Stephen J. Chanock, M.D.
Director, Division of Cancer Epidemiology and Genetics

The Complexity of Cancer Susceptibility & Cancer Genomics

Radiation Epidemiology & Dosimetry Course

National Cancer Institute www.dceg.cancer.gov/RadEpiCourse
Etiology of Cancer

Environment

Genetic Susceptibility

Lifestyle

Mutations
SNPs
STR’s
Chromosomes
(Epigenetics)

100% “Triggers”

“Chance”

100% “Set Point”
Cancer Genomics: 4 Spaces

Germline
- >115 Cancer Syndromes
- >25 Moderate Penetrant
- >475 GWAS Loci

Somatic
- ‘Drivers’
- ‘Passengers’
- TCGA/ICGC-Cosmic Data
- Heterogeneity
- Metastases

Discovery

Clinically Actionable
- BRCA1/2
- Lynch Syndrome
- ACMG “Actionable”
- Targeted Therapy
  - HER2
  - EGFR
  - BRAF600
Why Study Germline Susceptibility?

Explain heritability of cancers
  • Clustering - families and distinct populations
  • Sporadic cancer

Risk assessment
  • Individual
  • Population-based

Insights into the etiology of cancer
  • Gene-environment interactions
  • How the germline informs somatic alterations

Pharmacogenomics
  • Response
  • Toxicity profiles
Architecture of Genetic Susceptibility of Cancer
Defining ‘Distinct’ Spaces

After Manolio et al. 2009
>115 Genes Mutated in Cancer Susceptibility Syndromes

Ascertained in Families
Rare Mutation with Strong Effect
Oncogenes & Tumor Suppressors

Incomplete “Penetrance”
Not all affected develop cancer
Modifiers - genetic & environmental
Of the 115

• Roughly 1/3 are recognized by ACMG and trigger recommendations for counseling

• Types of Mutations
  • Indels/Stop Codons, NS & Structural

• Many fit the model of ‘Autosomal Dominant’

• Ascertainment Biased by Family Studies
  • Linkage followed by targeted Sequencing

• >50% are COSMIC ‘drivers’ in somatic databases
Virtually none are associated with outcomes.
Architecture of Genetic Susceptibility of Cancer
Defining Distinct Spaces

- **Rare** alleles causing Mendelian disease
- **Low-frequency** variants with intermediate effect
- **Common** variants implicated in common disease by GWA

Effect size
- High
- Intermediate
- Modest
- Low

Allele frequency
- Very rare
- Rare
- Low frequency
- Common

Damaging Drivers
Perturbation
Key pathways
9q22.33 (FOXE1)

- **FOXE1**- thyroid-specific transcription factor with pivotal roles in thyroid morphogenesis
- increased risk of papillary and follicular thyroid cancer
- associated in radiation exposed (Chernobyl) and unexposed thyroid cancer cases
14q13.3 (NKX2-1)

- NKX2-1- also thyroid-specific transcription factor with pivotal roles in thyroid morphogenesis
- altered NKX2-1 expression levels in thyroid tumors
- signal in both papillary and follicular, but not replicated in radiation exposed thyroid cases
9q22.33 and 14q13.3 Risk Alleles Result in Reduced TSH Levels

<table>
<thead>
<tr>
<th>Type of measurement</th>
<th>Individuals (n)</th>
<th>Effect per risk allele (95% CI)</th>
<th>P value</th>
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<tr>
<td><strong>Results for rs965513[A] on 9q22.33</strong></td>
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<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>12,035</td>
<td>−5.9% (−7.4%, −4.4%)</td>
<td>2.9 × 10^{−14}</td>
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<td>Free thyroxine (T4)</td>
<td>7,108</td>
<td>−1.2% (−1.8%, −0.6%)</td>
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<td>Free triiodothyronine (T3)</td>
<td>3,593</td>
<td>+1.2% (+0.4%, +2.0%)</td>
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<td><strong>Results for rs944289[T] on 14q13.3</strong></td>
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<tr>
<td>Thyroid stimulating hormone (TSH)</td>
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<td>Free thyroxine (T4)</td>
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<td>+0.5% (−0.1%, +1.0%)</td>
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<td>Free triiodothyronine (T3)</td>
<td>3,564</td>
<td>−0.3% (−1.1%, +0.5%)</td>
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Common SNP Variants
Influence Risk For

Interactions with Known Carcinogens
Radiation-induced Injury
Therapeutic Effects
**Gene-Environment Interaction for Bladder Cancer Risk: NAT2 Slow Acetylation Increases Risk only for Smokers**

Rothman et al., *Nat Genet* 2010

### P-interaction = $2.8 \times 10^{-4}$

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<tr>
<th>Study</th>
<th>Cases</th>
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<td>TBCS</td>
<td>25</td>
<td>117</td>
<td>0.80 (0.33, 1.90)</td>
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<td>NHSMPFS</td>
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<td>57</td>
<td>1.33 (0.63, 2.81)</td>
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<td>NCBCS</td>
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<tr>
<td>LWBCS</td>
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<tr>
<td>CerRePP</td>
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<td>76</td>
<td>0.55 (0.29, 1.20)</td>
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<tr>
<td>NEHH</td>
<td>57</td>
<td>136</td>
<td>0.91 (0.48, 1.70)</td>
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<td>EEBCS</td>
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<td>275</td>
<td>0.93 (0.50, 1.74)</td>
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<tr>
<td>LABCS</td>
<td>97</td>
<td>211</td>
<td>1.06 (0.64, 1.73)</td>
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<td>348</td>
<td>1.06 (0.65, 1.75)</td>
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<tr>
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<td>SBCS</td>
<td>152</td>
<td>303</td>
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<tr>
<td>CPSB</td>
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<td>PLCO</td>
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<td>489</td>
<td>1.06 (0.74, 1.52)</td>
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<tr>
<td>EPIC</td>
<td>176</td>
<td>359</td>
<td>0.78 (0.54, 1.13)</td>
</tr>
<tr>
<td>TXBCS1</td>
<td>255</td>
<td>407</td>
<td>1.16 (0.86, 1.53)</td>
</tr>
<tr>
<td>TXBCS2</td>
<td>207</td>
<td>464</td>
<td>0.85 (0.61, 1.19)</td>
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</table>

### Never Smokers

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<td>LWBCS</td>
<td>167</td>
<td>107</td>
<td>1.38 (0.84, 2.26)</td>
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<tr>
<td>NHSMPFS</td>
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<td>1.01 (0.60, 1.72)</td>
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<tr>
<td>NCBCS</td>
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<td>122</td>
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<td>NENH</td>
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<td>TBCS</td>
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<td>CPSE</td>
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<td>379</td>
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<tr>
<td>NBCCS</td>
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<td>1337</td>
<td>1.16 (0.99, 1.36)</td>
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</table>
Cumulative 30-year Absolute Risk for Bladder Cancer in a 50 Year Old Male in the U.S., Overall and by Quartiles (based on smoking + 12 SNPs)
RD = risk differences for current vs. never smokers

Garcia-Closas et al, *Cancer Research* 2013
Thought Experiment:

If 100,000 smokers with high genetic risk stopped smoking
  Eliminate  5,400 cases of bladder cancer
If 100,000 smokers with low genetic risk stopped smoking
  Eliminate  1,500 cases of bladder cancer

Possible example of how genetic & environmental risk stratification might translate into targeted prevention
  “Precision Prevention”
Brief Communications

Variants at 6q21 implicate PRDM1 in the etiology of therapy-induced second malignancies after Hodgkin's lymphoma

Timothy Best1, Dalin Li2, Andrew D Skol3, Thomas Kirchhoff4, Sarah A Jackson4, Yutaka Yasui5, Smita Bhatia5, Louise C Strong5, Susan M Dmochowski5, Katherine L Nathanson5, Oluwemilohun I Olopade6, R Stephanie Huang3, Thomas M Mack3,7, David V Couto1, Kenneth Offit8, Wendy Cancer9, Leslie L Robinson9 & Ken Onel10,11

Survivors of pediatric Hodgkin's lymphoma are at risk for radiation therapy-induced second malignant neoplasms (SMNs). We identified two variants at chromosome 6q21 associated with SMNs in survivors of Hodgkin's lymphoma treated with radiation therapy as children but not as adults. The variants comprise a risk locus associated with decreased basal expression of PRDM1 (encoding PR domain containing 1) with ZNF domain and impaired binding of the PRDM1 protein after radiation exposure. These data suggest a new gene-exposure interaction that may implicate PRDM1 in the etiology of radiation therapy-induced SMNs.

Patients treated successfully for Hodgkin's lymphoma in childhood develop SMNs with a cumulative incidence of 14.5% by 30 years after treatment and an absolute excess risk of 6.9 per 1,000 person-years of follow-up. This high prevalence makes SMNs the second leading cause of mortality in Hodgkin's lymphoma survivors. SMNs primarily affect organs in the involved mediastinal radiation field, including the thyroid, skin, gastrointestinal tract and female breast. Risk is positively associated with cumulative radiation dose and inversely correlated with age at treatment.

Despite the clinical importance of this devastating late consequence of radiation therapy exposure, little is known about predispersing risk factors. We performed a genome-wide association study (GWAS) to identify variants associated with radiation therapy-induced SMNs in Hodgkin's lymphoma survivors. In studies of sporadic cancers, non-metastatic lethargy can obscure genetic associations, but here radiation therapy exposure is common to patients with Hodgkin's lymphoma who did and did not develop SMNs. Thus, we hypothesized

that limiting our study to radiation therapy–treated survivors would improve our power to detect the genetic contribution to SMN risk.

The discovery set consisted of 100 SMN cases and 89 SMN free controls (Supplementary Table 1a and Supplementary Table 2). All cases and controls were diagnosed with Hodgkin's lymphoma as children (median age: 15.6, range: 4–20) and treated with 25–44 Gy radiation therapy with or without alkylating chemotherapy. Cases developed SMNs with a mean latency of 20.9 years (i.e., > 5.4 years, range: 4–34). Controls were followed for at least 27 years (median: 32 years, range: 27–38) to ensure that the maximal contamination of controls by future cases was < 2%. The Supplementary Methods contain a detailed description of the study populations and experimental protocols.

After genotype quality control, we successfully genotyped 465,513 single nucleotide polymorphisms (SNPs) in 96 cases and 82 controls. We compared allele frequencies between cases and controls using a Chi square test of homogeneity. A quantile-quantile plot of the expected and observed distribution of P values revealed no evidence for systematic genotype calling error or hidden population substructure (genomic control λ = 1.007) (Supplementary Fig. 1). Principal component analysis using Eigenstrat indicated cases and controls were of European descent (Supplementary Fig. 2).

We empirically determined the threshold for a genome-wide false positive rate of 0.05 by permutation (P < 1.0 × 10−7). At this threshold, our study had 80% power to detect a SNP with a frequency of 35% and an odds ratio (OR) of 3.5 (Supplementary Fig. 3). Three SNPs (rs6946728, rs1040441, and rs8083353) achieved genomewide significance (Supplementary Fig. 4 and Table 1). rs6946728 and rs1040441 mapped to chromosome 6q21, intergenic between ATG5 (encoding autophagy protein 5) and PRDM1. The strongest evidence for association in this region was for rs6946728 (P = 1.09 × 10−8, ORadj = 4.22 [95% confidence interval (CI): 2.53–7.05]); rs8083353 mapped to 14q21.2, intergenic to TAF4 (encoding transcription initiation factor TFIID subunit 4B) (P = 5.98 × 10−6, ORadj = 3.78 [95% CI: 2.31–6.14]). Logistic regression, adjusting for gender, age at diagnosis, year of Hodgkin's lymphoma diagnosis, general radiation (in female) and alkylating chemotherapy exposure, indicated that these risk variables had no effect on the observed associations (Supplementary Table 3).

We sought to replicate these findings in an independent set of 62 cases with SMNs and 71 SMN free controls, all treated for Hodgkin's lymphoma in childhood with 25–44 Gy mediastinal radiation therapy (Supplementary Table 1b). We observed significant associations with SMNs for both SNPs on chromosome 6q21, rs6946728 (P = 0.002) and rs1040441 (P = 0.03), but not for rs8083353 (P = 0.82) (Table 1). In the
Table 1 Association results for the three stages and the meta-analysis at the \textit{TANC1} locus

<table>
<thead>
<tr>
<th>SNP</th>
<th>Position</th>
<th>Allele</th>
<th>MAF</th>
<th>( R^2 )</th>
<th>( \beta ) (SE)</th>
<th>( P )</th>
<th>MAF</th>
<th>( R^2 )</th>
<th>( \beta ) (SE)</th>
<th>( P )</th>
<th>MAF</th>
<th>( R^2 )</th>
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<th>( P )</th>
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</table>

\( R^2 \): imputation accuracy info metric; \( \beta \): linear regression coefficient; SE: standard error; Q: Cochrane’s Q statistic \( P \) value; \( \hat{I} \): heterogeneity index.

aAccording to GRCh37/hg19. bMinor and risk allele. cG, genotyped. dLinear regression coefficient or effect size from unadjusted analysis (for each SNP, \( \beta \) is calculated from \( \text{STAT}_{\text{late}} = \beta_0 + \beta_1 \times \text{SNP} + E \)). eEffect size resulting from meta-analysis of unadjusted effect sizes for each cohort. frs264663 was not genotyped in the RAPPER cohort and could not be imputed because this SNP was monomorphic in the reference panel. grs264663 did not fulfill quality control criteria (genotyping call rate < 0.95%) in the Gene-PARE cohort. hrs264651 did not fulfill quality control criteria (Hardy-Weinberg equilibrium \( P \) value < 1 \times 10^{-6}) in the Gene-PARE cohort.
Architecture of Genetic Susceptibility of Cancer
Defining ‘Distinct’ Spaces

After Manolio et al 2009
Germline Susceptibility to Osteosarcoma: Most common primary bone tumors

Worldwide age-adjusted Incidence

Li-Fraumeni (TP53)
Rothmund-Thomson Syndrome (RECQL4)
Hereditary Retinoblastoma (RB) - as 2nd cancer
Number of Patients with Germline *TP53* Variants in 765 Unselected Osteosarcoma Cases

Mirabello et al. JNCI 2015
**Frequency of Germline TP53 Variants in 765 Unselected Osteosarcoma Cases**

Consider genetic counseling & TP53-mutation testing in *young* patients with osteosarcoma, Especially if there is history of cancer in close relatives

<table>
<thead>
<tr>
<th>Category</th>
<th>0-9</th>
<th>10-19</th>
<th>20-29</th>
<th>≥30</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFS-associated</td>
<td>3.13%</td>
<td>4.76%</td>
<td>3.84%</td>
<td>1.96%</td>
<td>0</td>
</tr>
<tr>
<td>Rare exonic</td>
<td>4.97%</td>
<td>3.18%</td>
<td>6.14%</td>
<td>5.88%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8.10%</td>
<td>7.94%</td>
<td>9.98%</td>
<td>7.84%</td>
<td>0</td>
</tr>
</tbody>
</table>

*P < 0.001*
Cancer Genomics: 4 Spaces

Germline
- >115 Cancer Syndromes
- >25 Moderate Penetrant
- >475 GWAS Loci

Somatic
- ‘Drivers’
- ‘Passengers’
- Heterogeneity
- Metastases

TCGA/ICGC-Cosmic Data

Discovery

Actionable
- BRCA1/2
- Lynch Syndrome
- ACMG “Actionable”

Clinically
- Targeted Therapy
  - HER2
  - EGFR
  - BRAF600
Pipeline for Comprehensive Characterization: The Cancer Genome Atlas (TCGA) >20 Cancers

- Tissue Sample
- Pathology QC
- DNA & RNA Isolation, QC
- Sequencing
- Expression, CNA & LOH, Epigenetics
- Data Storage at DCC & CGHub
- GDAC
- Integrative Analysis

Comprehensive Characterization of a Cancer Genome

- SNP 6.0 ~45d
- Methylation ~60d
- miRNAseq ~105d
- mRNAseq ~120d
- DNAseq Exome ~180d

3 months – 2 years
~90d

Target: 500 cases for Major Cancers and 50-100 for Rarer Cancers

~12-24 months
Lessons Learned from the Data
The Cancer Genome Atlas (TCGA)

Thyroid = 0.41 non-silent mutations per Mb
Many Cancer Drivers With <20% Prevalence Remain Undiscovered

Lawrence et al, Nature 2014
Simple model of thyroid cancer progression

80-85% TCGA

MAPK pathway (e.g. via BRAF^{V600E})

PTC

MAPK pathway

PI3K–AKT

Follicular thyroid cell

MAPK pathway

PI3K–AKT

FTA

FTC

PDTC

ATC

PI3K–AKT

Loss of differentiation

Nature Reviews | Cancer

Mingzhao Xing, JHU
## Driver Mutations in Thyroid -2013

### Table 2: Gene mutations in thyroid tumours

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Types of thyroid tumours</th>
<th>Approximate prevalence (%)</th>
<th>Primary signalling pathways affected</th>
<th>Functional impact on the protein and tumour</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF</strong></td>
<td>CPTC</td>
<td>45</td>
<td>MAPK</td>
<td>Activating; promoting tumorigenesis, invasion, metastasis, recurrence and mortality</td>
<td>6-12, 16-18</td>
</tr>
<tr>
<td></td>
<td>FVPTC</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TCTC</td>
<td>30–100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>FVPTC</td>
<td>5</td>
<td>MAPK</td>
<td>Activating; probably similar to BRAF&lt;sup&gt;mut&lt;/sup&gt;</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>TCPTC</td>
<td>20–25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTEN (mutation)</td>
<td>FTA</td>
<td>PI3K–AKT</td>
<td>Inactivating the gene but activating the PI3K pathway; promoting tumorigenesis and invasiveness</td>
<td>26,31–33, 212</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>10–15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>10–25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTC</td>
<td>1–2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>FTA</td>
<td>0</td>
<td>PI3K–AKT</td>
<td>Inactivating the gene but activating the PI3K pathway; promoting tumorigenesis and invasiveness</td>
<td>26,31–33, 212</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>10–15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>10–20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTC</td>
<td>1–2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>FTA</td>
<td>0</td>
<td>PI3K–AKT</td>
<td>Inactivating the gene but activating the PI3K pathway; promoting tumorigenesis and invasiveness</td>
<td>26,31–33, 212</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>10–15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>10–20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTC</td>
<td>1–2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PIK3CA</strong></td>
<td>FTA</td>
<td>0–5</td>
<td>PI3K–AKT</td>
<td>Activating; promoting tumorigenesis and invasiveness</td>
<td>25,26, 31–35</td>
</tr>
<tr>
<td></td>
<td>FTC</td>
<td>5–15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>15–25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PTC</td>
<td>1–2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AKT1</strong></td>
<td>Metastatic cancer</td>
<td>15</td>
<td>PI3K–AKT</td>
<td>Unclear; seems to favour metastasis</td>
<td>35</td>
</tr>
<tr>
<td><strong>CTNNB1</strong></td>
<td>PDTC</td>
<td>25</td>
<td>WNT–β-catenin</td>
<td>Activating; promoting tumour progression</td>
<td>37,38</td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>60–80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TPTP</td>
<td>5–25</td>
<td>p53–coupled pathways</td>
<td>Inactivating; promoting tumour progression</td>
<td>59,40</td>
</tr>
<tr>
<td></td>
<td>IDH1</td>
<td>FTC</td>
<td>5–25</td>
<td>IDH1-associated metabolic pathways</td>
<td>41,42</td>
</tr>
<tr>
<td></td>
<td>FVPTC</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATC</td>
<td>10–30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALK</strong></td>
<td>ATC</td>
<td>10</td>
<td>MAPK and PI3K–AKT</td>
<td>Activating; probably promoting tumour progression</td>
<td>43</td>
</tr>
<tr>
<td><strong>EGFR</strong></td>
<td>CPTC</td>
<td>5</td>
<td>MAPK and PI3K–AKT</td>
<td>Activating; impact on tumours is unclear</td>
<td>44</td>
</tr>
<tr>
<td>NDUFA13 (also known as CRM10)</td>
<td>HCTC</td>
<td>15</td>
<td>Component of complex I of the mitochondrial respiratory chain</td>
<td>Presumably inactivating; affecting mitochondrial metabolism and cell death</td>
<td>45</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; ATC, anaplastic thyroid cancer; CPTC, conventional PTC; CTNNB1, β-catenin; EGFR, epidermal growth factor receptor; FTA, follicular thyroid adenoma; FTC, follicular thyroid cancer; FVPTC, follicular-variant PTC; HCTC, Hürthle cell thyroid cancer; IDH1, isocitrate dehydrogenase 1; NDUFA13, NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 1; PDTC, poorly differentiated thyroid cancer; PTC, papillary thyroid cancer; TCPTC, tall-cell PTC.

*The values represent estimated overall prevalence of the indicated mutations.*
Integrated Genomic Characterization of Papillary Thyroid Carcinoma

The Cancer Genome Atlas Research Network1,*

1The Cancer Genome Atlas Program Office, National Cancer Institute at NIH, 31 Center Drive, Bldg. 31, Suite 3A20, Bethesda, MD 20892, USA

*Correspondence: giordano@umich.edu, gadgetz@broadinstitute.org
http://dx.doi.org/10.1016/j.cell.2014.09.050
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SUMMARY

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. Here, we describe the genomic landscape of 496 PTCs. We observed a low frequency of somatic alterations (relative to other carcinomas) and extended the set of known PTC driver alterations to include *EIF1AX*, *PPM1D*, and *CHEK2* and diverse gene fusions. These discoveries reduced the fraction of PTC cases with unknown oncogenic driver from 25% to 3.5%. Combined previous genetic studies report a high frequency (70%) of activating somatic alterations of genes encoding effectors in the mitogen-activated protein kinase (MAPK) signaling pathway, including point mutations of *BRAF* and the *RAS* genes (Cohen et al., 2003; Kimura et al., 2003; Lemoine et al., 1988; Suárez et al., 1988), as well as fusions involving the *RET* (Grieco et al., 1990) and *NTRK1* tyrosine kinases (Pierotti et al., 1995). These mutations are almost always mutually exclusive (Soares et al., 2003), suggesting similar or redundant downstream effects. The various MAPK pathway alterations are strongly associated with distinct clinicopathological characteristics (Adeniran et al., 2006), and gene expression (Giordano et al., 2005) and DNA
TCGA Thyroid- DNA Sequencing

Mutation density increases with age

- \( n=377 \), mean density: 0.401 mut/Mb
- \( \text{density} = a \times \text{(years)} + b \) mut/Mb
- \( a = 0.0072 \ [0.0057 \ 0.0087] \)
- \( b = 0.060 \ [-0.0128 \ 0.133] \)
- Pearson correlation = 0.442, p-value = 1.9e-19
Mutation density associated with high risk of recurrence (after correcting for age)
**New Finding: EIF1AX**
Translation initiation factor 1A, X-linked

THCA:
6 mutations

COSMIC:
19 mutations
Endometrium, breast, colon, lung, esophagus, ovary and prostate

Uveal melanoma
20 mutations

Exome sequencing identifies recurrent somatic mutations in EIF1AX and SF3B1 in uveal melanoma with disomy 3

Marcel Martin, Lars Maßhöfer, Petra Temming, Sven Rahmann, Claudia Metz, Norbert Bornfeld, Johannes van de Nees, Laidger Klein-Hitpass, Alan G Hinnebusch, Bernhard Horsthemke, Dietmar R Lohmann & Michael Zeschchnik

*Nature Genetics* Volume 45 | Number 8 | August 2013
Large Structural Events: Gene Fusions

- New RET partners
- Diverse BRAF fusions
- ALK fusions, diverse
  - (EML4-ALK)
- ETV6-NTRK3

Angela Hadjipanayis, Harvard
Katie Hoadley, UNC
Chip Stewart, Broad Institute
Overview of Somatic Alterations

**Mutation rate**

**Clinical info**

**Significant Mutations**

**Fusions**

**SCNAs**

**Driver summary**
The “Dark Matter” of the Cancer Genome

• Regions of the genome that we cannot easily interpret
• Examples:
  – regulatory regions
  – intergenic regions
  – repeat-rich DNA
  – “non-focal” copy number alterations
TERT Promoter Mutations in Thyroid Cancer

Highly prevalent TERT promoter mutations in aggressive thyroid cancers

Xiaoli Liu, Justin Bishop, Yuan Shan, Sara Patel, Dingxie Liu, Avanijaparam, Kannan Murugan, Huil Sun, Adel El-Naggar, and Mingzhe Xing

Frequent Somatic TERT Promoter Mutations in Thyroid Cancer: Higher Prevalence in Advanced Forms of the Disease

Migo Landa, Ian Ganiy, Timothy A. Chan, Norigato Mitsutake, Michiko Matsue, Tihane Ibrahimimasic, Ronald A. Ghosein, and James A. Fagin

Fig 2. Kaplan-Meier analyses of the impacts of BRAF V600E or TERT C228T alone or their coexistence on disease-free survival of patients with papillary thyroid cancer (PTC). (A) Results of the analyses of patients with PTC of all types. (B) Results of the analyses of conventional variant PTC only. Four groups of patients are indicated in A and B, including patients with neither mutation (gray lines), TERT C228T mutation only (gold lines), BRAF V600E mutation only (blue lines), and coexistence of the two mutations (red lines).

BRAF V600E and TERT Promoter Mutations Cooperatively Identify the Most Aggressive Papillary Thyroid Cancer With Highest Recurrence

Mingzhe Xing, Rongyun Liu, Xiaoli Liu, Avanijaparam Kannan Murugan, Guangwei Zhu, Martha A. Zeiger, Sara Patel, and Justin Bishop
TERT promoter mutations are associated with high risk of recurrence, poor survival prediction and low thyroid differentiation.
BRAF-V600E and RAS Mutations are Mutually Exclusive

Giovanni Ciriello at MSKCC and Katie Hoadley at UNC developed a gene expression based score that measures whether a tumor has expression like a BRAF- or a RAS-mutant tumor.
Thyroid Differentiation Score Gene Expression Set

Remember miR-21 and miR-146b
Visual Summary

Thyroid

TCGA

496 Papillary thyroid carcinomas

Mutations
Copy number alterations
mRNA expression
miR expression
Protein expression
DNA methylation

Braf<sup>V600E</sup> v. Ras signaling

Thyroid differentiation

BRAF<sup>V600E</sup>-RAS score

Thyroid differentiation score

Molecular classification of papillary carcinoma

RAS-like papillary carcinoma

BRAF<sup>V600E</sup>-like papillary carcinoma

Subtypes of BRAF<sup>V600E</sup>-like papillary carcinoma
Gene-Environment Opportunity

Full Genomic Characterization (TCGA-style) of Radiation-Related Thyroid Cancer in the Ukraine
Focused Molecular Studies of Thyroid Cancer: UkrAm

• Somatic mutation analyses (jointly with Dr. Nikiforov)
  - Dose-related increase in MAPK* gene rearrangements, but not in BRAF/RAS point mutations
  - Strong dose response for remaining 30% of tumors with no candidate-gene mutations

• Gene expression studies (jointly with Dr. Abend)
  - Differential tumor/non-tumor gene expression in relation to dose identified several candidate genes/pathways
  - Additional genes with dose-dependent gene expression either in tumor or non-tumor thyroid tissue found

*Mitogen-activated protein kinase signaling pathway

Specific Aims & Analysis Plan

• **Primary** – Comprehensive characterization of the genomic alterations of radiation-related PTC
  
  ➢ Compare radiation-related PTCs against sporadic PTC in TCGA to identify possible signature of radiation-related somatic alterations
  
  ➢ Across levels of I-131 exposure
  
  ➢ Prefer Fresh Frozen but can use FFPE

• **Secondary** – Evaluate gene-radiation interactions and contribution of genetic susceptibility to risk of PTC using germline DNA data
# CTB: I-131 thyroid doses

<table>
<thead>
<tr>
<th>Group</th>
<th>Basis for dose reconstruction</th>
<th>Available, N</th>
<th>Mean I-131 dose, Gy (range)</th>
<th>Mean GSD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Direct thyroid measurement and personal interview</td>
<td>165</td>
<td>1.2 (0.001-13)</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>Direct thyroid measurement, but no personal interview</td>
<td>19</td>
<td>1.9 (0.008-13)</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>No direct thyroid measurement and no personal interview</td>
<td>1,685</td>
<td>0.13 (0.001-24.1)</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>Exposed <em>in utero</em></td>
<td>64</td>
<td>0.10 (&lt;0.001-2.1)</td>
<td>3.8</td>
</tr>
<tr>
<td>5</td>
<td>Not-exposed, born after Jan 1, 1987</td>
<td>310</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2,243**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Geometric standard deviation, measure of dose uncertainty
**For 24 cases place of residence in 1986 is unknown

Likhtarov et al. Radiat Prot Dosimetry, 2013
UkrAm Pilot
Molecular-Genetic study

12 PTC cases:
- 4-low; 4-middle; 4-high dose groups;
- 6 – from Zhitomir; 6 – from Chernigov regions;
- 7-Female; 5-Male

- Paraffin embedded blocks
- Frozen tissue samples
- Blood samples EDTA x2
- Pathology information
- Clinical information
- IRB permission

Comprehensive Characterization in TCGA Pipeline
Exome Sequencing

**Figure 5: Median Insert Size in sequencing libraries; FF and Blood samples are shaded blue, FFPE samples are shaded green**
Exome Coverage Uniformity Metrics; the red dotted line represents typical target coverage for 80% of targets for germline variant exome sequencing; FF and blood sample codes are shaded blue, and FFPE sample codes are shaded green.
Pilot study: Exome Analysis: Preliminary Assessment of DNA Seq

- Known Mutations
  - \textit{BRAF} (2)
    - \textit{V600E in RNA & Exome} (1)
  - \textit{TP52}
  - \textit{ALK}
  - \textit{CHEK2}
Distribution of log2 fold-change between a matched FF and FFPE sample
Pairwise Analysis of Matched Tumor/Normal Data - Significantly Dysregulated miRs

### miRNAs Significantly Up-regulated in Tumor vs Normal (>8-fold)

<table>
<thead>
<tr>
<th>miR</th>
<th>Follicular Variant (n=5)</th>
<th>Papillary, Other (n=4)</th>
<th>Classical subtype (n=1)</th>
<th>All Tumor Pairs (n=10)</th>
<th>Reference(s) (Thyroid Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsa-mir-221</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>hsa-mir-222</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>hsa-mir-31</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td>Tetzlaff et al., 2007, Nikiforova et al. 2008</td>
</tr>
<tr>
<td>hsa-mir-375</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>Dettmer et al. 2013</td>
</tr>
<tr>
<td>hsa-mir-34a</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>Tetzlaff et al., 2007</td>
</tr>
<tr>
<td>hsa-mir-187</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>Nikiforova et al. 2008</td>
</tr>
<tr>
<td>hsa-mir-891a</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

### miRNAs Significantly Down-regulated in Tumor vs Normal (<-8-fold)

<table>
<thead>
<tr>
<th>miR</th>
<th>Follicular Variant (n=5)</th>
<th>Papillary, Other (n=4)</th>
<th>Classical subtype (n=1)</th>
<th>All Tumor Pairs (n=10)</th>
<th>Reference (Thyroid Studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsa-mir-486</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>7</td>
<td>Braun et al. 2010</td>
</tr>
<tr>
<td>hsa-mir-675</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>hsa-mir-144</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>Rossing et al. 2012</td>
</tr>
<tr>
<td>hsa-mir-7-3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>hsa-mir-136</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Note: Tumors without matching normals were excluded from this analysis; Differential expression using a pairwise approach was measured by calculating the log2 fold-change of tumor miRNA counts relative to the matched normal (DESeq/Bioconductor); miR’s were ranked according to the most significant fold-change (cut-off of log2FC of <-3 and >3; equivalent to 8-fold/-8-fold change)
Significantly Up-Regulated miRs 146b, 221 & 222 – Cell Cycle Regulation

Integration of Methylation & miRNA Data – miR-146b

- Identified reduced methylation at predicted transcription start site (TSS) of miR-146b in tumor samples
- Methylation was reduced by 40 - 50% on average in tumors relative to normals
- Demethylation in the tumors may be contributing to the over-expression of miR-146b observed in the miRNA data

<table>
<thead>
<tr>
<th>probeID</th>
<th>hg19 Coordinates</th>
<th>arm</th>
<th>Gene</th>
<th>P.Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cg09701700</td>
<td>chr10:104194843</td>
<td>q</td>
<td>MIR146B</td>
<td>3.46E-06</td>
</tr>
<tr>
<td>cg05251190</td>
<td>chr10:104196206</td>
<td>q</td>
<td>MIR146B</td>
<td>2.73E-04</td>
</tr>
<tr>
<td>cg05858126</td>
<td>chr10:104196213</td>
<td>q</td>
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Demethylation near miR-146b

- Average methylation level in tumors vs. normals
Ukrainian CTB Cases:
1998-2012

2,267 cases of benign and malignant thyroid pathology

- Paraffin embedded blocks: 2,267 cases
  Tumor(s) – 1-4 blocks per case
  Normal – 1-3 blocks per case
  Mts - 1-3 blocks per case

- Frozen tissue samples: 1,726 cases
  Tumor(s) – 1-4 samples per case
  Normal – 1-3 samples per case
  Mts - 1-3 samples per case

- Blood samples: 919 cases
  EDTA - 2 samples per case
  Serum - 2 samples per case

Courtesy of Dr. Bogdanova
Target for Number of Cases

• 450 radiation-related PTC cases from CTB
  ➢ 100 UkrAm*
  ➢ 350 non-UkrAm*

• 550 sporadic (non-irradiated) PTC cases
  ➢ 50 CTB* cases born after Jan 1, 1987
    ➢ Part of this proposal
  ➢ 500 cases from TCGA
    ➢ Available to researchers based on *Cell* 159:676, 2014

*From Zhytomyr, Chernihiv, Kyiv region, and Kyiv city
Parental irradiation of Ukrainian clean-up workers and evacuees and germline mutations in their offspring (TRIO Study)
Background

- No reliable evidence of untoward pregnancy outcomes, childhood mortality, or sex chromosome aneuploidy associated with parental radiation exposure in Japanese A-bomb F₁ or other studies
  - Statistical power in A-bomb F₁ study is low for endpoints

- Based on 7-locus mouse data (Russell et al) and non-significant indications from the A-bomb F₁ study, ICRP assumes parental radiation exposure induces a large spectrum of genetic effects in offspring
  - Doubling dose (DD) of about 1 Gy

DD = Radiation dose expected to double the spontaneous mutations rate in a generation
Objectives

• Comprehensive characterization of genomic alterations and inherited variation patterns in trios (parents and children) associated with pre-conception exposure to radiation from the Chernobyl accident:
  – de novo mutations
  – Single nucleotide polymorphisms
  – Minisatellite mutations
  – Copy number variations
  – Somatic mutations
  – Mosaicism
  – Variation in telomere length
  – Methylation

• Overlap of de novo mutations, copy number changes with genes linked to known diseases
Timeframe of Exposure

- **Time of the Chernobyl accident**: April 26, 1986
- **Evacuation from Pripyat-town**: April 27, 1986
  - Staying at place of evacuation up to a few weeks
- **Moving to place of permanent residence**
- **Time of conception**
- **Childbirth**

**Exposure during clean-up mission**

**Exposure during residence in Pripyat-town**

**Residential exposure**

**All trios with children born > 1 year accident**
Target Trio Numbers

• Initial study: Recruit 50 trios, selected from risk categories (10 trios for each of 5 groups):
  • Exposed father, exposed mother
  • Exposed father, unexposed mother
  • Unexposed father, exposed mother
  • Unexposed father, unexposed mother
  • High dose emergency worker (fathers only, with acute radiation syndrome)

• Full study aims to recruit up to 450 trios from exposed and/or unexposed parents
Future collaborations

• Existing radiation studies
  – RERF atomic-bomb survivors
  – Mayak nuclear plant workers
  – Childhood cancer survivors
BD2K enables biomedical researchers to capitalize on Big Data advances.

Big Data to Knowledge (BD2K)

The ability to harvest the wealth of information contained in biomedical Big Data will advance our understanding of human health and disease; however, lack of appropriate tools, poor data accessibility, and insufficient training are major impediments to rapid translational impact. To meet this challenge, the National Institutes of Health (NIH) launched the Big Data to Knowledge (BD2K) Initiative in 2012.

BD2K is a trans-NIH initiative established to enable biomedical research as a digital research enterprise, to facilitate discovery and support new knowledge, and to maximize community engagement.

Read More

BD2K Recent News

- NIH BD2K ENIGMA Center is published in Nature
- NIH BD2K ENIGMA Center is published in Nature
- Important Information for BD2K Centers RFA HG-13-009 Applicants
- NIH BD2K Seeks Input on Making Data Usable!

See more news
Mission

To accelerate progress in human health by helping to establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data, and by catalyzing data sharing projects that drive and demonstrate the value of data sharing.
Utility of a Cancer Knowledge System

- Identify low-frequency cancer drivers
- Define genomic determinants of response to therapy
- Compose clinical trial cohorts sharing targeted genetic lesions
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Robert Hoover
Peggy Tucker
Meredith Yeager
Lisa Mirabello
Sharon Savage
Nat Rothman
Deborah Silverman
Lindsay Morton
Kiyo Mabuchi
Maureen Hatch
Alina Brenner

NCI-Special Experts
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Montse Garcia-Closas-ICR

More than 400 Collaborators
TCGA Thyroid Analysis Working Group

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