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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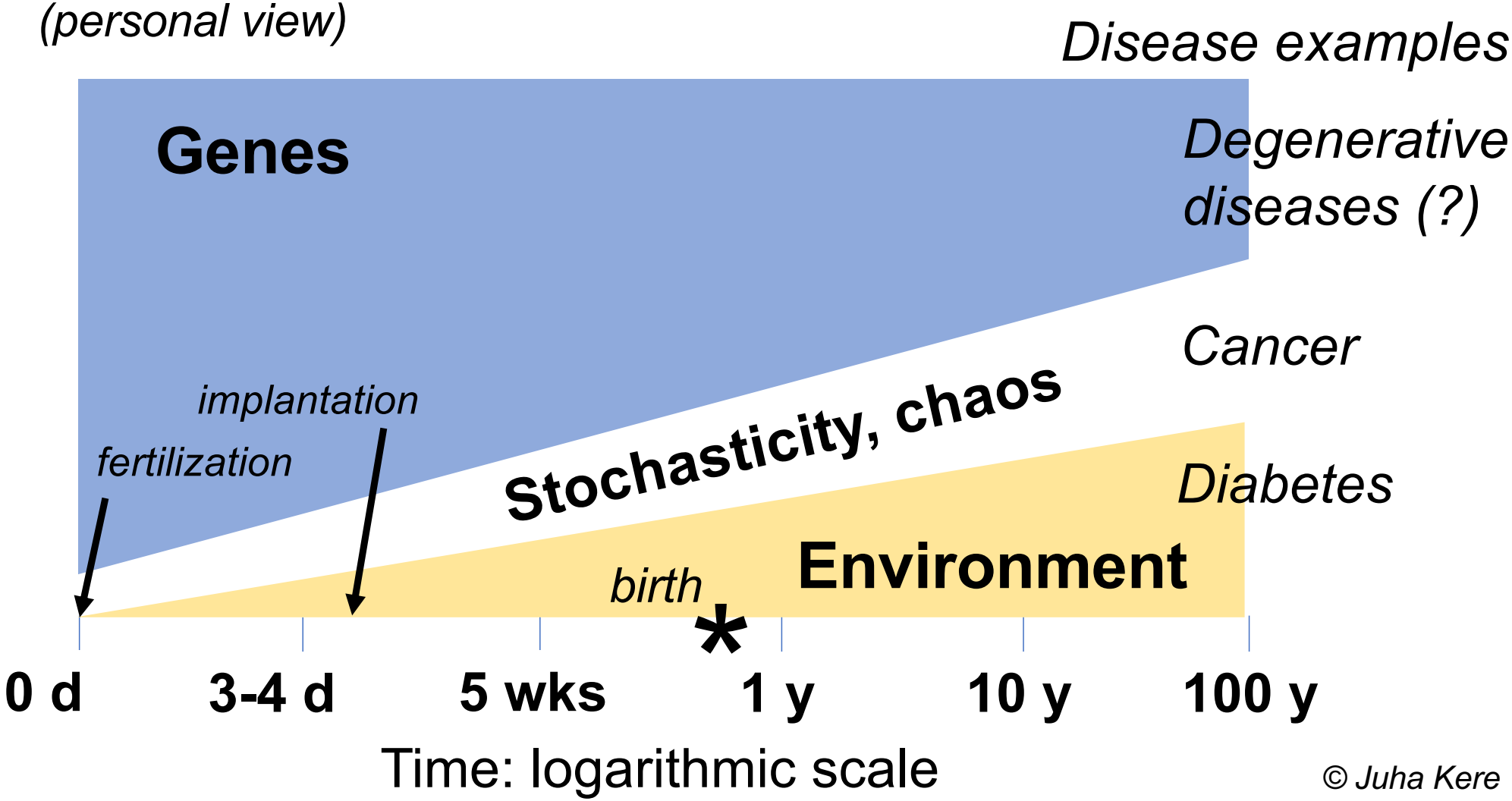
3 kg of cells in a healthy baby
50-80 years later: 70 kg (≈ 37,000,000,000,000)
cells with advanced disease processes
Image:pixabay.com


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)



Understanding genetics: GWAS studies in complex disorders

≈ 8,000 studies, over 160,000 significant (5×10^{-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

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 c studies (23,948 asthma cases, 118,538 controls) of individuals from ethnicall asthma loci, found two new associations at two known asthma loci, establish implicated in the comorbidity of asthma plus hay fever, and confirmed nine know overlaps in genetic variants with autoimmune and inflammatory diseases. The loci, especially in immune cells, suggested a major role of these loci in the regul

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

Meta-analysis of asthma GWAS

≈ 24,000 cases; 119,000 controls

	Proportion of all cell types (blood cell types) showing enrichment with a given FDR	
Type of regulatory elements	**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%)

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

Understanding gene regulation: Finding enhancer elements

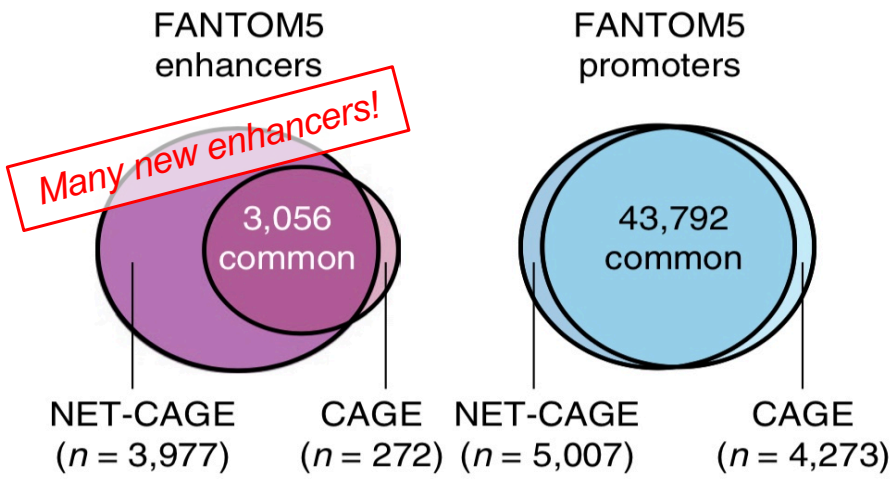
nature genetics

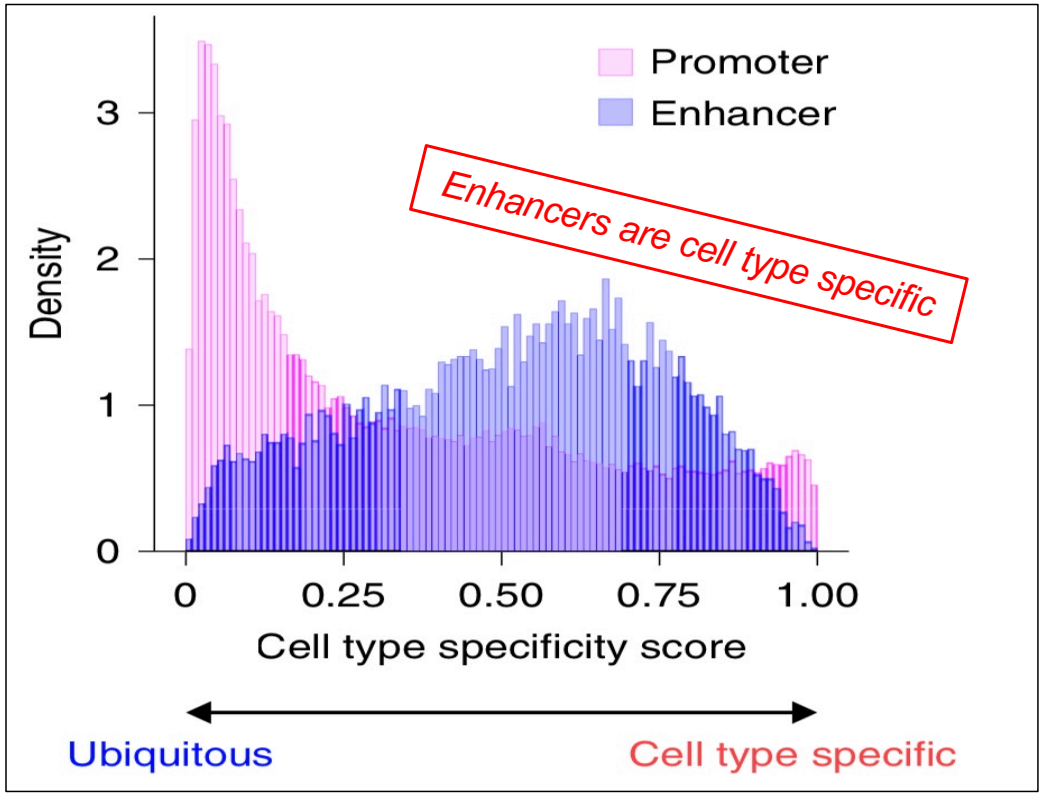
ARTICLES

https://doi.org/10.1038/s41588-019-0485-9

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

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





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**