The complex genetic spectrum of vascular anomalies elucidated via cancer genomics

LEANNA HANSEN, BS
Study Sites

- Brown University
- Children’s Hospital of Colorado
- Children’s Hospital of Philadelphia
- CHU Sainte-Justine, Montreal
- Columbia University
- Hospital de la Santa Creu i Sant Pau, Barcelona
- Indiana University-Purdue University of Indianapolis
- MAYO clinic
- Medical College of Wisconsin
- Phoenix Children’s Hospital
- Sanford Children’s Hospital
- Stanford School of Medicine
- The Hospital for Sick Children, Toronto
- University of California, Los Angeles
- University of California, San Francisco
- University of California, San Diego
- University of Iowa
- University of Minnesota
- University of Missouri
Study Population

- All subjects with vascular anomalies and overgrowth were eligible for inclusion
- 233 patients enrolled
- 108 affected tissue samples
- 75 affected tissue samples sequenced
- 57 affected tissue samples sequenced and fully analyzed
Somatic drawing of post-zygotic mosaicism
Somatic variant in GNAQ183
GNAQp.R183Q

PIK3R1p.578_580del
Methods: Genotyping

- Next generation sequencing
  - Hybrid capture
  - Semi-targeted-not whole exome or whole genome
  - Washington University, Saint Louis
  - Exome of 131 cancer-related genes
    - Sequence the entire exome of the gene-not just hot spots
    - Very high depth coverage 1000x
    - Highly sensitive to detect low allele frequency variants

- Tumor genomic profiling
Methods: Pathogenic?
Dr. Catherine Cottrell, PhD

- **Review of Variant Attributes**
  - Variant type/location; VAF >1%
  - *In silico* impact to protein/splicing
  - Population frequency
  - Visualization in Integrative Genomics Viewer (IGV)

- **Interpretation**
  - Assessment of variant pathogenicity
  - Medical literature and databases-Cosmic, dbGap
Results

- 42/57 patients had pathogenic or likely pathogenic variants in 10 genes
- Low allele frequency indicates a somatic variant (range 1-34.9%)
- All variants were in cell growth signal pathways
  - 25 PIK3CA
  - 12 G-proteins
    - GNAQ
    - GNA11
  - 5 additional genes
- Identified possible acquired and germline variants
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1</td>
<td>CARD11</td>
<td>ERBB2</td>
<td>GATA2</td>
<td>MAP2K1</td>
<td>PALB2</td>
<td>RHOA</td>
<td>TET2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKT1</td>
<td>CBL</td>
<td>ERBB3</td>
<td>GATA3</td>
<td>MAP2K2</td>
<td>PAX5</td>
<td>GIT1</td>
<td>TNFAIP3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKT2</td>
<td>CD79A</td>
<td>ERBB4</td>
<td></td>
<td>GNA11</td>
<td>MET</td>
<td>PDGFR</td>
<td>ROS1</td>
<td>TNFRSF14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKT3</td>
<td>CD79B</td>
<td>ESR1</td>
<td></td>
<td>GNAQ</td>
<td>MLH1</td>
<td>PDGFRB</td>
<td>RUNX1</td>
<td>TP53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK</td>
<td>CDH1</td>
<td>ETV6</td>
<td>GNAS</td>
<td>MPL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASXL1</td>
<td>CDK4</td>
<td>EZH2</td>
<td>HRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>CDKN2A</td>
<td>FANCA</td>
<td>IDH1</td>
<td>MYC</td>
<td>PIK3CA</td>
<td>SF3B1</td>
<td>TSC2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATRX</td>
<td>CEBPA</td>
<td>FBXW7</td>
<td>IDH2</td>
<td>MYD88</td>
<td>PIK3R2</td>
<td>SMAD4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAP1</td>
<td>CIC</td>
<td>FGFR1</td>
<td>IL7R</td>
<td>NF1</td>
<td>POLE</td>
<td>SMARCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCL6</td>
<td>CREB1</td>
<td>FGFR2</td>
<td>JAK1</td>
<td>NOTCH1</td>
<td>PTCH1</td>
<td>SHH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCO1</td>
<td>CSF1R</td>
<td>FGFR3</td>
<td>JAK2</td>
<td>NOTCH2</td>
<td>PTEN</td>
<td>SRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIRC3</td>
<td>CSF3R</td>
<td>FGFR4</td>
<td>JAK3</td>
<td>NPM1</td>
<td>PTPN1</td>
<td>TSC2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td>CTNNB1</td>
<td>FLT1</td>
<td>KDM6A</td>
<td>NRAS</td>
<td>RAC1</td>
<td>STAG2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>DDR2</td>
<td>FLT3</td>
<td>KDR</td>
<td>NSD1</td>
<td>RAD54</td>
<td>STK11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>DNMT3A</td>
<td>FLT4</td>
<td>KIT</td>
<td>NTR1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRI1</td>
<td>EGFR</td>
<td>FUBP1</td>
<td>KMT2A</td>
<td>NTR2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALR</td>
<td>EP300</td>
<td>GATA1</td>
<td>KRAS</td>
<td>NTR3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key:**
- **Pathogenic and previously described in vascular anomalies.**
- **Pathogenic and not previously described in vascular anomalies.**
- **Likely pathogenic**
Somatic cutaneous vascular syndromes
Cancer (COSMIC): Identical AA change
Cancer (COSMIC): Other missense change at codon
Conclusion

- Most vascular anomalies harbor post-zygotic variants
- Most are gain of function variants in highly conserved oncogenes that impact cell growth and survival
- Improved understanding may lead to a pragmatic genetic-based therapeutic focus
- Continued interrogation of oncogenes in benign developmental disorders could provide insight into fundamental mechanisms regulating cell growth, differentiation and the development of cancer