



*RIKEN Europe Office Anniversary symposium:  
Cutting-edge STI to shape the future society, 2 December, 2019*

# **KI-RIKEN Collaboration: Problems from biomedicine, solutions from advanced genomics**

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A photograph of two newborn babies sleeping peacefully in a woven basket. The basket is lined with a thick, shaggy, cream-colored wool rug. The babies are wrapped in a brown, textured cloth. The background is a dark, rustic wooden surface. The text is overlaid in white, bold font.

**3 kg of cells in a healthy baby**  
**50-80 years later: 70 kg ( $\approx 37,000,000,000,000$ )**  
**cells with advanced disease processes**

The image shows two elderly men sitting side-by-side on a brown sofa. Both men are wearing white shirts and dark patterned ties. They are holding white teacups. The man on the left is wearing a plain white shirt, while the man on the right is wearing a white shirt with thin vertical stripes. The background is a light-colored wall with a framed picture. The text 'Celebrating 80 years' is overlaid in white on the top part of the image. A large semi-transparent grey box in the center contains the main title and subtitle in white text. At the bottom, another semi-transparent grey box contains the names of the men and the image credit.

**Celebrating  
80 years**

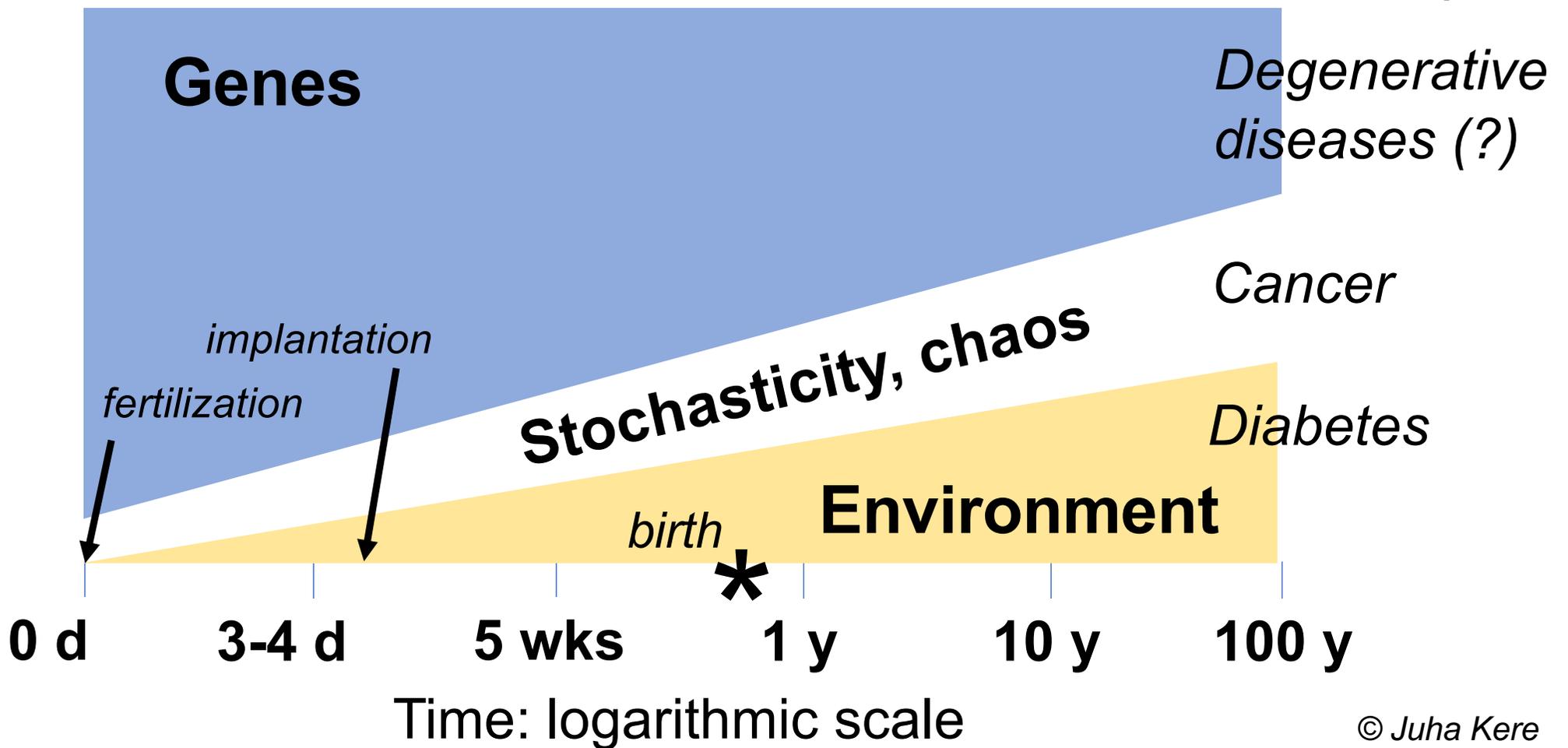
***How to ensure healthy ageing  
and prevent common diseases?  
A common theme for the EU and Japan***

**Mauno and Paavo Hakala (image credit: ET-lehti, Finland)**

# Genes, the environment, and chaos

(personal view)

*Disease examples*



# Understanding genetics: **GWAS** studies in complex disorders

≈ 8,000 studies,  
over 160,000  
significant ( $5 \times 10^{-8}$ )  
associations  
(21 November 2019)



<http://www.ebi.ac.uk/gwas/diagram>

# Many GWAS hits involve *enhancers*

ARTICLES

<https://doi.org/10.1038/s41588-017-0014-7>

nature  
genetics

## Meta-analysis of asthma GWAS

≈ 24,000 cases; 119,000 controls

### Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks

We examined common variation in asthma risk by conducting a meta-analysis of GWAS studies (23,948 asthma cases, 118,538 controls) of individuals from ethnically diverse populations. We identified new asthma risk loci, found two new associations at two known asthma loci, established the comorbidity of asthma plus hay fever, and confirmed nine known overlaps in genetic variants with autoimmune and inflammatory diseases. The results suggest a major role of these loci in the regulation of immune cells, especially in immune cells, suggested a major role of these loci in the regulation of immune cells.

*The exact functions of enhancer elements are largely unknown. Many of them are gene-specific, some act on multiple genes, and most of them are tissue-specific.*

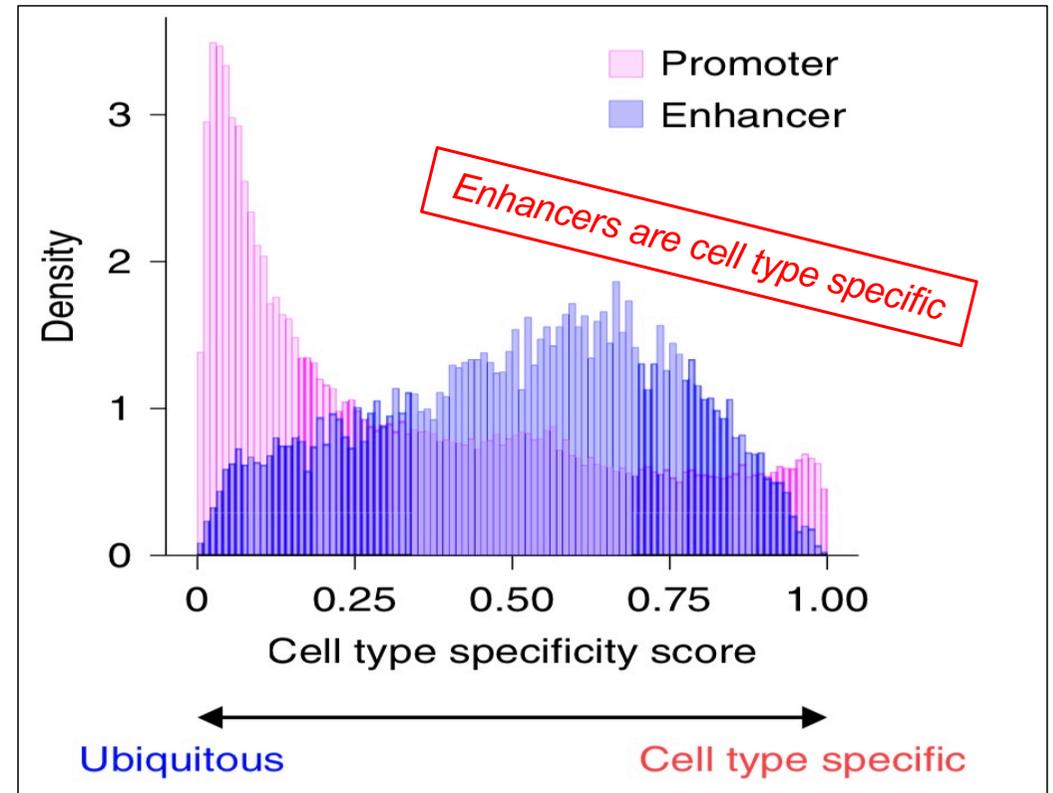
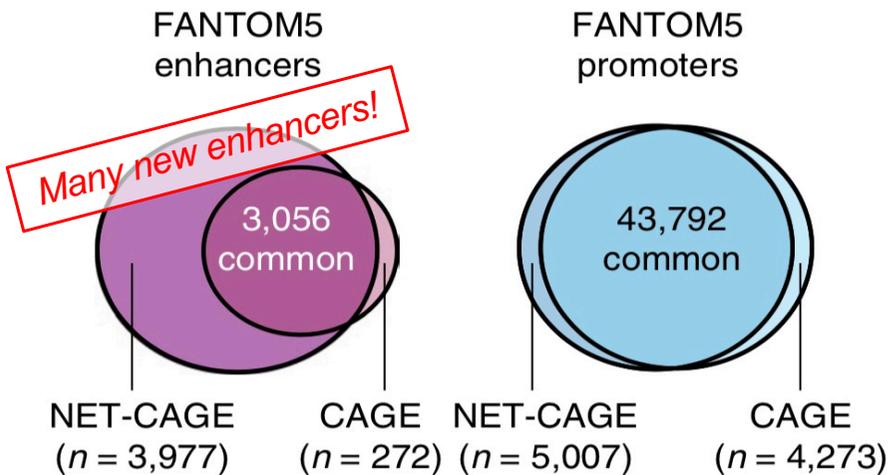
Type of regulatory elements	Proportion of all cell types (blood cell types) showing enrichment with a given FDR	
	FDR ≤10%	FDR ≤5%
All promoter states	6% (26%)	0
Active promoter states	13% (33%)	0
All enhancer states	57% (100%)	44% (89%)
Active enhancer states	66% (100%)	50% (100%)
DNase I-hypersensitive sites	16% (50%)	12% (40%)

Deménais F & al. *Nat Genet* 50:42, 2018

# Understanding gene regulation: Finding enhancer elements

## NET-CAGE characterizes the dynamics and topology of human transcribed *cis*-regulatory elements

Shigeki Hirabayashi<sup>1,2,3,14</sup>, Shruti Bhagat<sup>3,4,14</sup>, Yu Matsuki<sup>3,5,14</sup>, Yujiro Takegami<sup>3,5</sup>, Takuya Uehata<sup>6,7</sup>, Ai Kanemaru<sup>5</sup>, Masayoshi Itoh<sup>8</sup>, Kotaro Shirakawa<sup>2</sup>, Akifumi Takaori-Kondo<sup>2</sup>, Osamu Takeuchi<sup>6,7</sup>, Piero Carninci<sup>3</sup>, Shintaro Katayama<sup>4</sup>, Yoshihide Hayashizaki<sup>8</sup>, Juha Kere<sup>4,9,10,11</sup>, Hideya Kawaji<sup>3,8,12\*</sup> and Yasuhiro Murakawa<sup>1,3,8,13\*</sup>



Hirabayashi S & al. *Nature Genet* 51:1369, 2019

# The future of genomic medicine

*(personal view)*

- ✓ Predictive genetic markers will not be generally useful in common, complex diseases of public health importance (the problem: they are **static**, not reflecting disease processes)
- ✓ Instead, **dynamic gene tests** will find clinical utility in population screening approaches — e.g., early cancer detection by liquid biopsies (cell-free DNA testing)
- ✓ To understand disease mechanisms, we need to understand **cell-specific enhancer functions** — need for collaboration
- ✓ The study of rare and common allele effects on phenotypes will help pharma in **selecting drugs for clinical trials**