Tumor Syndromes Predisposing to Osteosarcoma

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Dr. Meera Hameed declares she has no conflict(s) of interest to disclose.

Osteosarcoma

- Most cases are sporadic
- Very small percentage occur in association with Cancer Predisposition Syndromes
  - Li-Fraumeni Syndrome
  - Hereditary Retinoblastoma
  - Rothmund-Thomson Syndrome (RTS Type 2)
  - Werner Syndrome
  - Bloom Syndrome
  - RAPADILINO Syndrome
  - Diamond Blackfan Anemia

19 year old male water polo athlete presented with shooting pain of right leg

- Metastases to spine, right ischium and lungs
- Aik Phos: >8355; LDH: 512

Osteosarcoma

IMPACT: Integrated Mutation Profiling of Actionable Cancer Targets

Adapted from Wagle, Berger et al., Cancer Discovery, 2:82-93, 2012

Sample DNA prep
Bar coded Lib prep
Pooled lib & capture
Sequence to 500-1000X (HiSeq 2500)
Align to genome and analyze

Somatic Mutations (Tumor-Normal Pairs):
Base Substitutions
Small Indels
Copy Number Alterations
Select Rearrangements

Hybridize and select (NimbleGen SeqCap)
Probes for 410 genes

Prepare 24-48 libraries
### Tumor-Normal sequencing

<table>
<thead>
<tr>
<th>Somatic variant</th>
<th>Germline variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>Tumor</td>
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<tr>
<td>Normal</td>
<td>Normal</td>
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### Copy Number Alterations

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<td>Amp</td>
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<tr>
<td>MDM2 (12q15)</td>
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<tr>
<td>CDKN2A (9p21.1)</td>
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<td>EGFR (9p21.1)</td>
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<td>STOR (1p36.22)</td>
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<td>SPEN (1p36.13)</td>
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<td>PTEN (17p13.3)</td>
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### MSK IMPACT Results

- ATRX exon 15 c.4540C>T (p.R1514*)


### SNP array- Copy Neutral LOH (17p13)

- Patient's father with history of melanoma developed left groin mass
  - Leiomyosarcoma

- SNP array- Copy Neutral LOH (17p13)
# Li-Fraumeni Syndrome

(Tumor spectrum-SBLA)

**Classic Criteria**
- Proband with sarcoma before 45
- 1st degree relative with sarcoma before 45
- 1st or 2nd degree relative with any cancer before 45 or sarcoma before 60

**Chompret Criteria (2009)**
- Proband with LFS tumors before 46 and one or two 1st degree relatives with LFS tumors before 56 or with multiple tumors
- Proband with multiple tumors of LFS spectrum and first one occurring before 46 years or Patients with adrenocortical ca or choroid plexus tumors

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## Germline MSK-IMPACT - Secondary germline Testing

- Tumor and Normal Pairs
- Option for germline analysis for 76 hereditary cancer predisposition genes
- Variants —reviewed and classified
- Likely pathogenic and pathogenic variants are sent to clinical report.

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## Secondary Germline IMPACT

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<th>Tier 2</th>
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# Li-Fraumeni Syndrome

- Germline mutations in TP53
- Autosomal Dominant
- Sarcomas, Breast Carcinoma, Brain tumors
- Leukemia, Lung Cancer and Adrenocortical Carcinoma (SBLA)
- Classic Criteria and Chompret Criteria (2009)
- Genetic anticipation
TTP53 mutations in Li-Fraumeni Syndrome

Transactivation

DNA binding

TD
RD

Proline Rich

Distributions of mutations

175
245
248
249
273
282
306

DBD

Codon 273- Rhabdomyosarcoma
Codon 245, 282- Osteosarcoma
Outside DBD

Leiomyosarcoma


DBD

Codon 273- Rhabdomyosarcoma
Codon 245, 282- Osteosarcoma
Outside DBD

Leiomyosarcoma

Retinoblastoma

Bilateral Leukocoria

Adapted from: Chapter 21, Retinoblastoma and Simulating Lesions Ralph C. Eagle JR

Hereditary Retinoblastoma

WT/mut

WT

WT/WT

Zygote

WT/mut

Second Mutation

Mitotic recombination

Retinoblastoma Germline Mutation Spectrum

Washington Post July 12, 2016
Alfred G. Knudson Jr., geneticist who decoded a mystery of cancer, dies at 93

“The Two-Hit Hypothesis”

Interviewed for the book “The Emperor of All Maladies: A Biography of Cancer” by Siddhartha Mukherjee. Dr. Knudson reflected on the knowledge of the disease that he divined. It was, he said, like inferring “the wind from the movement of the trees.”


Second Cancers among Retinoblastoma Survivors

- Osteosarcoma
- Soft Tissue Sarcoma
- Melanoma
- Lung Cancer
- Lymphoma
- Bladder Cancer
- Uterine Cancer
- Breast Cancer
- Brain Tumors
- Cancers of Mouth or Nose

14 year old male with bilateral retinoblastoma at 23 months of age s/p chemoradiation and enucleation, developed metastases to right distal femur at 4 years of age

Therapy: Radiation

10 years later patient presented with right leg pain

Chondroblastic Osteosarcoma

Bone Sarcoma in Retinoblastoma Survivors

- Standardized incidence and mortality of bone sarcoma- several hundred fold higher
- Cumulative incidence is 7% over 20 years
- Non-irradiated tumors- lower risk
- Osteosarcoma is the most common

Kleinerman et al. Clinical Sarcoma Research 2:15, 2012

Retinoblastoma

- "Two-hit" Hypothesis by Dr. Alfred Knudson
- Bialleic mutation of RB1
- Autosomal Dominant
- Increased risk of subsequent malignancies
- Post Radiation Osteosarcoma
- Mutations distributed throughout the gene

Rothman-Thomson Syndrome

- Poikiloderma
- Alopecia
- Aplasia of thumb
- Valgus deformity
- Short stature
- Frontal bossing
- Skeletal abnormalities

Helicase family gene mutations identified in 1999

Adapted from
Lerice et al. Rothman-Thomson Syndrome
Helicases

- Enzymes which unwind double-helix of DNA
- Preparation for cell division
- Repair of damaged DNA
- RecQ helicases- Cancer Predisposition

Rothmund-Thomson Syndrome

- RecQ Helicase associated Autosomal Recessive Disorder
- RTS Type I and RTS Type II
- RecQL4 helicase mutation predisposes to Osteosarcoma (RTS Type II)
- Range of mutations (nonsense, frame-shift, intronic deletions)
- RecQL4 mutations are not seen or only very rarely seen in sporadic osteosarcoma

RecQ Helicases: Werner Syndrome

- Autosomal Recessive WRN gene
- Premature aging
- Short Stature
- Scleroderma-like Skin Changes
- Cataracts

Werner Syndrome

- WRN gene

Rothmund-Thomson Syndrome

- RecQL4

- Truncating Mutations
- Frame shift
- Nonsense
- Splicing
- Intronic deletions

- Massense mutations

**RecQ Helicases: Bloom Syndrome**

- Autosomal Recessive
- Sensitive to sun
- Rashes
- Sparse subcutaneous fat
- Carcinomas, lymphomas and leukemias
- Osteosarcoma rate higher than general population

**Other Syndromes**

**RAPADILINO Syndrome**
- RecQ4 mutations
- RA: Radial Dysplasia
- PA: Patella aplasia or hypoplasia
- DI: Diarrhea and dislocated joints
- LI: Little size and limb malformations
- NO: Long slender nose and normal intelligence

**Diamond-Blackfan Anemia**
- Ribosomal S19 mutations
- Pure red cell aplasia
- Congenital abnormalities (craniofacial, thumb, heart, renal)
- Predisposition to cancer
- 6 Osteosarcoma cases reported

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**Osteosarcoma**

**Predisposition**
- TP53 - LFS
- RB1 - Retinoblastoma
- RecQL4 - RTS Type II
- RecQ Helicase WRN - Werner
- RecQ - BLM - Bloom Syndrome
- Pathology: Conventional OS
- Sites: Multicentric, unusual sites
- Radiation association in RB1-200-400 fold increase

**Sporadic**
- TP53 -30-95%
- RB1 -30%
- RecQL4 - not reported
- RecQ WRN - not reported
- RecQ BLM - not reported
- Pathology: same
- Sites: Metaphyses of long bones, pelvis
- Radiation association: less common

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**Summary**

- Osteosarcoma can be the presenting diagnosis of LFS, RTS, WS and BLM
- Potential value for broad germline sequencing approach in tumor-normal analysis
- Early detection: Better surveillance for subsequent cancers and at-risk family members
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Thank you

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