SNP array karyotyping for clinical cancer applications

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Disclosures

Jill Hagenkord is a co-founder and on the board of directors of iKaryos Diagnostics, Inc.

Jill Hagenkord is the Chief Medical Officer at Complete Genomics, Inc.
Overview

• Introduction
  – Array-based karyotyping with cytogenomic arrays
  – Constitutional vs Cancer cytogenomic arrays
  – Advantages of SNP array karyotyping
  – Acquired UPD

• Clinical cases demonstrating impact on patient care
Virtual and Conventional Karyotypes

- **Virtual karyotype, low resolution array**
  - **Copy number arrays**
    - Assess relative DNA copy number and generate virtual karyotypes.
    - Can be done on formalin fixed paraffin embedded (FFPE) tumors.
  - Conventional karyotypes
    - Low resolution and are technically laborious
    - Can see balanced translocations, inversions, and tetraploidy.
    - Requires culture (cannot be performed on FFPE tumors)
History of Array-based Karyotyping

• 2000, Array CGH
  – 2004 Signature Genomics 1st to market for constitutional samples
  – By 2008, >60 CLIA certified labs offer aCGH for constitutional abnormalities
  – aCGH is 1st line testing for many applications*

• 2005-2006, SNP array karyotyping
  – Designed for GWAS and linkage
  – Genome-wide copy number and LOH in one assay at unprecedented resolution.

• 2009, SNP array karyotyping of cancer
  – iKaryos Diagnostics/Creighton Medical Laboratories 1st to market for cancer
  – Founding of Cancer Cytogenomic Microarray Consortium (CCMC)

*ACMG Practice Guidelines, 09/2010
Special considerations for Cancer

• **Array-based karyotyping of constitutional samples**
  - Always fresh sample
  - Genetic lesion present in 100% of cells (mostly)
  - Single copy gains or losses

• **Array-based karyotyping of cancer**
  - Both fresh and FFPE samples
  - Genetic lesion *never* present in 100% of cells = normal clone contamination
  - Copy number: 0, 1, 2, 3, 4, 5, amplification
  - Tetraploidy, Subclones
  - Nomenclature
SNP Array Karyotype (SNP cytogenomic array)

- Obtain hybridization intensity values for each probe set
  - \( \log_2 \) Ratio (T/N)
  - Genome-Wide Copy Number
  - Genotype (AA, AB, or BB)
  - Genome-wide LOH Status

- Reconstruct genome *in silico* → Virtual karyotype
  - Line the SNPs up in chromosomal order
  - Look for consecutive SNPs with same change
Allele-Specific Analysis

Lung cancer (100K)

Copy neutral LOH
Copy loss LOH
Copy gain LOH
Normal diploid
CN = 4

Homozygous deletion

www.Affymetrix.com
Acquired UPD

• Acquired uniparental disomy (aUPD)
  – Copy neutral LOH
  – Segmental UPD

• Reported to constitute 50-80% of the LOH in human tumors (Tuna 2009, Beroukhim 2006, Ishikawa 2005)

• Biological implications of aUPD in cancer
  – Can be 2\textsuperscript{nd} hit of a TSG (similar to a deletion)
  – Duplication of activating somatic mutation
  – Duplication or deletion of methylation pattern
Deletion-associated LOH as the 2\textsuperscript{nd} Hit

Knudson Two Hit Hypothesis of Tumorigenesis

- **First Hit**: Usually a point mutation or small deletion
- **Second Hit**: Often a large-scale event

**Het**
- CN = 2

**LOH**
- CN = 1

No functional TSG
Cancer initiation or progression
Copy neutral LOH in tumorigenesis

Acquired UPD of p53 in CLL

Sequence analysis of key exons in TP53 revealed a homozygous c.14070G>A (R248Q) mutation, which is one of the most common somatic mutations in TP53.

Loss of p53 in chronic lymphocytic leukemia (CLL) is a bad prognostic indicator and directly impacts patient management.

This copy neutral LOH was missed by conventional cytogenetics and FISH, and it would have been missed by arrayCGH.

SNP array karyotyping readily detects copy neutral LOH.

Acquired UPD of 17p (including TP53 locus) in CLL sample. Peripheral blood, 250K Nsp array.
Clinically relevant UPD overlying confirmed bi-allelic mutations

Hematologic malignancies only. Similar review of solid tumor literature has not been published.

Yin, et al Mol Cancer Res 2009 May;7(5)

Glioblastoma on SNP Arrays:
- Of patients with 17p abnormality, ~50% were deletions and ~50% were aUPD
- Both 17p del and 17p UPD were associated with worse outcome.
- 9/13 had homozygous TP53 mutations underlying the 17p UPD.

Table III. Biallelic mutations coinciding with segmental UPD.

<table>
<thead>
<tr>
<th>Area of UPD</th>
<th>Gene</th>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPD9q</td>
<td>JAK2</td>
<td>MPD</td>
<td>Kralovics et al (2002, 2005)</td>
</tr>
<tr>
<td>UPD13q</td>
<td>FLT3-ITD</td>
<td>AML</td>
<td>Raghavan et al (2005)</td>
</tr>
<tr>
<td>UPD17q</td>
<td>NF1</td>
<td>JMML</td>
<td>Flotho et al (2008)</td>
</tr>
<tr>
<td>UPD21q</td>
<td>RUNX1</td>
<td>AML</td>
<td>Raghavan et al (2005)</td>
</tr>
<tr>
<td>UPD19q</td>
<td>CEBPA</td>
<td>AML</td>
<td>Fitzgibbon et al (2005); Raghavan et al (2005)</td>
</tr>
<tr>
<td>UPD4q</td>
<td>KIT</td>
<td>AML</td>
<td>Unpublished observations</td>
</tr>
<tr>
<td>UPD1p</td>
<td>MPL</td>
<td>MDS/MPD, MPD</td>
<td>Szpurka et al (2009)</td>
</tr>
<tr>
<td>UPD11p</td>
<td>WT1</td>
<td>AML</td>
<td>Raghavan et al (2005)</td>
</tr>
<tr>
<td>UPD11q</td>
<td>CBL</td>
<td>CMML, sAML</td>
<td>Dunbar et al (2008)</td>
</tr>
</tbody>
</table>

MPD, myeloproliferative disease; (s)AML, (secondary) acute myeloid leukaemia; JMML, juvenile myelomonocytic leukaemia; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukaemia.

Probe coverage comparison

• FISH: 1 probe/arm (1p)

• Microsatellite LOH: 3-5 probes/arm (1p)

• SNP array karyotyping (Affymetrix arrays)
  – 10K 2.0 array: 400 probes/arm (1p)
  – 250K array: 10,000 probes/arm (1p)
  – 2.7M array: 115,000 probes/arm (1p)
Benefits of Higher Probe Coverage

- Depending on where your targeted probes hybridize, you may get different results.
- Also explains why FISH and microsatellite LOH results are sometimes discordant.

Copy loss LOH, CN = 1
Homozygous deletion, CN = 2

Copy neutral LOH, CN = 2

Red dots: log2ratios for each probe
- Het calls in tumor
- Discordant call btw tumor and normal
Advantages of SNP array karyotyping

• “Genome-wide” copy number and LOH status in one assay.

• Per chromosomal arm resolution is increased by several thousand fold (250K array) compared to FISH or microsatellite LOH.

• 250K array provides 100-fold greater resolution than conventional cytogenetics, does not require culture, can be performed on FFPE tumor samples, and the software interfaces with genome databases.

• Detects abnormalities missed by other techniques
  • Acquired uniparental disomy (UPD), aka copy neutral LOH
  • “Atypical” deletions missed by FISH
  • Genomic complexity
# Summary of Strengths and Limitations

<table>
<thead>
<tr>
<th></th>
<th>Cytogenetics</th>
<th>FISH</th>
<th>arrayCGH</th>
<th>SNP array karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Use</strong></td>
<td>1970s</td>
<td>1990s</td>
<td>2005</td>
<td>2009</td>
</tr>
<tr>
<td><strong>Genome wide</strong></td>
<td>Yes</td>
<td>No</td>
<td>Some</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Resolution</strong></td>
<td>Low</td>
<td>High</td>
<td>Variable</td>
<td>High</td>
</tr>
<tr>
<td><strong>FFPE samples</strong></td>
<td>No</td>
<td>Some</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Subjectivity</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Less</td>
<td>Less</td>
</tr>
<tr>
<td><strong>Balanced translocations</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Copy neutral LOH</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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CASE EXAMPLES

- CLL
- MDS
- Glial tumors
- Malignant rhabdoid tumor
- Renal tumors
- Her2 “double equivocal” breast cancer
## Genomic Status in CLL

### Cytogenetic Aberrations in CLL

<table>
<thead>
<tr>
<th>Cytogenetic aberration</th>
<th>Gene involved</th>
<th>% cases</th>
<th>Prognosis (median survival)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del(13)(q14)</td>
<td>Unknown</td>
<td>55 – 64%</td>
<td>Good (133 months)</td>
</tr>
<tr>
<td>Trisomy 12</td>
<td>Unknown</td>
<td>16 – 25%</td>
<td>Intermediate (114 months)</td>
</tr>
<tr>
<td>Del(6)(q21-q23)</td>
<td>Unknown</td>
<td>0 – 6%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Del(11)(q22.3-q23.1)</td>
<td><em>ATM</em></td>
<td>15 – 18%</td>
<td>Poor (79 months)</td>
</tr>
<tr>
<td>Del(17)(p13)</td>
<td><em>TP53</em></td>
<td>7 – 8%</td>
<td>Poor (32 months)</td>
</tr>
</tbody>
</table>

CLL and Genomic Complexity

- FISH panel: Normal
- Cytogenetics: No growth in culture

Genomic complexity is an adverse prognostic factor in CLL (Stilgenbauer, 2007).
- 21% of CLL cases had genomic lesions beyond what is tested for by a FISH panel (Gunn, et al and Hagenkord, et al).
- Suggests that genomic complexity is the 2nd most common cytogenetic marker in CLL.
Acquired UPD in MDS

Yes, it’s clonal. And it has IPSS poor prognosis

Good Prognosis: normal karyotype, isolated del(5q), isolated del(20q), -Y
Poor Prognosis: complex abnormalities (ie, >=3 abnormalities), -7 or del(7q)
Intermediate Prognosis: all other abnormalities, including trisomy 8 and del(11q)

Prognostic impact of SNP array karyotyping in myelodysplastic syndromes and related myeloid malignancies.

Refined Grading of Astrocytomias

**CC:** 49 year old male with severe headaches x 3 months.
**MRI:** 3.8cm right frontal infiltrative, non-enhancing, subcortical mass with a focus with contrast enhancement.
**Brain biopsy:** Low grade astrocytoma (WHO grade II)
**Conventional cytogenetics:** Normal diploid
**Rx:** Radiation only.
• Concomitant gain of chromosome 7 with loss of chromosome 10 is essentially pathognomonic for glioblastoma (WHO grade 4).*

• SNP array karyotype results would have justified use of Temozolamide 13 months earlier.

• Disease recurred 5 months after initial diagnosis. 13 months after diagnosis there was clear radiologic evidence of GBM.

Refinement of Diagnosis

75 year old male with a brain mass. Based on morphology, what is your diagnosis?
Now what is your diagnosis?

Diagnosis: Small cell glioblastoma
Refined Diagnosis in Rhabdoid Tumors

Female child with bilateral renal tumors with lung mets suspicious for malignant rhabdoid tumor.
Virtually all malignant rhabdoid tumors are associated with abnormalities of INI1 on 22q. Cytogenetics and INI1 (SMARCB1; 22q11.2) FISH studies were negative for an abnormality. Suspicion remained high that this was a malignant rhabdoid tumor.
Genomic Analysis Using High-Density Single Nucleotide Polymorphism-Based Oligonucleotide Arrays and Multiplex Ligation-Dependent Probe Amplification Provides a Comprehensive Analysis of INI1/SMARCBI in Malignant Rhabdoid Tumors

Eric M. Jackson,1 Angela J. Sievert,2,3 Xiaowu Gai,5 Hakon Hakonarson,2,4 Alexander R. Judkins,6 Laura Tooke,4 Juan Carlos Perin,5 Hongbo Xie,5 Tamim H. Shaikh,2,4 and Jaclyn A. Biegel2,4

~50/50 deletion to aUPD of 22q

From Jackson, et al. 2009
aUPD of 22q confirms diagnosis of MRT
Renal Tumors: Diagnosis

-3p
Clear cell RCC

+7/+17
Papillary RCC

Multiple monosomies
Chromophobe RCC

Normal/-1
Benign Oncocytoma

# Morphologically Challenging RCC’s

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Expert Panel Diagnosis</th>
<th>Microscopic Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRCC28</td>
<td>No Majority Opinion</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microscopic Description</th>
<th>Individual Opinions</th>
</tr>
</thead>
</table>
| Homogeneous tumor arranged in compact anastomosing micro-papillae with areas with glomeruloid architecture and scattered foamy histiocytes. The tumor cells are small, and monotonous. | - Unclassified RCC  
- Papillary RCC  
- Bipapillary RCC  
- Clear Cell (CRCC): -3p  
- Papillary (PRCC): +7/+17  
- Chromophobe (CHRCC): multiple monosomies  
- Oncocytoma: normal or -1/parital -1 |

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<tr>
<th>Virtual Karyotype</th>
<th>Molecular Diagnosis</th>
</tr>
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<tr>
<td>+7, +16, +17</td>
<td>Papillary RCC</td>
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"Double Equivocal" Breast Cancers

**Diagnosis:**

RIGHT BREAST, HER2/neu DNA TESTING by FISH

HER2/neu is EQUIVOCAL by FISH, see comment.

*(Interpretation performed by Dr. Hagenkord)*

**COMMENT:**

There is amplification of the centromere enumeration probe for chromosome 17 (CEP17) in this case which confounds interpretation of the Her2/CEP17 ratio. On average, tumor cells had 5.7 Her2 signals per nucleus. CAP/ASCO guidelines require a FISH result of ≥6 Her2 copies per nucleus to be considered amplified. Approximately 50% of the tumor nuclei had 6 or more Her2 signals. Precise enumeration of Her2 signals was confounded by the amplified CEP17 signal.

**Evaluation:**

1. Average CEP17 number: 7.7 per cell.
2. Average HER2 number: 5.7 per cell.
3. HER2/CEP ratio: 0.7
RESULTS:
Array-based comparative genomic hybridization (array CGH) analysis of chromosome 17 resolved HER2 gene status in [20/20] (100%) of cases and revealed additional chromosome 17 copy number changes in [18/20] (90%) of cases. Array CGH analysis also revealed two false positives and one false negative by FISH due to "ratio skewing" caused by chromosomal gains and losses in the centromeric region. All cases with complex rearrangements of chromosome 17 showed genome-wide chromosomal instability.
## Summary of Cases

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<thead>
<tr>
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<th>SNP array karyotype impact</th>
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<td>Detected genomic complexity missed by targeted FISH panel</td>
</tr>
<tr>
<td>MDS</td>
<td>Detected aUPD of 7q → confirmed clonality and detected important genomic changes that other methods would miss.</td>
</tr>
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<td>Glial Tumors</td>
<td>Refinement of morphologic diagnosis and grade.</td>
</tr>
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<td>Breast cancer</td>
<td>Resolution of Her2 “double equivocal” cases.</td>
</tr>
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Virtual Karyotype

Virtual Karyotype (also Array comparative genomic hybridization, CMA, Chromosomal Microarray Analysis, Microarray-based comparative genomic hybridization, array CGH, a-CGH, aCGH, or molecular karyotyping. If using SNP-based arrays, also SNP array karyotyping, molecular allelomapping or SOMA) detects genomic copy number variations at a higher resolution level than conventional karyotyping or chromosome-based comparative genomic hybridization (CGH).[1]

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2 Virtual karyotype
   2.1 What is a virtual karyotype?
   2.2 How to get a virtual karyotype
   2.3 Different platforms for virtual karyotyping
3 Applications
   3.1 Detecting copy number changes
   3.2 Loss of Heterozygosity (LOH), Autozygous Segments, and Uniparental Disomy
4 Examples of clinical cancer applications
   4.1 Neuroblastoma
   4.2 Wilms' Tumor
   4.3 Renal cell carcinoma
   4.4 Chronic lymphocytic leukemia
   4.5 Multiple Myeloma
   4.6 Medulloblastoma
   4.7 Oligodendrogloma
   4.8 Glioblastoma
   4.9 Acute lymphoblastic leukemia
   4.10 Myelodysplastic syndrome
   4.11 Myeloproliferative Neoplasms/Myeloproliferative Disorders
   4.12 Colorectal cancer
   4.13 Malignant Rhabdoid Tumors
   4.14 Uveal Melanoma
References


References

Thanks to

• **Creighton University**
  – Shera Kash, PhD, Laboratory Director (Co-founder, iKaryos)
  – Roger Brumback, MD, Chairman, Dept of Pathology

• **Scientific Advisory Board, iKaryos Diagnostics**
  – Federico Monzon, MD, The Methodist Hospital, TX (Co-founder, iKaryos)
  – Jeffrey Kant, MD, PhD, University of Pittsburgh
  – Julia Bridge, MD, University of Nebraska
  – Zoran Gatalica, MD, Caris Life Science, Inc.

  – Robert Klein, PhD, Co-founder and CEO of iKaryos

• **Consultants**
  – Michael Becich, MD, PhD University of Pittsburgh (Informatics)
  – Craig Horbinski, MD, PhD University of Kentucky (Neuropathology)
Genomic Profiling of Neuroblastomas

Two Genetic Classes of NBs:
1. whole chromosome gains/losses have good prognosis.
2. segmental gains/losses have poor prognosis.

*Segmental genomic alterations, with or without MYCN amplification, are the strongest predictor of relapse in neuroblastomas.*

MNA and 11q del groups are (essentially) mutually exclusive.
MNA and 11q del are both independent adverse prognostic factors.


**Neuroblastoma**

**Summary:** High-risk neuroblastoma with segmental aberrations and deletion of 11q.
4 more neuroblastomas
Colorectal Carcinoma
Responsiveness to 5-FU and more


Case X: Colorectal Carcinoma

Summary: Chromosomal instability (CIN) pathway colorectal carcinoma with 18q LOH. Amplification of EGFR is not detected. Activating point mutations of KRAS or BRAF are not detected.
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<tr>
<td>Neuroblastoma</td>
<td>Detected segmental changes --strongest genetic indicator of recurrence</td>
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<td>Colorectal Carcinoma</td>
<td>MSS– responsiveness to 5FU 18q LOH– adverse prognostic factor EGFR amplification (EGFR pathway somatic mutations)</td>
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<td>Breast Cancer</td>
<td>Resolved Her2 status in case that was indeterminate by IHC and FISH.</td>
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*ACMG Practice Guidelines, 09/2010

Shelly R. Gunn, *The Vanguard Has Arrived in the Clinical Laboratory: Array-Based Karyotyping for Prognostic Markers in Chronic Lymphocytic Leukemia* J Mol Diagn 2010 12: 144-146
25 year old male with history of mixed germ cell tumor 3 years ago (2007)
- Features of embryonal carcinoma, immature teratoma, and choriocarcinoma
- 2.5cm, pT3pNXMX

Now with atrial mass
- Myxoid and hypocellular with areas concerning for metastasis
- IHC positive for AE1/AE3
- IHC negative for CD30, PLAP, CD31, CD34, S-100, calretinin
Myxoma vs GCT

RESULT
Tumor, atrium, SNP oligonucleotide microarray karyotype (___, block A2):
Gain of 12p relative to 12q consistent with isochromosome 12p.
Complex karyotype with additional chromosomal changes, see comment.

A 2
CN = 3  CN = 4  CN = 2  CN = 4

B
1+1 = 2

C
1+2 = 3  0+4 = 4  1+3 = 4

D

E

6p:4q
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<tr>
<td>Myxoma vs. Germ Cell Tumor</td>
<td>Detected isochromosome 12p-- supports diagnosis of GCT.</td>
</tr>
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<td>MSS– responsiveness to 5FU 18q LOH– adverse prognostic factor EGFR amplification (EGFR pathway somatic mutations)</td>
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*SNP array karyotyping does not require culture and overcomes the problem of stromal cell overgrowth.*
Robust, Reproducible (CLL, 24%, enriched)

250K Nsp

2.7M

200KB gains & losses plus 3MB LCSH