Cytogenetic and clinical refinement of the rare but recurrent unbalanced t(1;16) translocation in MDS

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Introduction

- Several cytogenetic abnormalities associated with prognosis in MDS - IPSS(R)

| Intermediate (13%/19%)† | del(7q), +8, +19, i(17q), any other single or double independent clones |

- A proportion of these fall into ‘Intermediate’ category
  - Including ‘any other independent clones’
- Current goals including refining prognostic significance of some of these ‘other’ abnormalities
Case Study

- Bone marrow
- 65 year old male
- Possible MDS
- Immunology consistent with myelodysplasia; RAEB1.

46,XY,+1,der(1)t(1;16)(p11;p11.1),-16[28]/
47,XY,+1,der(1)t(1;16)(p11;p11.1),+14,-16,-21,+mar[cp2]
### t(1;16) in MDS in the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Case</th>
<th>Karyotype</th>
<th>MDS subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mugneret et al 1995</td>
<td>1</td>
<td>46,XY,der(16)t(1;16)(q11;q11)[15]/46,XY[5]</td>
<td>RAEB</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>46,XY,der(16)t(1;16)(q11;q11)[19]/46,XY[1]</td>
<td>RARS</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>46,XY,der(16)t(1;16)(q11;q11)[8]/46,idem,+8[12]/46,XY[1]</td>
<td>RAEB</td>
</tr>
<tr>
<td>Dean &amp; Mohamed 2007</td>
<td>1</td>
<td>46,XY,+der(1)t(1;16)(p11;p11.1),-16</td>
<td>RCMD</td>
</tr>
<tr>
<td>Lunghi et al 2010</td>
<td>1</td>
<td>46,XY,+1,der(1)t(1;16)(p11;p11.1)</td>
<td>RAEB1</td>
</tr>
</tbody>
</table>

- Unbalanced translocation resulting in 1q trisomy
- Only single cases/small studies described to date
- Aim is to combine data from these studies with WMRGL cases
Trisomy 1q in myeloid neoplasia

• Whole/partial trisomy for 1q is seen in most haematological malignancies including MDS.

• Thought to arise due to instability of paracentric heterochromatin, although exact mechanism unclear.
  • Why does this lead to gain of an extra copy of 1q?

• Gene dosage effect?
  • Proliferative advantage?
  • Drives clonal evolution?
  • Primary or secondary genetic event?
WMRGL Cases

- Retrospective search of WMRGL records;
  - identified 5 cases (+1 case from Dundee Lab)
- FISH analysis:
  - Which centromere involved – is it consistent?
  - Were these cases reported correctly?
- Microarray analysis:
  - Are the breakpoints consistent
  - Do they fall within any areas of candidate genes/gene fusions?
- Grouped with published cases
  - Are there any clinical association (e.g. MDS subtype or prognosis)?
FISH results

Case 1

46,XY,+1,\(\text{der}(1)t(1;16)(p11;p11.1),-16[28]/\)
47,XY,+1,\(\text{der}(1)t(1;16)(p11;p11.1),+14,-16,-21,+\text{mar}[cp2]\)

Case 2

46,XX,\(\text{der}(16)t(1;16)(p1;q1)[4]/47,\text{idem},+19[3]/\)
46,XX [3]
FISH results

**Case 3**

45,XX, inv(3)(q21q26), -7, der(16)t(1;16)(q12;q1)[24]

**Case 4**

47,XX, +8, der(16)t(1;16)(q?21;q?12)[9]/46,XX[1]
FISH results

Case 5

46,XY,inv(3)(q21q26),der(16)t(1;16)(q2;q12)[10]

Case 6

47,XX, +der(1)t(1;16)(p11;p11.1), add(6)(p21)[10]
Microarray analysis

- 4/6 cases with DNA available for analysis
- Affymetrix Cytoscan® HD array platform
- 2.67 million markers for copy number (CN) analysis
  - 750,000 SNP probes
  - 1.9 million non-polymorphic probes
- >99% sensitivity and specificity for CN changes >400 kb
Microarray analysis – Chromosome 1

Case 1

Case 4

Case 3

Case 6

Centromere
## Summary of Array findings

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Karyotype</th>
<th>Array finding</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46,XY,+1,der(1)t(1;16)(p11;p11.1),−16[28]/47,XY,+1,der(1)t(1;16)(p11;p11.1),+14,−16,−21,+mar[cp2]</td>
<td>Gain 1p11.2-qter&lt;br&gt;Loss 16q</td>
<td>LOH 14&lt;br&gt;475kb del 22q13.1</td>
</tr>
<tr>
<td>3</td>
<td>45,XX,inv(3)(q21q26),−7,der(16)t(1;16)(q12;q1)[24]</td>
<td>Gain 1q&lt;br&gt;Loss 16q&lt;br&gt;Gain 3q21-qter&lt;br&gt;Loss of 7</td>
<td>2.5mb del 17q11.2</td>
</tr>
<tr>
<td>4</td>
<td>47,XX,+8,der(16)t(1;16)(q?21;q?12)[9]/46,XX[1]</td>
<td>Gain 1p11.2-qter&lt;br&gt;Loss 16q11.1-qter&lt;br&gt;Mosaic gain of 8</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>47,XX,+der(1)t(1;16)(p11;p11.1),add(6)(p21)[10]</td>
<td>Gain 1q21-qter&lt;br&gt;Gain 16p11.2-pter&lt;br&gt;Loss 6p22-pter</td>
<td>LOH 13&lt;br&gt;dup(3)(q27.3-qter)</td>
</tr>
</tbody>
</table>
Other array findings - Case 1

- LOH 14
- 475kb del 22q13.1
  - Includes MAFF

MAFF:
- (V-MAF avian musculoaponeurotic fibrosarcoma oncogene family, protein F)
- No specific association with myeloid neoplasia described but some association with cutaneous melanoma
Other array findings - Case 3

- 2.5mb del 17q11.2
  - Includes CRLF3 & NF1

- NF1 (Neurofibromin 1/Neurofibromatosis 1)
  - Tumour suppressor gene
  - Deletion/alteration leads to predisposition to JMML and/or AML

- CRLF3 (Cytokine receptor-like factor 3)
  - Overexpression in *in situ* models induces cell cycle arrest
  - No specific association with myeloid neoplasia described
Other array findings - Case 6

- LOH 13
  - FLT3-itd status currently unknown – testing on-going
- Loss of 6p and gain of 3q
  - Therefore possible refinement of add(6p) to der(6)t(3;6)(q27;p22)?
# Patient Characteristics

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Patient Sex</th>
<th>Patient Age</th>
<th>IPSS</th>
<th>% BM blasts</th>
<th>Hb</th>
<th>Plts</th>
<th>Number cytopenias</th>
<th>Neutrophil count</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM1</td>
<td>RAEB1</td>
<td>M</td>
<td>66</td>
<td>2</td>
<td>5</td>
<td>100</td>
<td>93</td>
<td>N/A</td>
<td>3.1</td>
<td></td>
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<tr>
<td>WM2</td>
<td>RAEB1</td>
<td>F</td>
<td>93</td>
<td>1.5</td>
<td>6</td>
<td>11</td>
<td>33</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>WM3</td>
<td>Hypoplastic MDS</td>
<td>F</td>
<td>65</td>
<td>1</td>
<td>&lt;5%</td>
<td>8.1</td>
<td>45</td>
<td>3</td>
<td>0.6</td>
<td>6 months to AML</td>
</tr>
<tr>
<td>WM4</td>
<td>NK</td>
<td>F</td>
<td>99</td>
<td>N/A</td>
<td>N/A</td>
<td>126</td>
<td>47</td>
<td>N/A</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>WM5</td>
<td>RAEB2</td>
<td>M</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD1 (6)</td>
<td>MDS/MPN-U</td>
<td>F</td>
<td>N/K</td>
<td>N/K</td>
<td>N/K</td>
<td>N/K</td>
<td>N/K</td>
<td>N/K</td>
<td>N/K</td>
<td></td>
</tr>
<tr>
<td>Mugneret 1</td>
<td>RAEB2</td>
<td>M</td>
<td>74</td>
<td>N/K</td>
<td>11</td>
<td>111</td>
<td>N/K</td>
<td>2</td>
<td>2.6</td>
<td>Evolving</td>
</tr>
<tr>
<td>Mugneret 2</td>
<td>RARS</td>
<td>M</td>
<td>60</td>
<td>N/K</td>
<td>N/K</td>
<td>69</td>
<td>N/K</td>
<td>1</td>
<td>N/K</td>
<td>Previous cyclophosphamide treatment</td>
</tr>
<tr>
<td>Mugneret 3</td>
<td>RAEB2</td>
<td>M</td>
<td>56</td>
<td>N/K</td>
<td>12</td>
<td>N/K</td>
<td>N/K</td>
<td>2</td>
<td>N/K</td>
<td>Transformed 1 year later</td>
</tr>
<tr>
<td>Dean &amp; Mohammed</td>
<td>RCMD</td>
<td>M</td>
<td>30</td>
<td>N/K</td>
<td>3.4</td>
<td>11.3</td>
<td>125</td>
<td>N/K</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Lunghi</td>
<td>RAEB1</td>
<td>M</td>
<td>81</td>
<td>1</td>
<td>&lt;5%</td>
<td>8.5</td>
<td>53</td>
<td>3</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>
Summary of patient characteristics

- 6/11 cases RAEB
  - RAEB1 – 3
  - RAEB2 – 3
- Male predominance (almost 2:1)
- No other apparently significant associations
Conclusions

- Breakpoints are not centromere specific
  - Array analysis did not identify any breakpoints within candidate genes
    - But array coverage at centromeres and heterochromatic regions is poor & high incidence of benign CNV
  - Cases all reported accurately
    - Correct centromere assigned to derivative chromosome

- Although cohort is small
  - Association with RAEB1/2
    - 55% vs 40% quoted prevalence of RAEB in MDS
  - Association with patient sex

- Further work:
  - Identification of other t(1;?) translocations resulting in T1q
  - Is T1q associated with prognosis?
  - 1q as a potential target of mutation detection/identification of minimal regions of CNV
Examples of other rare rearrangements leading to trisomy 1q in MDS

<table>
<thead>
<tr>
<th>Rearrangement</th>
<th>Image</th>
<th>Diagnosis</th>
<th>Rearrangement</th>
<th>Image</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,XY,+1,der(1;22)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>MDS, no excess of blasts</td>
<td>47,XX,+der(1)t(1;19)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>?MDS</td>
</tr>
<tr>
<td>46,XY,+1,dic(1;15)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>MDS-RAEB1</td>
<td>47,XY,+add(1)(p1)</td>
<td><img src="image4.png" alt="Image" /></td>
<td>MDS in transformation</td>
</tr>
<tr>
<td>46,X,-Y,+1,add(1)(p1)</td>
<td><img src="image5.png" alt="Image" /></td>
<td></td>
<td>46,XY,+1,der(1;6)(q10;q10)</td>
<td><img src="image6.png" alt="Image" /></td>
<td>MDS</td>
</tr>
</tbody>
</table>
Acknowledgements

- WMRGL
  - Fiona Togneri
  - Julian Borrow
  - Susanna Akiki
  - Mike Griffiths
  - Central England Haematology Research Biobank (CEHRB)
- Dundee
  - Sudhir Tauro
- Tayside Tissue Bank

Thank you