumour DNA in a Broad Cohort of Sarcoma Patients: A Gutteridge; VM Rathbone; R Gibbons; F Amary; N Archard; K Davies; J Brown; M Jorgensen; M Gupta; AM Flanagan; T Forshew.
Examples

?Potential biomarker for recurrent/metastatic disease

249485 (G4)
Chondrosarcomas

ÅCOL2A1 37%
ÅTP53 20%
ÅRB1 33%
ÅHedgehog signaling 18%
loss of p16/CDKN2A

- 60% of HG chondrosarcomas
- No low grade CHS

- 102 samples from 37 patients.
  - IDH1 mutation - primary / recurrences
  - Loss of p16 can be acquired with disease progression.
Mesenchymal chondrosarcoma

- Rare
- 1/3 occur in the soft tissue
- HEY1-NCOA2
Chondromyxoid Fibroma

All ages, peak: 2nd - 3rd decades.
Eccentric elongated, well-defined border of sclerotic bone
The glutamate receptor gene GRM1 recombines with several partner genes. The GRM1 coding region remains intact showed a more than 100-fold and up to 1,400-fold increase in GRM1 expression levels compared to control tissues.
Chondroblastoma

• Epiphyseal tumour

• Young patients with immature skeleton

• Chondroblasts + osteoclast-like giant cells
Distinct H3F3A and H3F3B driver mutations define chondroblastoma and giant cell tumor of bone

Sam Behjati1,2,12, Patrick S Tarpey1,12, Nadège Presneau3,4, Susanne Scheipl3,5, Nischalan Pillay3,6, Peter Van Loo1,7, David C Wedge1, Susanna L Cooke1, Gunes Gundem1, Helen Davies1, Serena Nik-Zainal1, Sancha Martin1, Stuart McLaren1, Victoria Goodie1, Ben Robinson1, Adam Butler1, Jon W Teague1, Dina Halai6, Bhavisha Khatri6, Ola Myklebost8, Daniel Baumhoer9, Gernot Jundt9, Rifat Hamoudi3,4, Roberto Tirabosco6, M Fernanda Amary6, P Andrew Futreal1, Michael R Stratton1, Peter J Campbell1,10,11 & Adrienne M Flanagan3,4,6
Giant cell tumour of bone
Malignant GCT of Left Talus - Wild type for H3.3 mutation