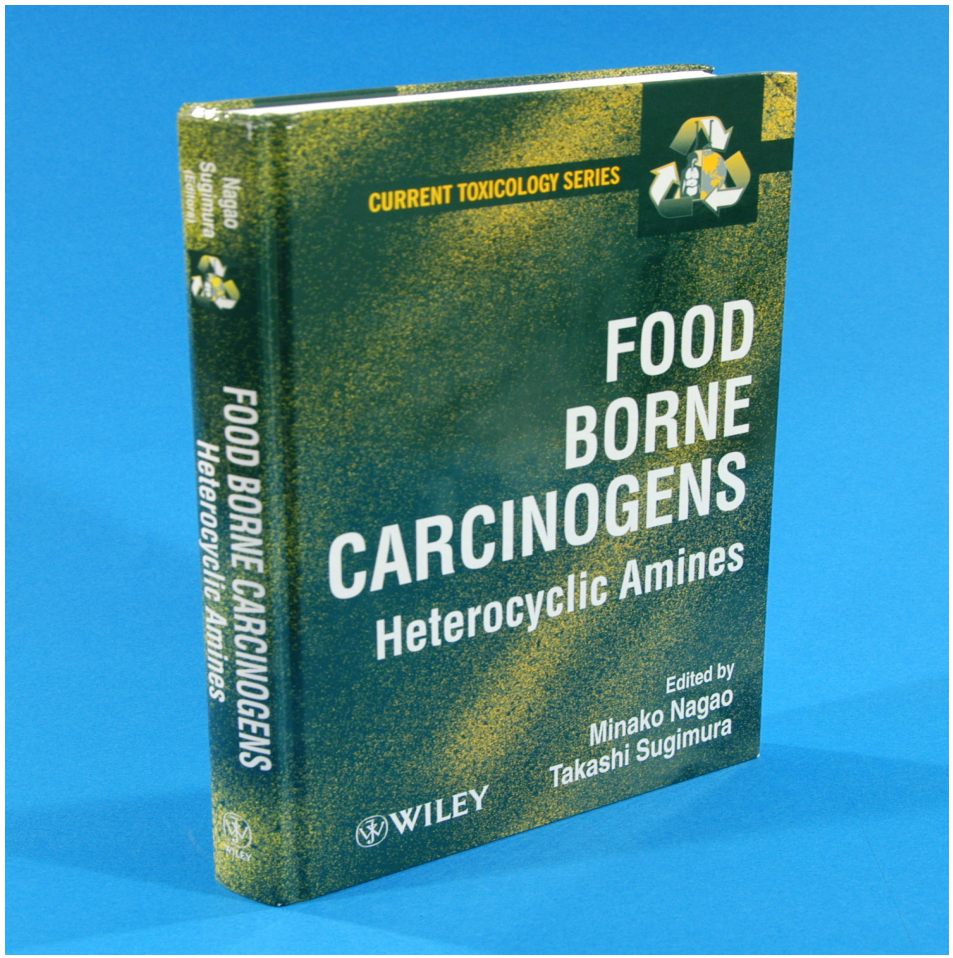
IARC 50th Anniversary Conference
Global Cancer Occurrence, Causes and Avenues to Prevention

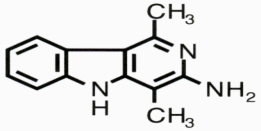
Mechanisms: DNA damage, Repair and Mutagenesis

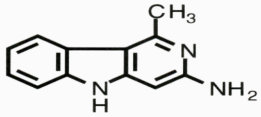
Exploration of Cancer Etiology using Whole Genome/Exome Analysis and Comprehensive DNA Adduct Analysis

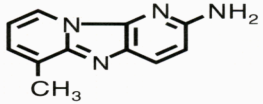
Hitoshi Nakagama
National Cancer Center, Japan

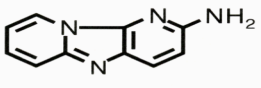
Heterocyclic Amine (HCA)；Food-borne Carcinogens Produced in Cooked Meats

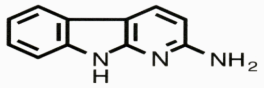


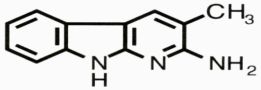

Trp-P-1

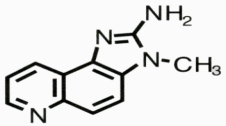

Trp-P-2

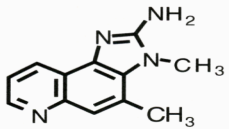

Glu-P-1

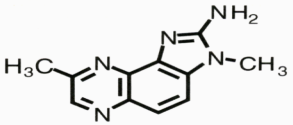

Glu-P-2

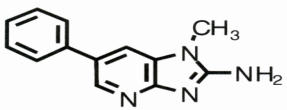

AαC


MeAαC

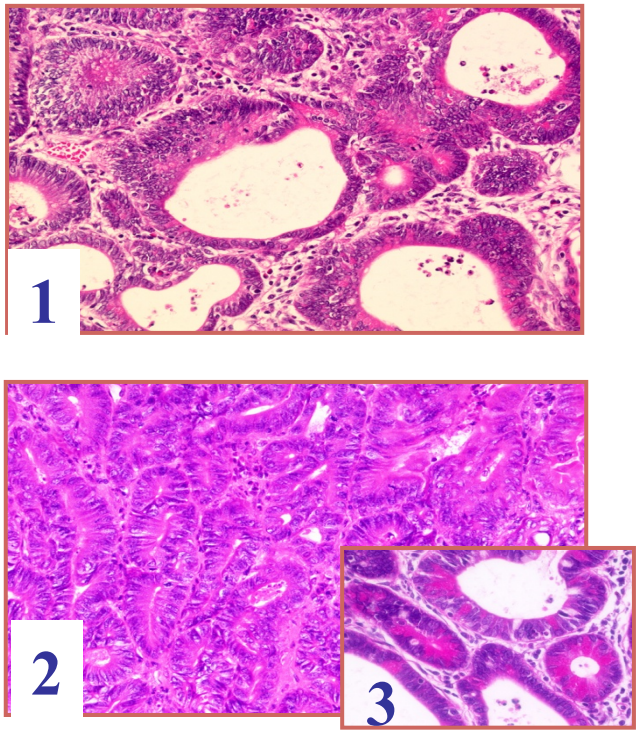

IQ


MeIQ


MeIQx


PhIP

Representative Histological Features and Genetic Alterations observed in PhIP-induced Rat Colon Cancers



Tubular growth pattern (*No. 1, 2*), and differentiation into Paneth cells (*No. 3*)

1. Apc (approx. 10 ~ 15 %)

Exon 14 or 15 (codons 635, 869, 1413)
5'-GTGGGAT-3' to 5'-GTGGAT-3'
(G deletion)

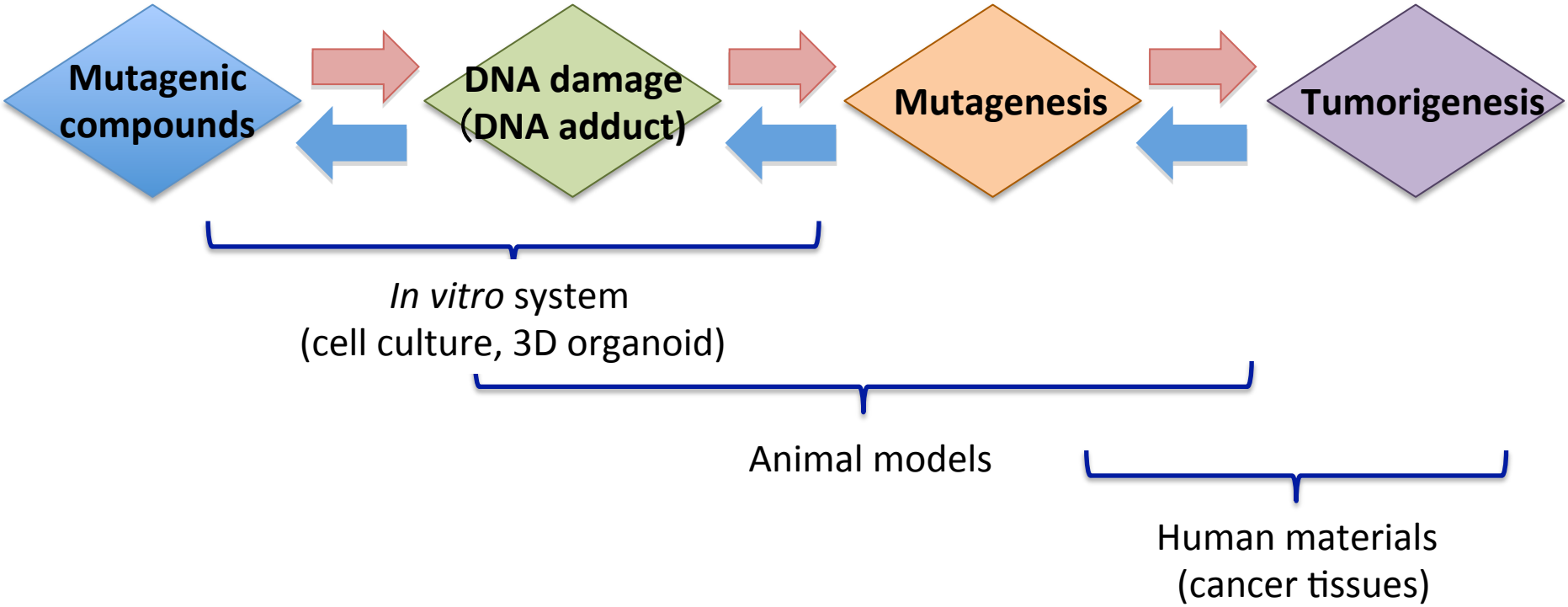
Intron 10 & exon 11 junction
5'-*tag*GGGGG-3' to 5'-*tat*GGGGG-3'
(G to T)
5'-*tag*GGGGG-3' to 5'-*tag*GGGG-3'
(G deletion)

2. β–catenin (25 ~ 50 %)
Codons 32, 34, 36, 37, 38 (mainly G to T/A)
& G:C to C:G

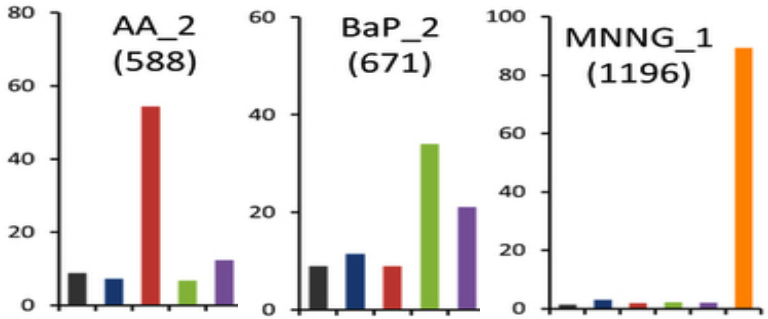
*3. K-ras and p53 mutation*s are rarely observed.
Genomic instability (MSI) is not evident.

* IQ-induced colon cancers
→ Codons 523 or 921 in *Apc* (C to T / T to C)

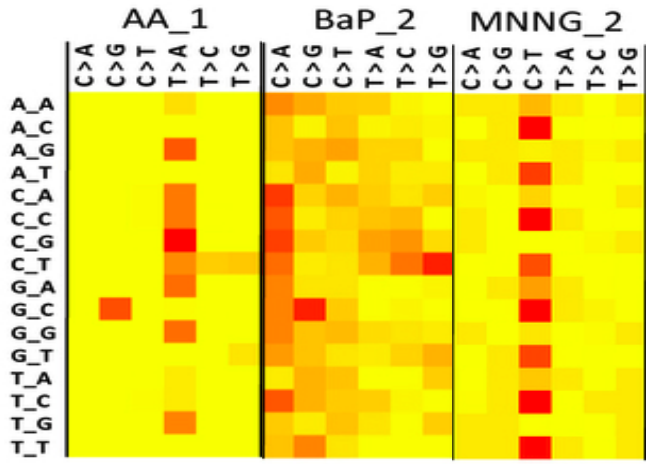
Bottom-up and Top-down Approaches for Exploration of Cancer Etiology



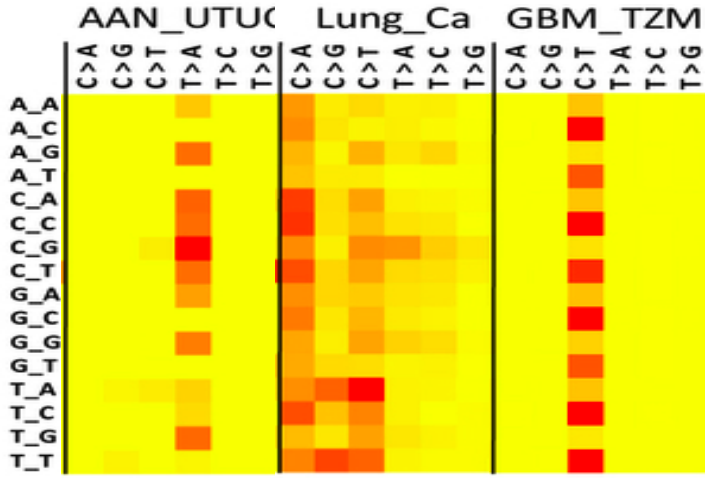
Mutagens/Carcinogens Induce Specific Mutation Patterns and Mutational Signature



Mutation Signature induced in Culture Cells by Chemicals



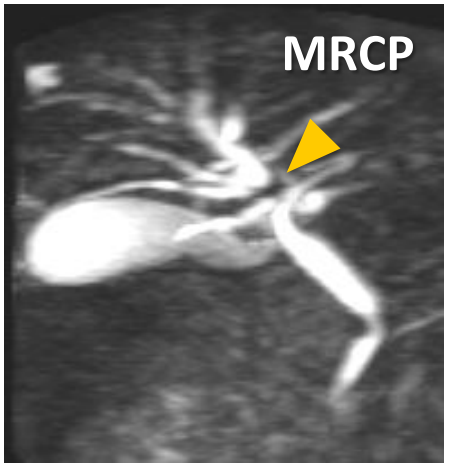
Mutation Signature observed in Human Cancers



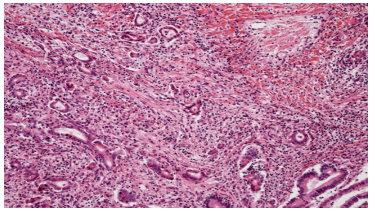
Olivier et al., Scientific Reports, 2014

Analysis of Somatic Mutations observed in Occupational Cholangiocarcinoma

	Case 1	Case 2	Case 3	Case 4
Age	40	39	31	34
Sex	M	M	M	M
Duration of Exposure	DCM; 1y5m	DCM; None	DCM; None	DCM; None
	DCP; 11y11m	DCP; 7y4m	DCP; 6y6m	DCP; 6y1m
Smoking Habit (/Day)	20 cigarette	20 cigarette	None	None



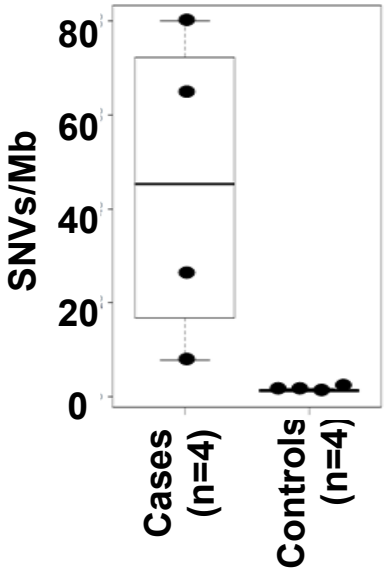
Histology of Cholangiocarcinoma

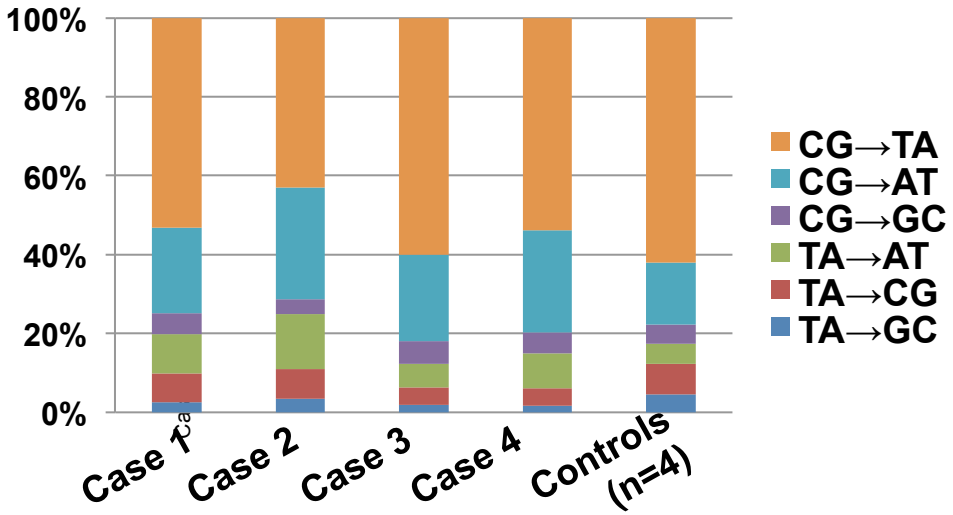


- Massive fibrosis
- Infiltration of inflammatory cells

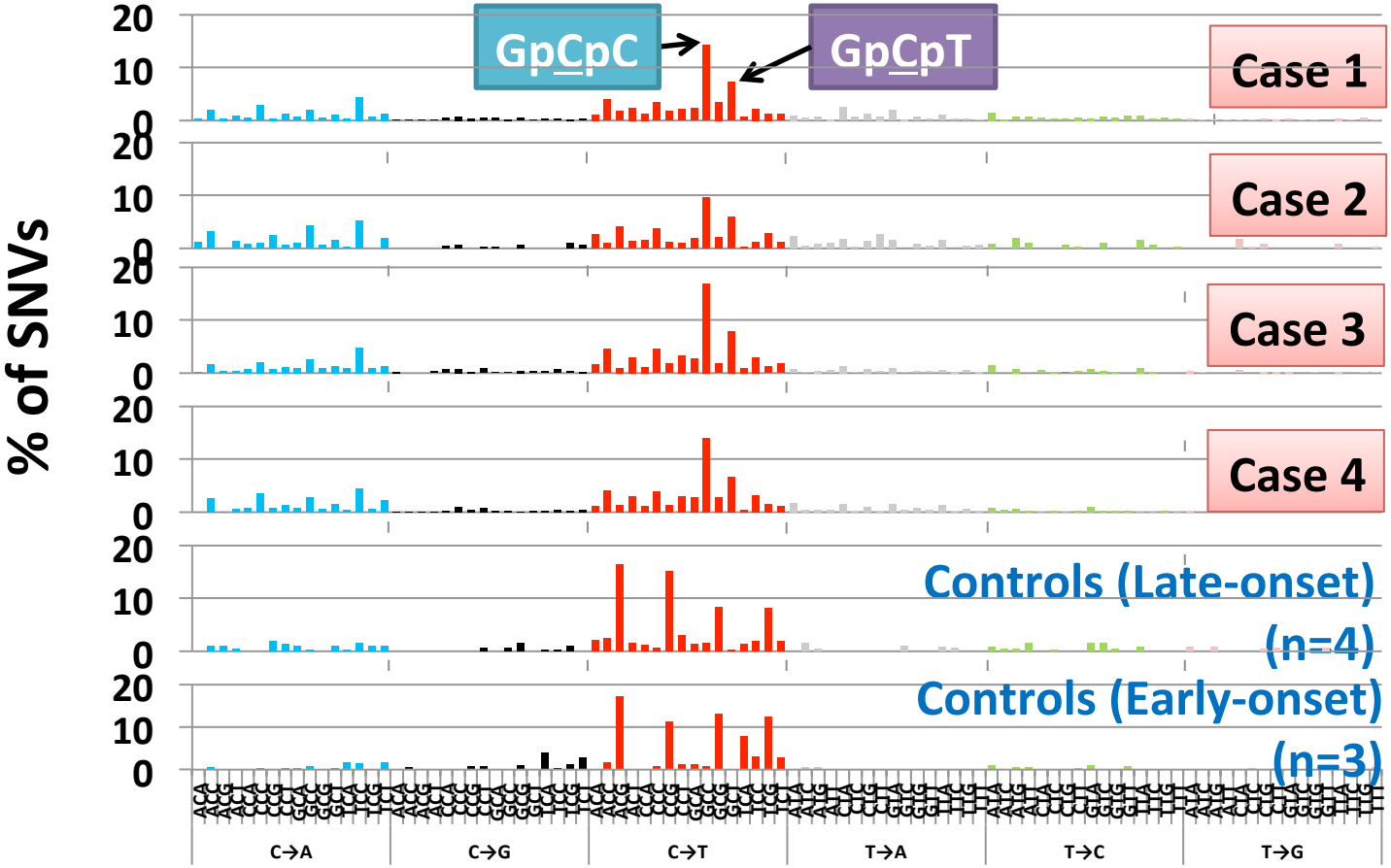
Number of SNVs Analyzed by whole exon analysis

Total number of SNVs in Cases; 1,451±1,089

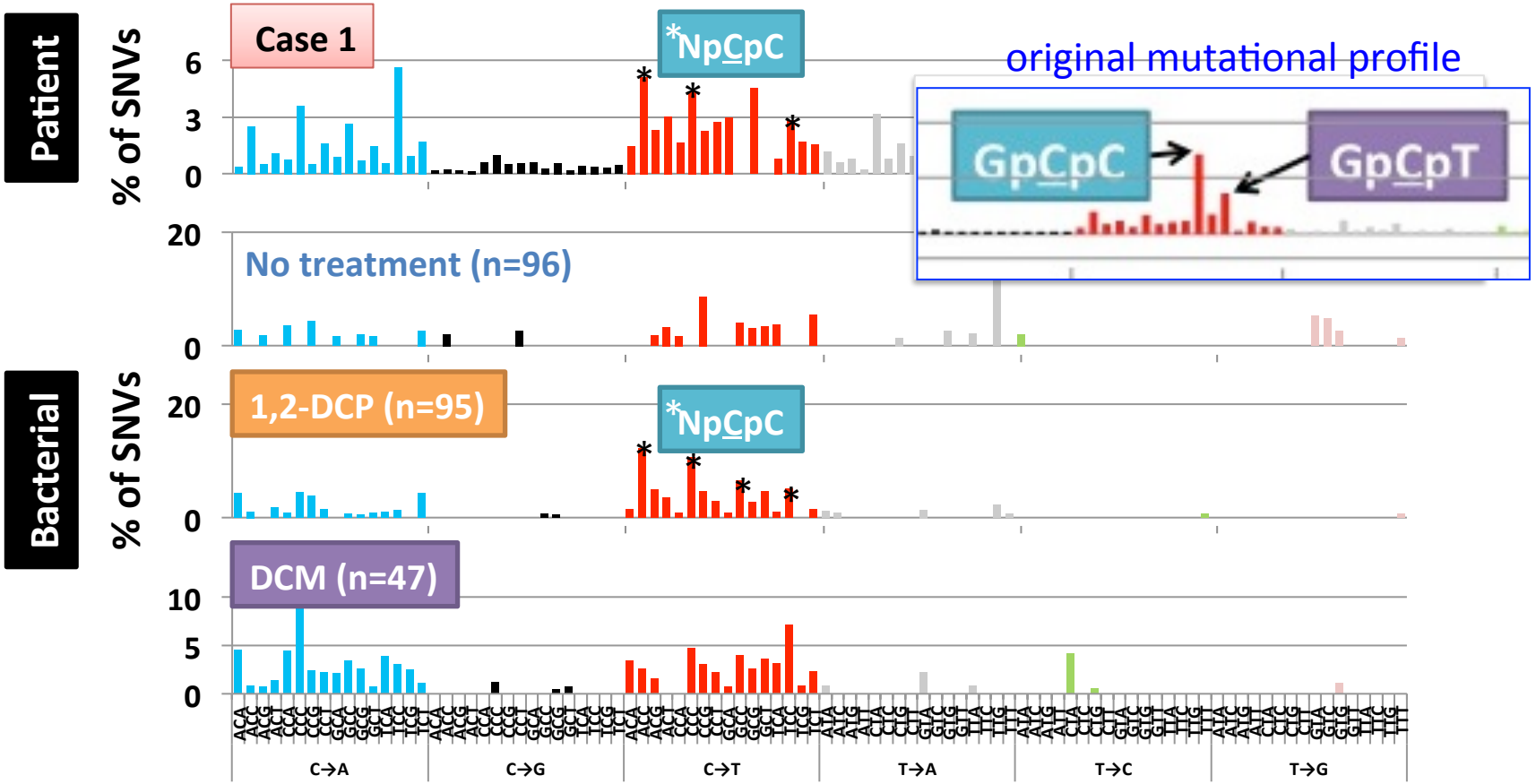




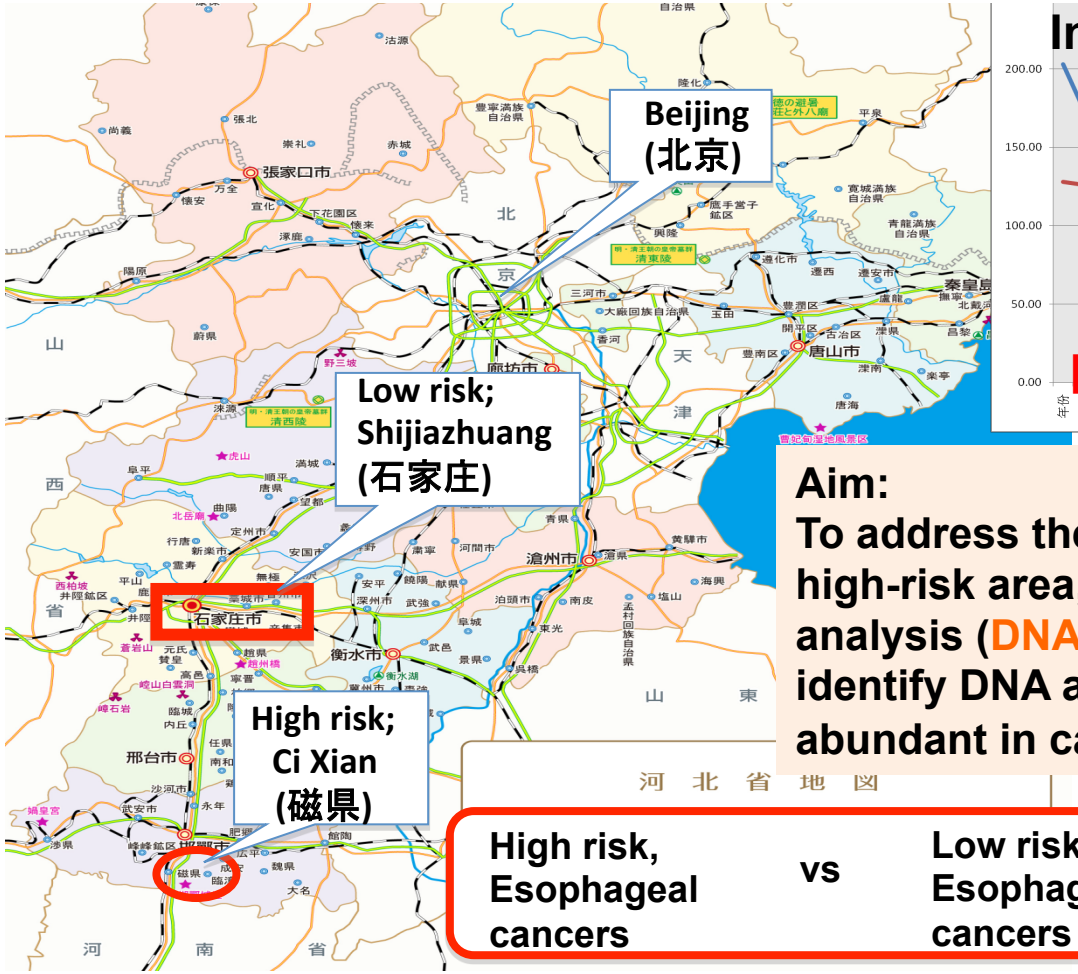
Predominant GpCpY Trinucleotide Mutational Signatures in C:G to T:A Transitions

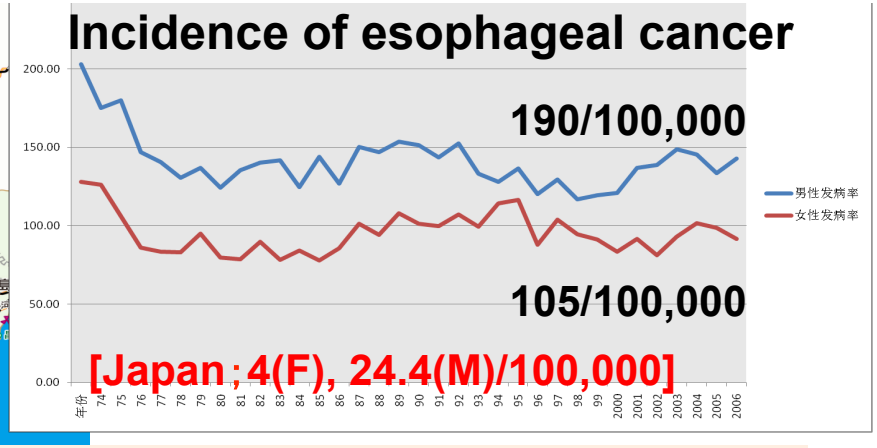


Overlapped Mutational Signatures among 1,2-DCP Exposed Bacteria and Occupational Cholangiocarcinoma Genomes



Esophageal Cancer (EC) ---Several high risk areas exist in China---

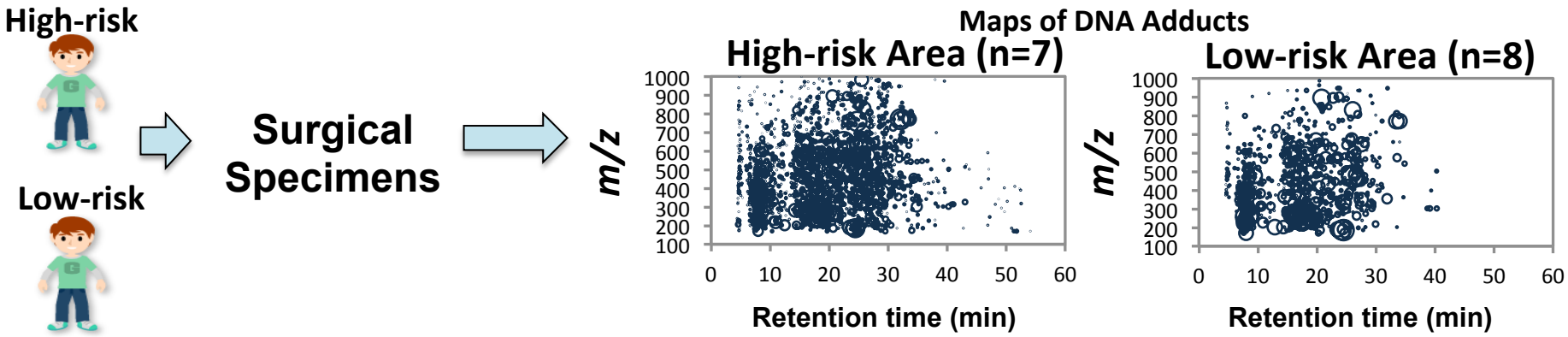


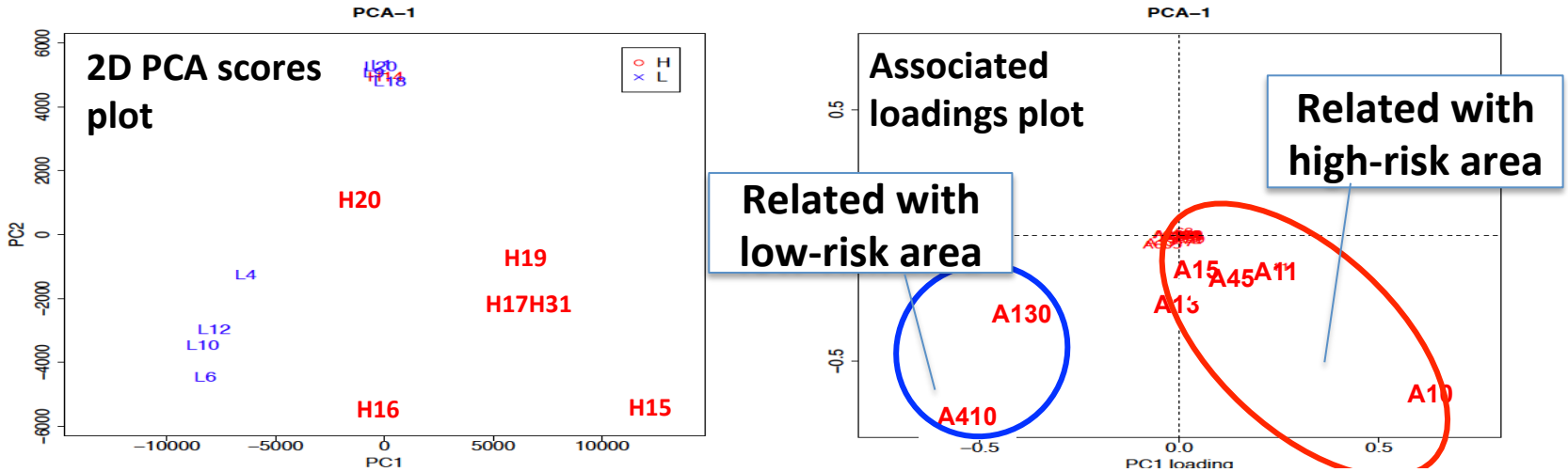


Aim:
To address the etiology of esophageal cancer in high-risk area, a comprehensive DNA adduct analysis (DNA adductome) was conducted to identify DNA adducts that are specific and/or abundant in cases of the high-risk area.

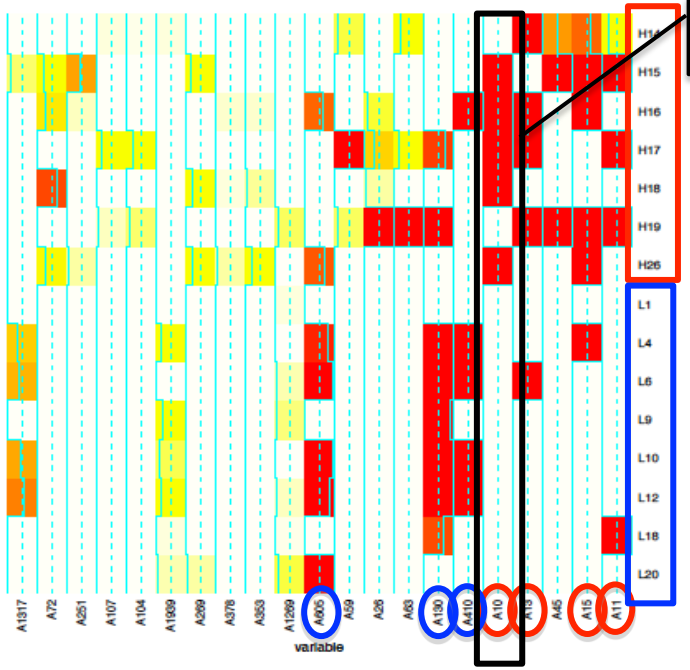
High risk, Esophageal cancers **vs** **Low risk, Esophageal cancers** → **Specific DNA adducts exist in high risk area**

DNA Adductome Analysis of Esophagus Cancers in China: Surgical Specimens Collected from Cases in High- and Low-risk Areas





DNA Adductome Analysis Revealed Adduct A10 Is Specific and/or Abundant in Cases from High-risk Area



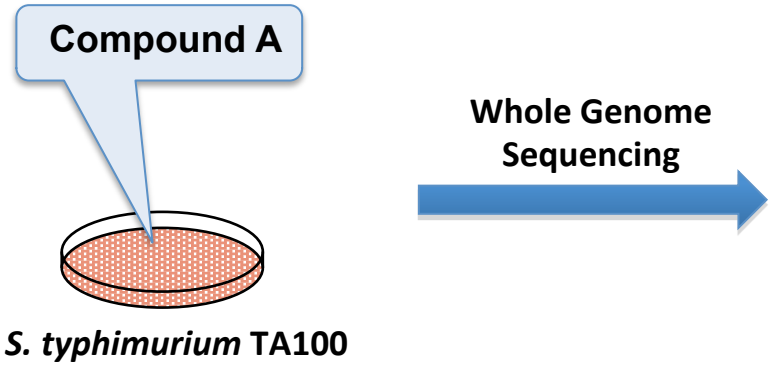
A10 (m/z [M+H] ; 352.18)

Compound A

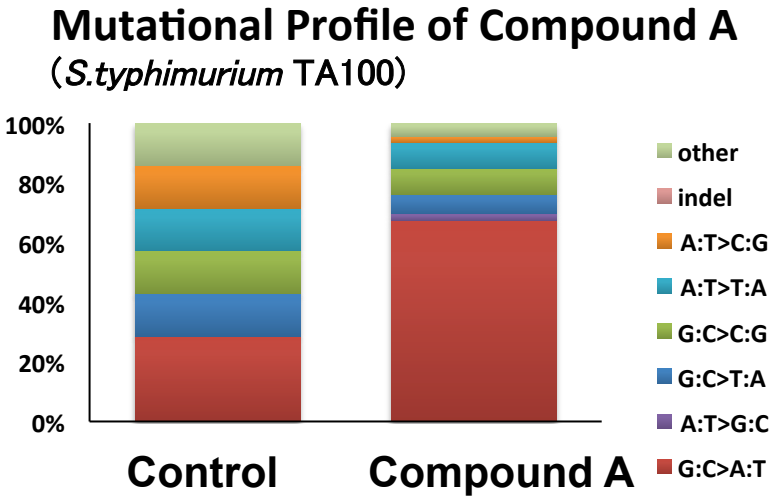
Compound A is deduced precursor of adduct A10

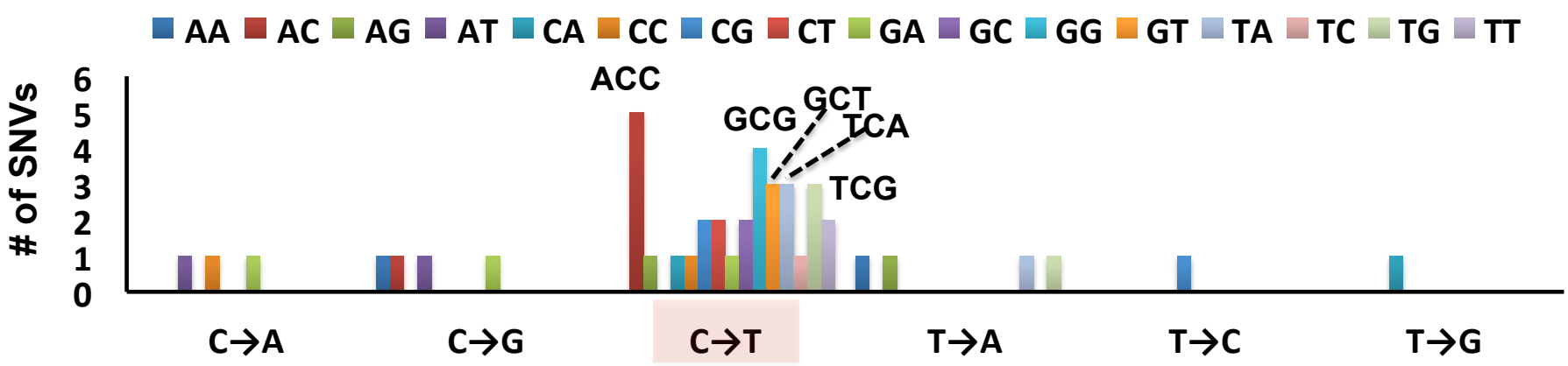
DNA Adduct Database

Global Mutations Analyzed by Next-Generation Sequencing

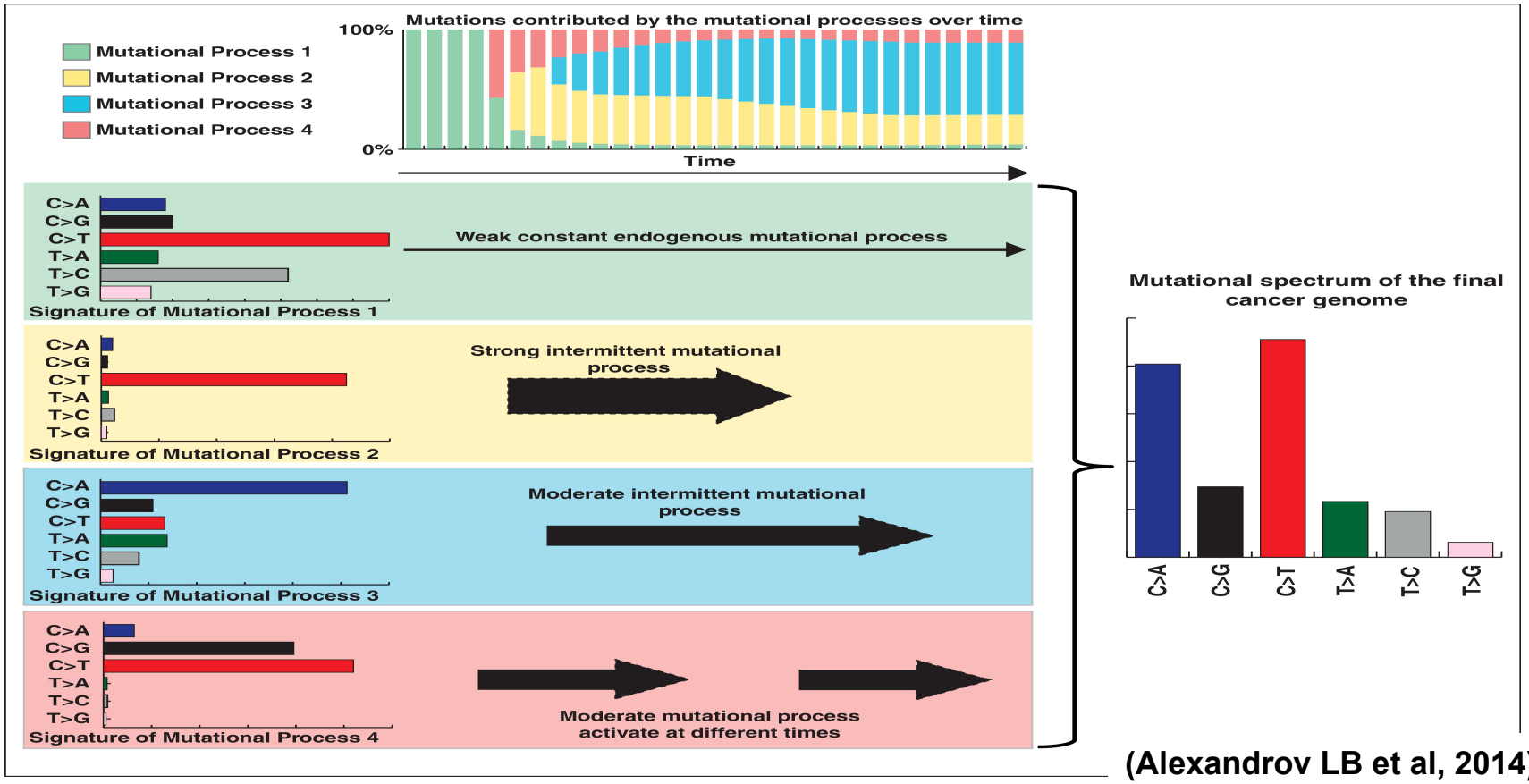


Whole Genome Sequencing



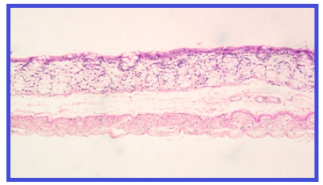


Somatic Mutations in Cancer Genomes are the Cumulative Result of the Mutational Processes Over Time

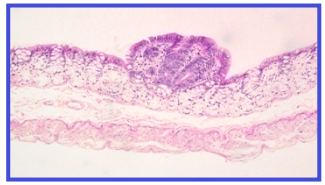


(Alexandrov LB et al, 2014)

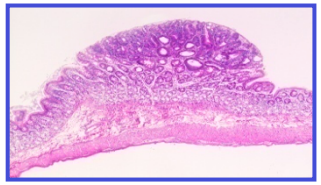
Chronological Profiles of Mutational Signatures during Sequential Progression of Colonic Lesions in Animal Models



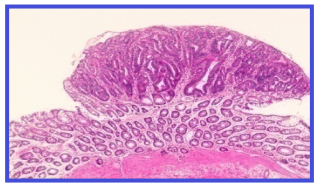
Normal mucosa



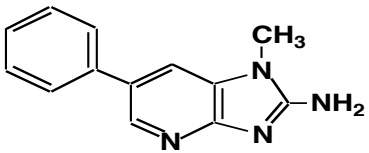
ACF



Adenoma



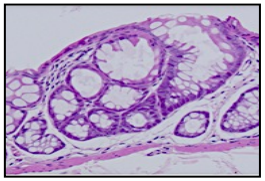
Adenocarcinoma



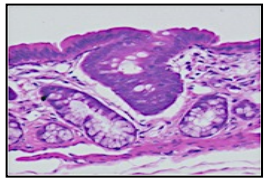
PhIP

2-Amino-1-methyl-6-phenyl-imidazo[4,5-*b*]pyridine

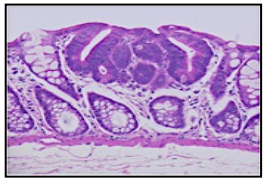
Hyperplasia

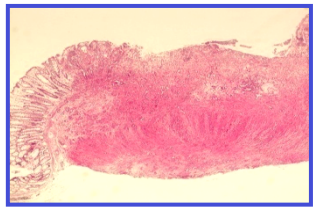


Dysplasia (low grade)



Dysplasia (high grade)





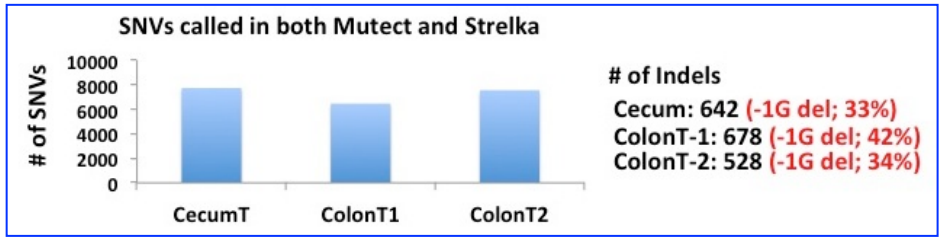
Invasive tumor

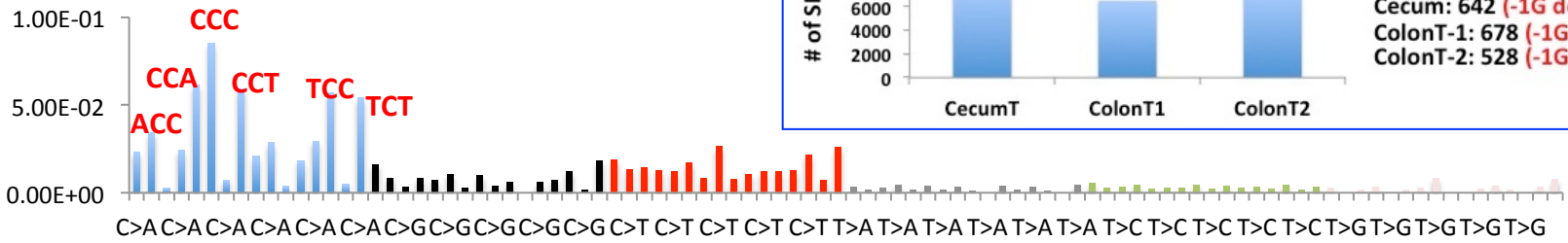
Experimental Protocol

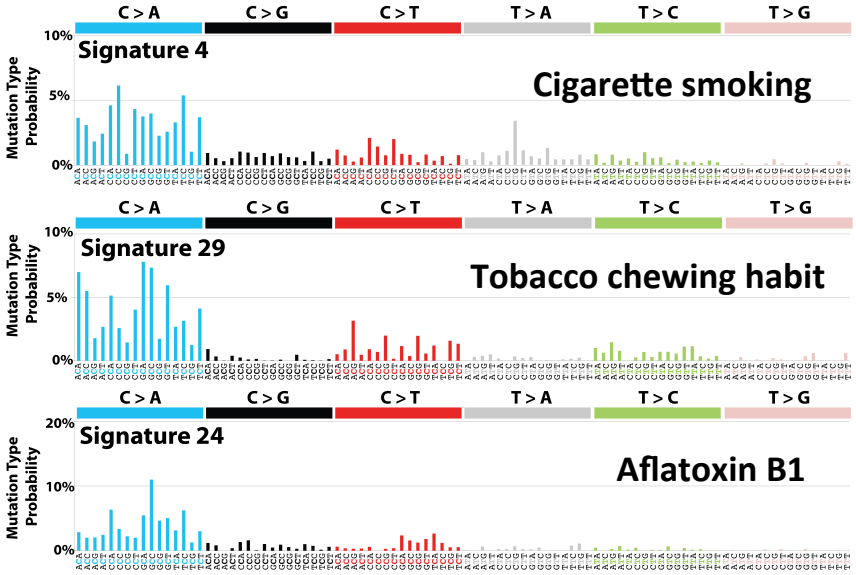
Animals : F344 rat (♂)

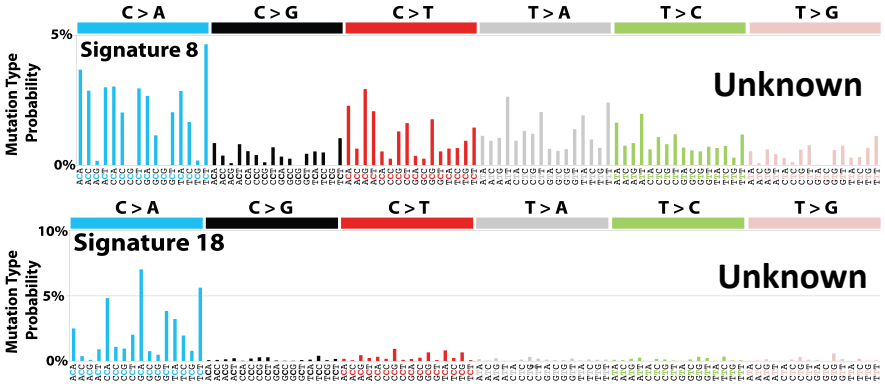
400 ppm PhIP in basal diet
High fat diet

Trinucleotide Mutational Signature of PhIP-induced Colon Tumor





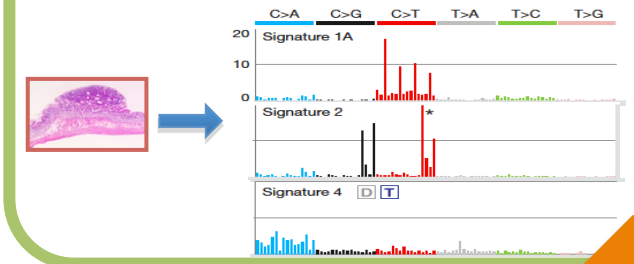




A Comprehensive Approach for Exploration of Cancer Etiology

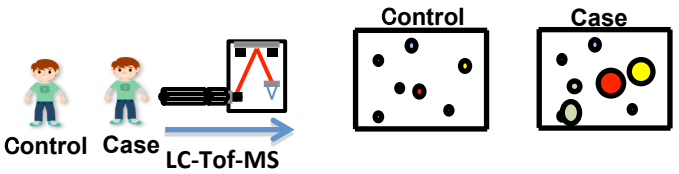
Genome analysis

Analysis of characteristic mutational signature observed in human cancers



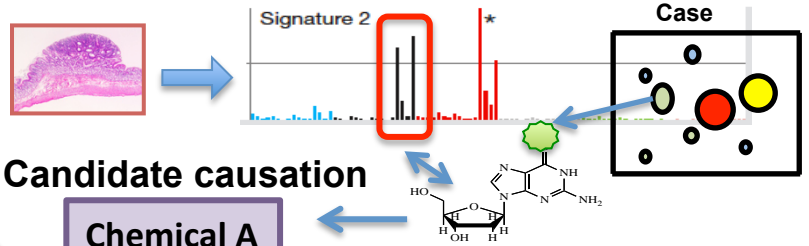
Adductome analysis

Comprehensive DNA adduct analysis



Exploration of cancer etiology

- Identification of DNA adducts, being directly responsible for mutational signatures and multistep cancer development

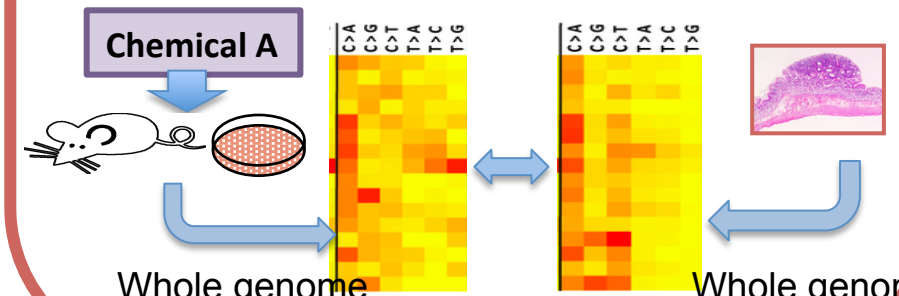


Candidate causation

Chemical A

- Verification for candidate etiology using genome analysis

Chemical A



Whole genome analysis

Whole genome/ exon analysis

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