

Genomic (Genome) Instability in Gulf War Illness

Search for the general basis for common and complex
diseases/illness

Henry Heng

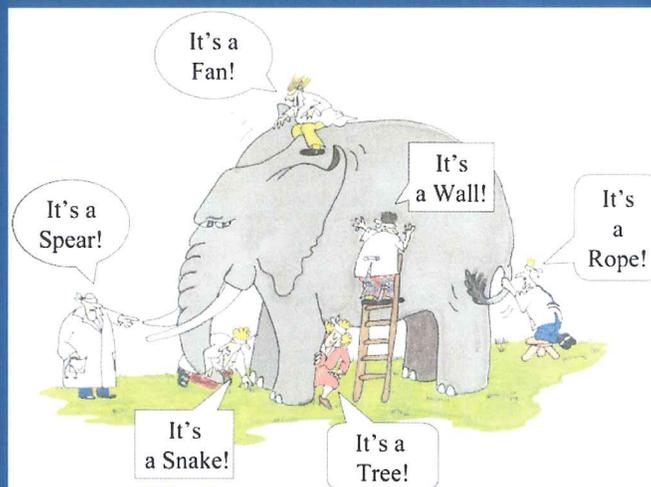
Wayne State University School of Medicine, Detroit

hheng@med.wayne.edu

313-577-9544

17 June 2013

We all know it: it is laughable...



but that's what we're doing right now!

Challenging #1

It is a complex illness (system behavior)
and It is hard to be dissected into “parts”

Individual genetic and environmental factors

- Specific gene mutation
- Specific harmful condition

The Conflict Between Complex Systems and Reductionism

Henry H. Q. Heng

JAMA. 2008;300(13):1580-1581 (doi:10.1001/jama.300.13.1580)

J.P. Sturmberg and C.M. Martin (eds.), *Handbook of Systems and Complexity in Health*,
DOI 10.1007/978-1-4614-4998-0_12. © Springer Science+Business Media New York 2013

193

Bio-Complexity: Challenging
Reductionism

12

Henry H.Q. Heng

Back to the Future

Cytogenet Genome Res 2013;139:141-143
DOI: 10.1159/000347035

Understanding the contribution of genomic heterogeneity to the genetic basis of human diseases is a crucial yet largely overlooked issue. Genomic-based studies have unexpectedly revealed a high degree of heterogeneity at mul-

We used to be very good at identifying causes by using reductionist approaches

Traditional concept is based on the success of studying infectious diseases and single gene diseases:

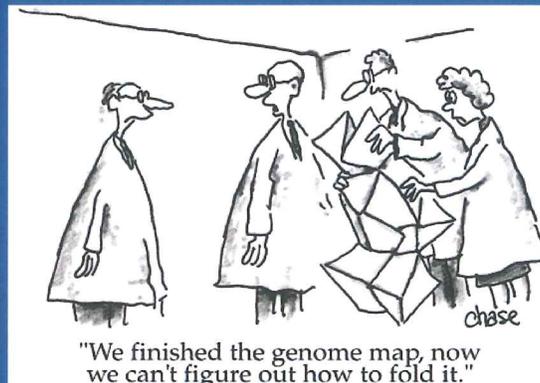
Same cause

Same specific signs or symptoms

Same treatment response

Therefore, GWI had been denied as a real illness

We are no longer certain about the causes of complex diseases despite the cutting edge genetics/genomics



Cataloging parts is easy; understanding the whole system is hard

Where to look for molecular causes and have we missed the target?

- For most traits, the majority of the heritability remains unexplained. Missing heritability? Where are these disease genes?
- Key (common driver) gene mutations cannot be found for many common/complex diseases
- Everything is involved and nothing is very important (>10,000 different genetic variants for Schizophrenia)

Heng Nat Rev Genet 2010

When identified, not very useful clinically

Reported by JAMA

101 of well characterized genetic markers were found to not be useful in predicting heart disease in a clinical setting (among 19,000 women who had been monitored for 12 years), despite the fact that all these genetic variants had been statistically linked to heart disease in various genome-scanning studies. *(Parts information)*

In contrast, asking about the family history had better prediction success *(System inheritance)*

SOS: We have major problems

“... Bert Vogelstein has watched first-hand as complexity **dashed one of the biggest hopes** of the genome era: that knowing the sequence of healthy and diseased genomes would allow researchers to find the genetic glitches that cause disease, paving the way for new treatments. An individual patient's cancer has many mutations, but **they differ between individuals**. So the search for drug targets has **shifted away from individual genes...**” Nature 2010 646: 664-667

Gene is not the answer for cancer

Craig Venter (sequencing guru): ...*We couldn't even be certain from my genome what my eye color was. Isn't that sad? Everyone was looking for miracle 'yes/no' answers in the genome. "Yes, you'll have cancer." Or "No, you won't have cancer." But that's just not the way it is.*

SPIEGEL (reporter): *So the Human Genome Project has had very little medical benefits so far?*

Venter : *Close to zero to put it precisely...*

REALITY

All of those and many more are involved,
yet most really don't matter
(we all have over 300 gene mutations)

WHY?

Current concept of gene –centric genetics
is limited
(Gene mediated genetic determinism
and reductionism)

Limitations for gene theory

- Individual gene's function is differently defined by the system/environment interaction. Most genes are not independent information units^{HH1}
- Most of the gene mutations are low penetration within patient population
- There is no absolute "good" or "bad" genes for many diseases (P53 gene mutation story)

If the gene is not responsible for most human diseases, what genetic organization it should be?

Simple answer:

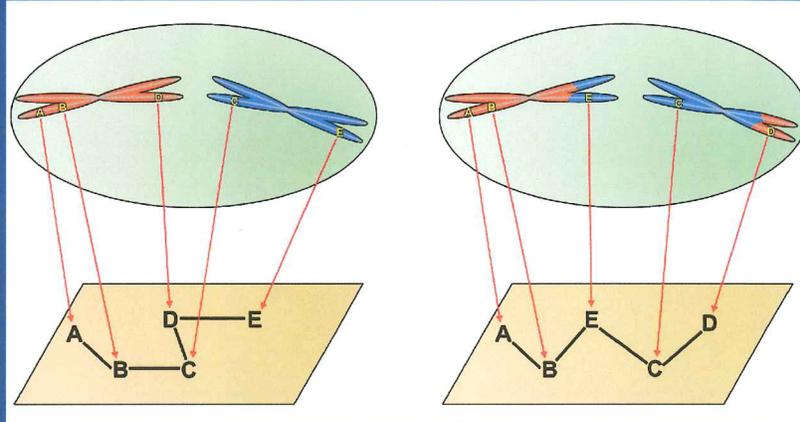
Genome or all sets of chromosomes

What is the Genome?

- Genomes contain all genes and other sequences, but the genome is much more (not just a bag of genes):
- Genome = All sequences + **genomic topology**
- Genome = blueprint of system architecture;
- Gene = genetic materials
- All gene sequencing = parts list

Genome Topology Defines the Network Structure

Gene codes parts and tools, genome codes system



Heng 2009 BioEssays; Heng et al, 2011, Genomics

System inheritance is not due to the gene, but the genome!

Human vs. Chimp

One chromosomal fusion, 5 inversions

Sponges have 18,000 genes

Most mammals have similar genes but different chromosomes

Key: where the gene is located within the genome matters!

Answer #1: We need to monitor changes at genome level

Challenging #2

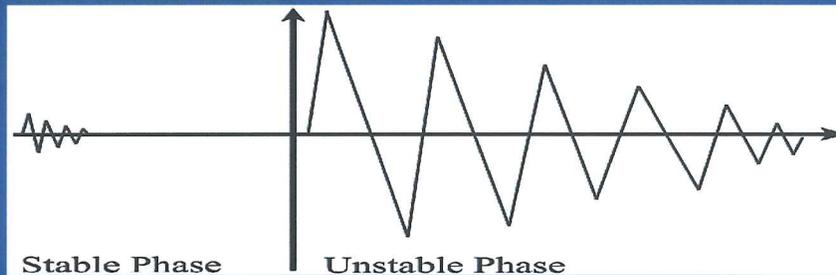
What should we measure?

- Specific pattern or nonspecific “noise”?

Specific gene mutation/chromosomal change
or stochastic genome alterations?

System based approach

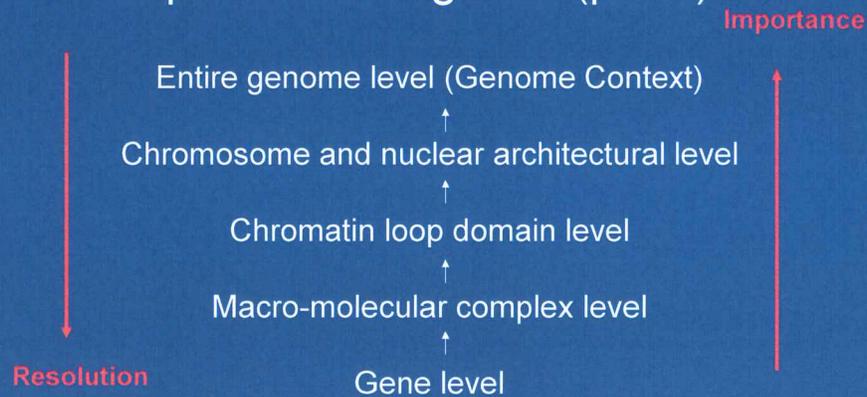
When a given system is under attack, the initial response is stochastic reaction; the time and level of reaction is defined by the system stability – (system dynamics)



Using frequencies of stochastic changes to measure system stability

NCCA: Non clonal chromosome aberrations

Genome organization (system) is more important than genes (parts)



Tips: According to information theory: for multiple levels of a system, the information from the lower level is easily obtainable, but has little to do with system control

Answer #2:

We need to study the stochastic genome alterations

Challenge #3: Connect the Dots

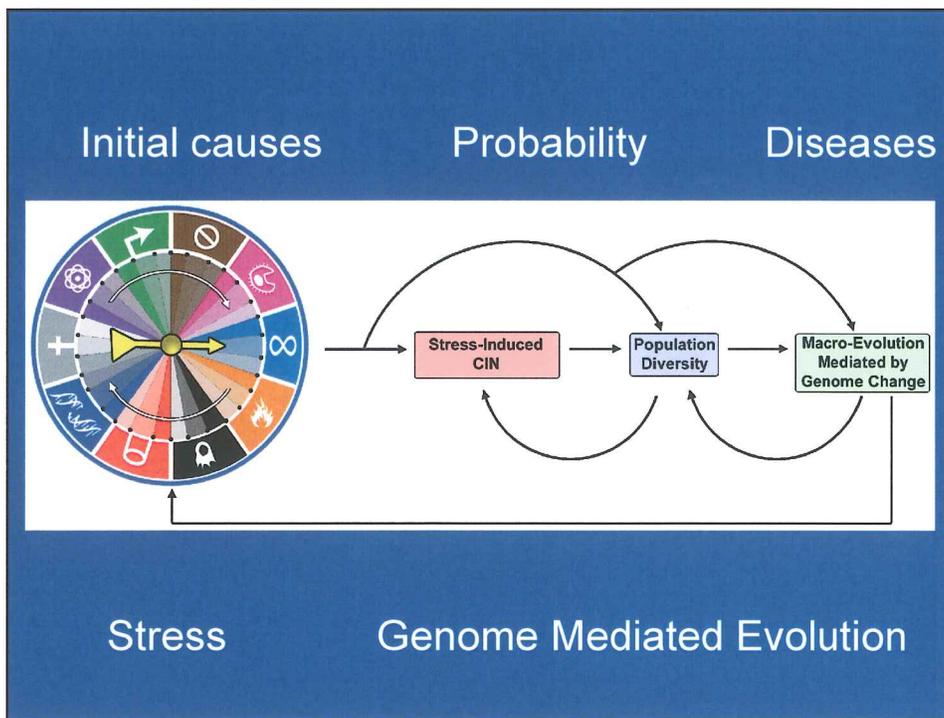
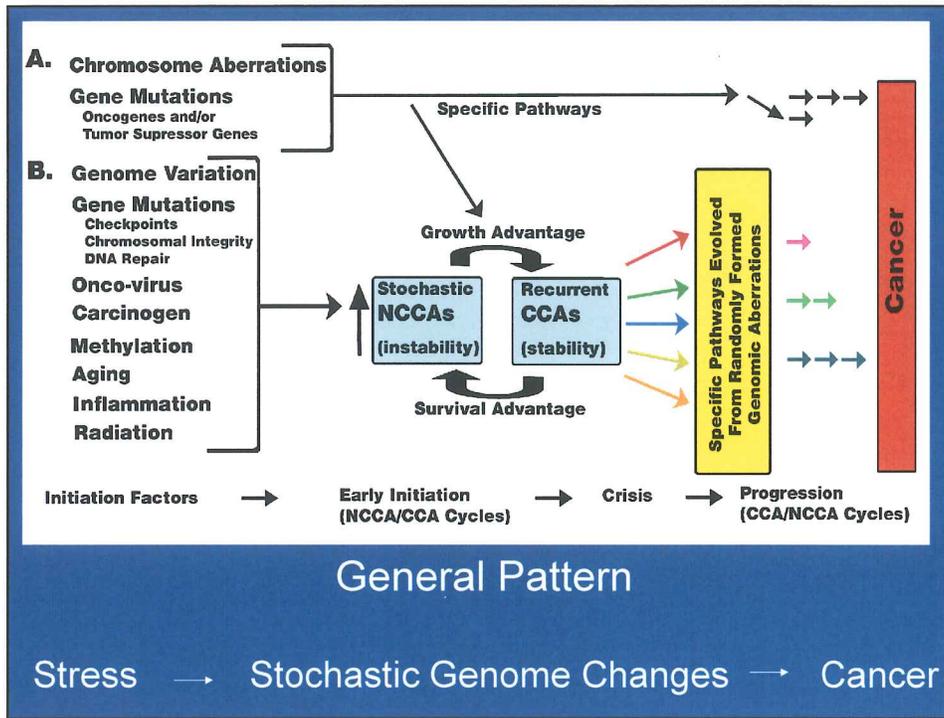
Link specific genes and environmental insults to general stress and then to stochastic genome alterations

Unify

stress,

genome alteration,

diseases/illness through somatic cell evolution



New Biomarker at system level

- Using stochastic genome alteration (Non clonal chromosome aberrations) to measure genome instability
- Previously, the seemingly random chromosomal aberrations have been regarded as insignificant noise
- Links to the tumorigenicity

Heng et al, JCP 2006; Ye et al, 2009

Mechanism of Cancer

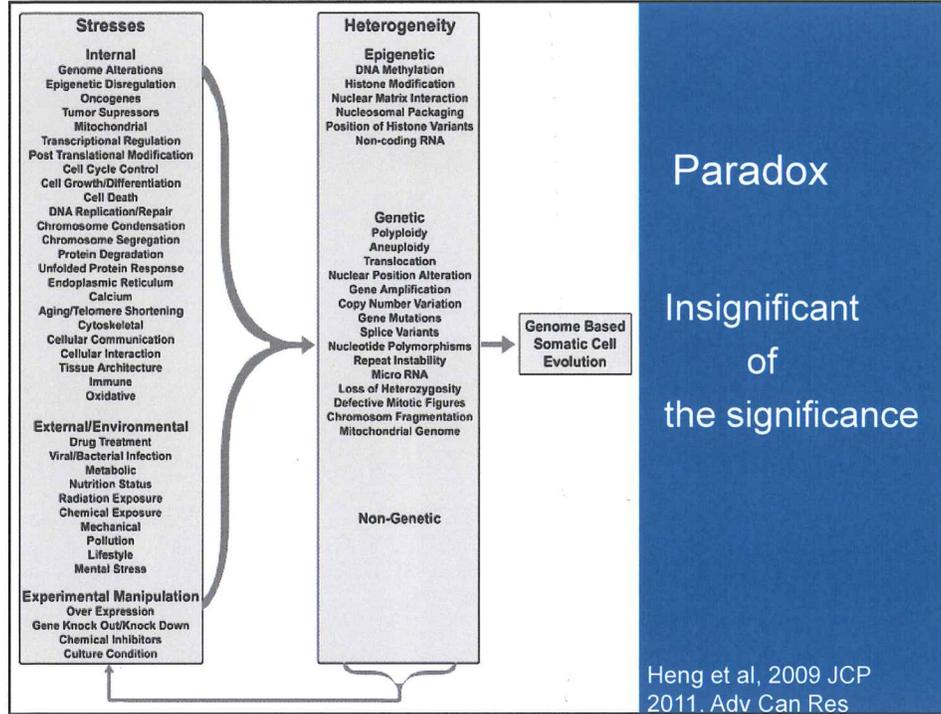
Evolutionary mechanism:

1. **Stress** induced system dynamics – increased stochastic changes
2. Population diversity (**genome heterogeneity**)
3. Natural selection based on **genome** package

Evolutionary Mechanism (1→2→3) =

\sum Individual Molecular Mechanisms

Ye et al, 2009 JCP
Heng et al, 2010 JCB
Heng et al, 2011, Adv Can Res



Lessons from Cancer Research

Genome instability (rather than specific gene mutations) is the key for complex disease and illness

Monitoring stochastic genome alteration can measure the genome instability

Stress can cause genome instability, and the altered genomes are the materials for somatic cell evolution-potential for diseases

Answer #3:

We need to study the **stress** induced **stochastic genome alteration** within the framework of somatic cell **adaptation/evolution**

Hypothesis for GWI

- Various war specific stresses induce genome instability (different causative factors lead to illness)
- Unstable genome stochastically impact different pathways/biological systems
- Patients display diverse symptoms (progress and response to treatment differs)

It is already known

Various stress (genetic and non-genetic alike) induce NCCAs (stochastic chromosomal aberrations) in vitro and animal model of cancer

Altered genome determines a specific transcriptome (interactive gene expression)

This demands investigation

Genome of GWI patients display unstable genome

Outlines of Procedure

- Collect blood and cell culture
- Chromosomal Preparation
- SKY (spectral karyotyping) or cytogenetic analysis
- Data collection (score frequencies of NCCAs, the non clonal chromosome aberrations; and record specific chromosomal alterations)
- Data analysis

Spectral karyotyping: SKY

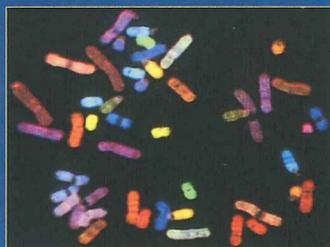
Components

1. CCD camera
2. Interferometer
3. SKY filter
4. Computer
5. Microscope
6. SkyPaint
7. Camera controller
8. OPD Scanner controller
9. Monitor

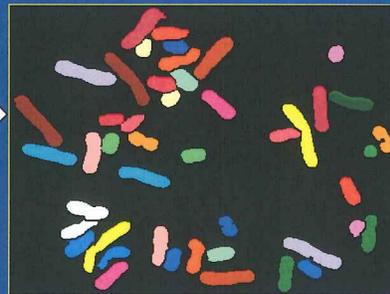


Image Analysis

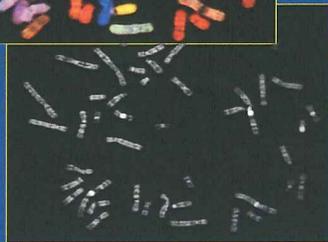
Every pixel is assigned a unique classification color



Display Image

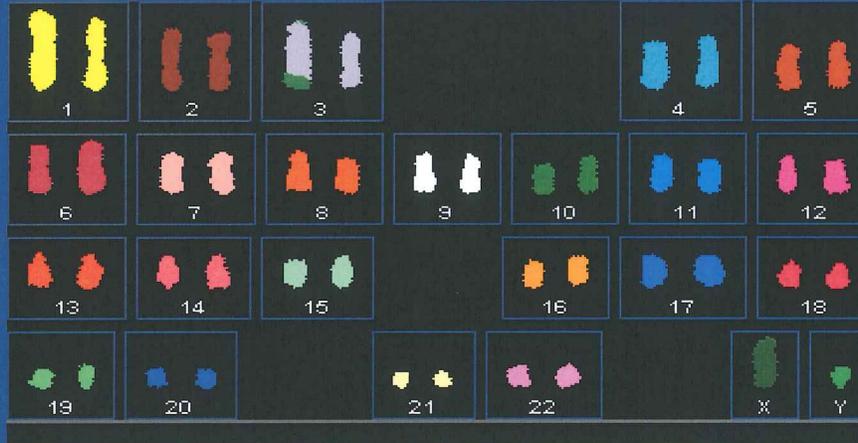


Classified Image

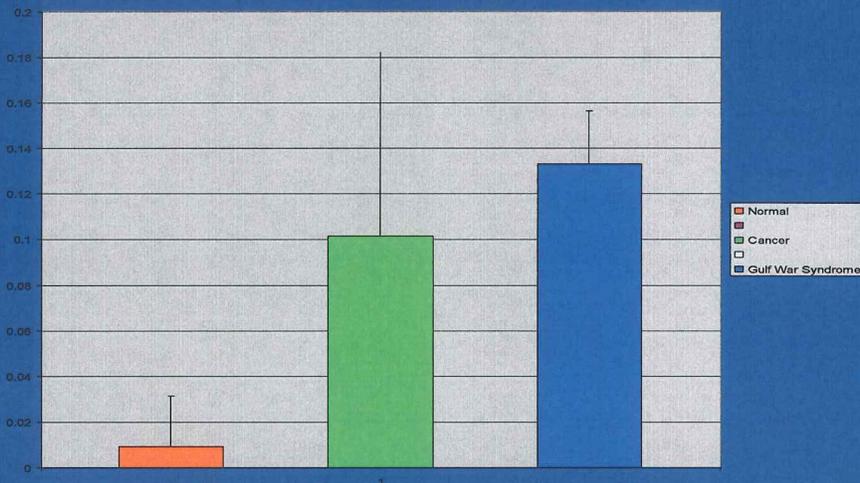


DAPI Image

SKY karyotyping to trace all CCAs (clonal) and NCCAs (non clonal)

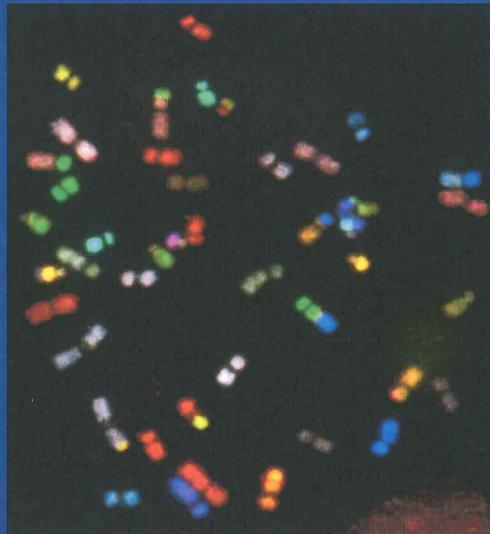


NCCAs levels normal: Cancer: GWI



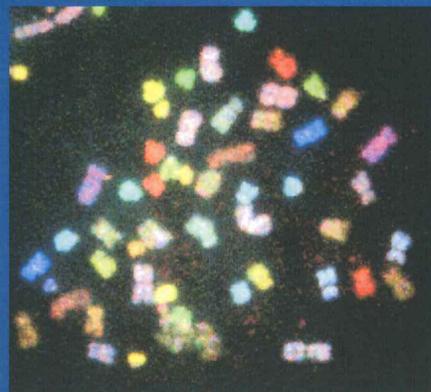
5 GWI patients from test for Discovery Channel program 2007

Examples of multiple translocations

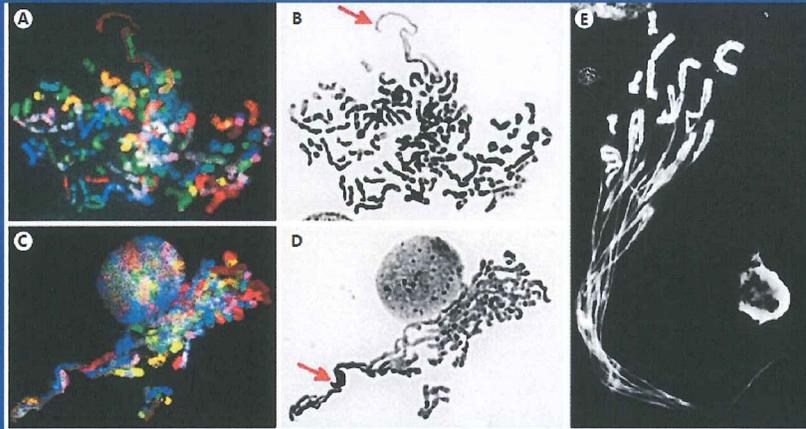


From individual
whose NCCA is over 40%

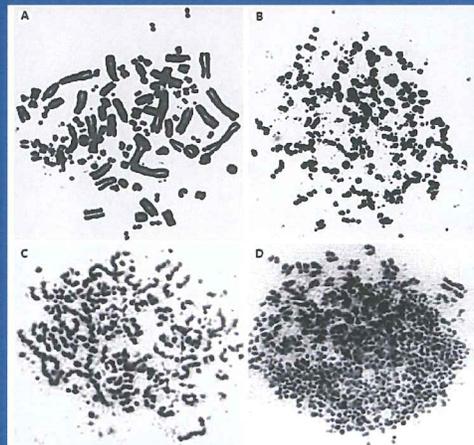
Example of chromosome condensation defects



Following types of NCCAs are also detected from GWI



Chromosome fragmentation



Chromosome fragmentation

A new form of cell death and chromosome aberrations

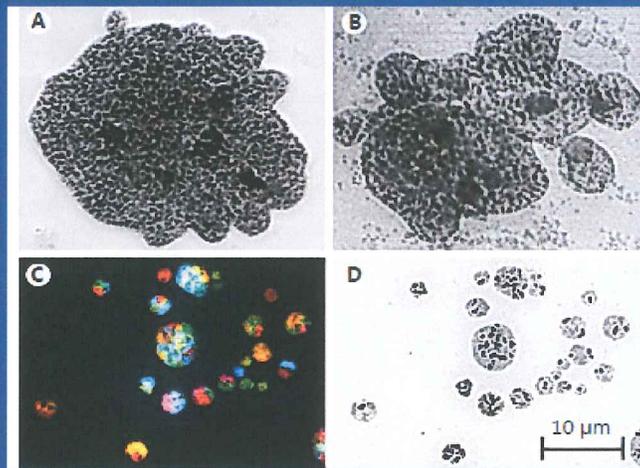


Under stress, cell death occurs
But also generate new genomes for further somatic cell evolution

Clinical implications?

Stevens et al, 2007 Cancer Res 67: 7686-94

Micro-nuclei



Thanks!

Saroj Chowdhury M.D. (VA)

Steve Bremer M.D.
Joshua Stevens Ph.D.
Guo Liu M.S.
Steven Horne M.S.
Batoul Abdallah M.S.
Karen Ye M.D.

Grants from the DOD (GW093028),
The National CFIDS Foundation,
The Nancy Taylor Foundation for
Chronic Diseases