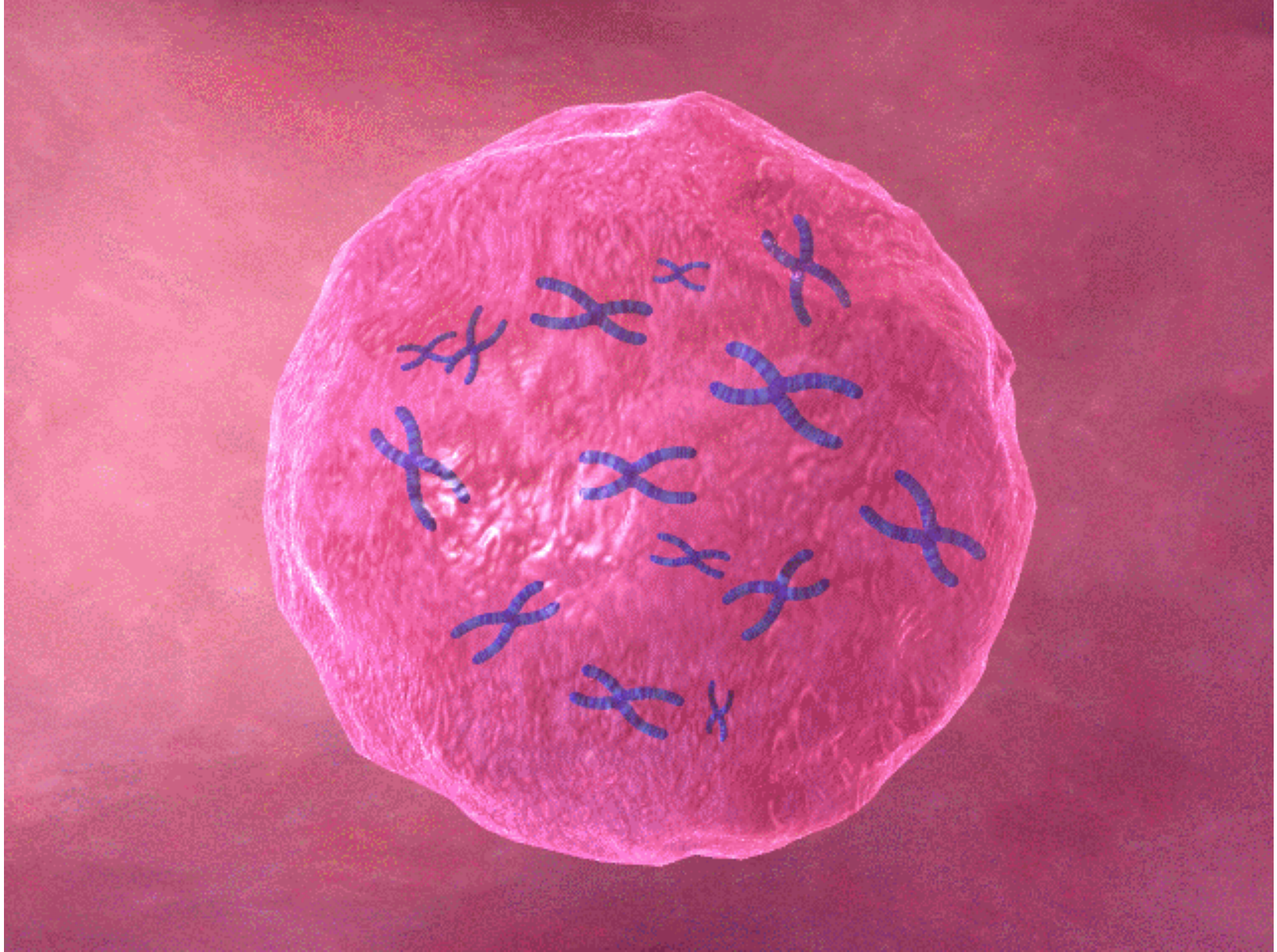
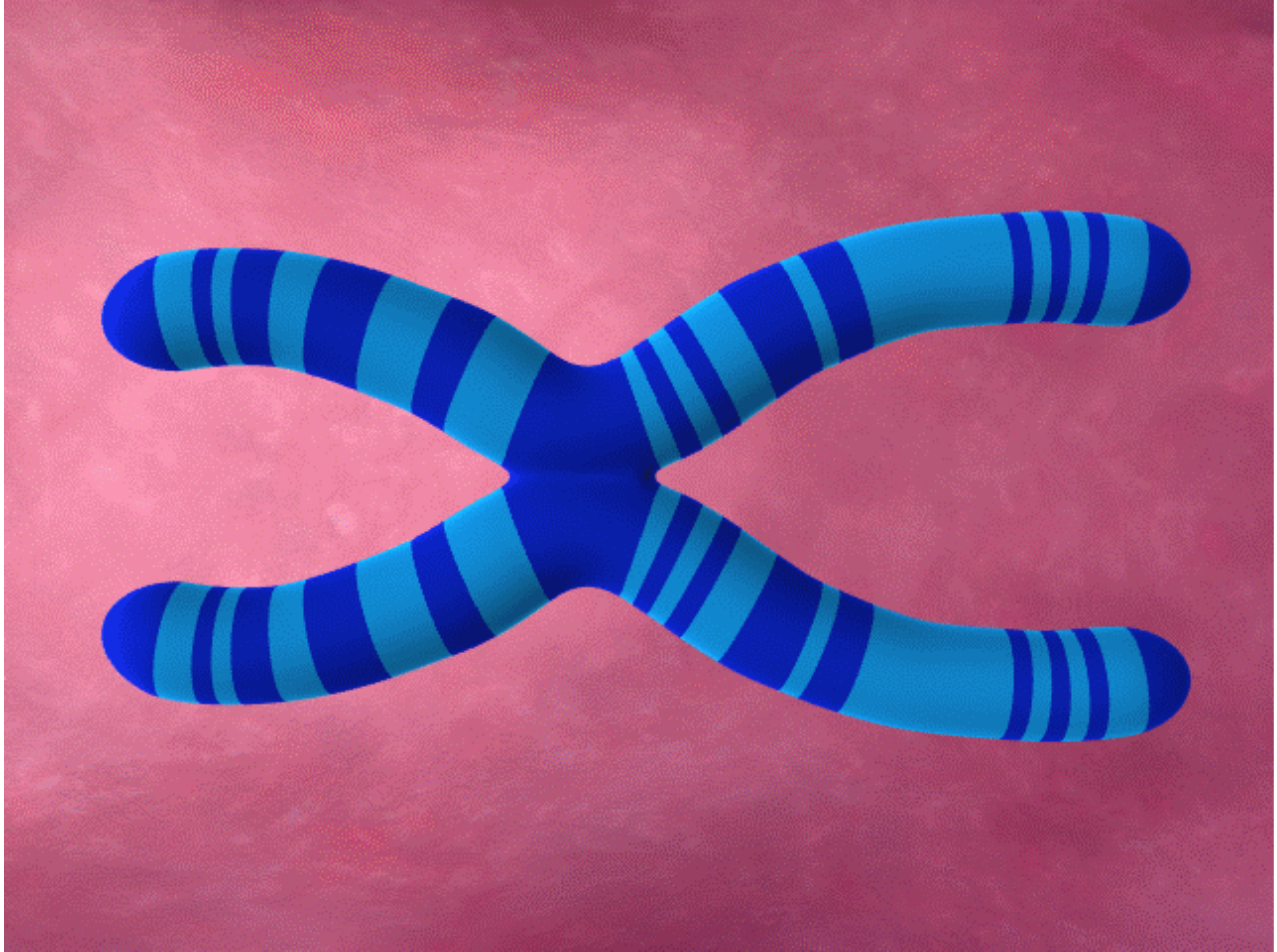
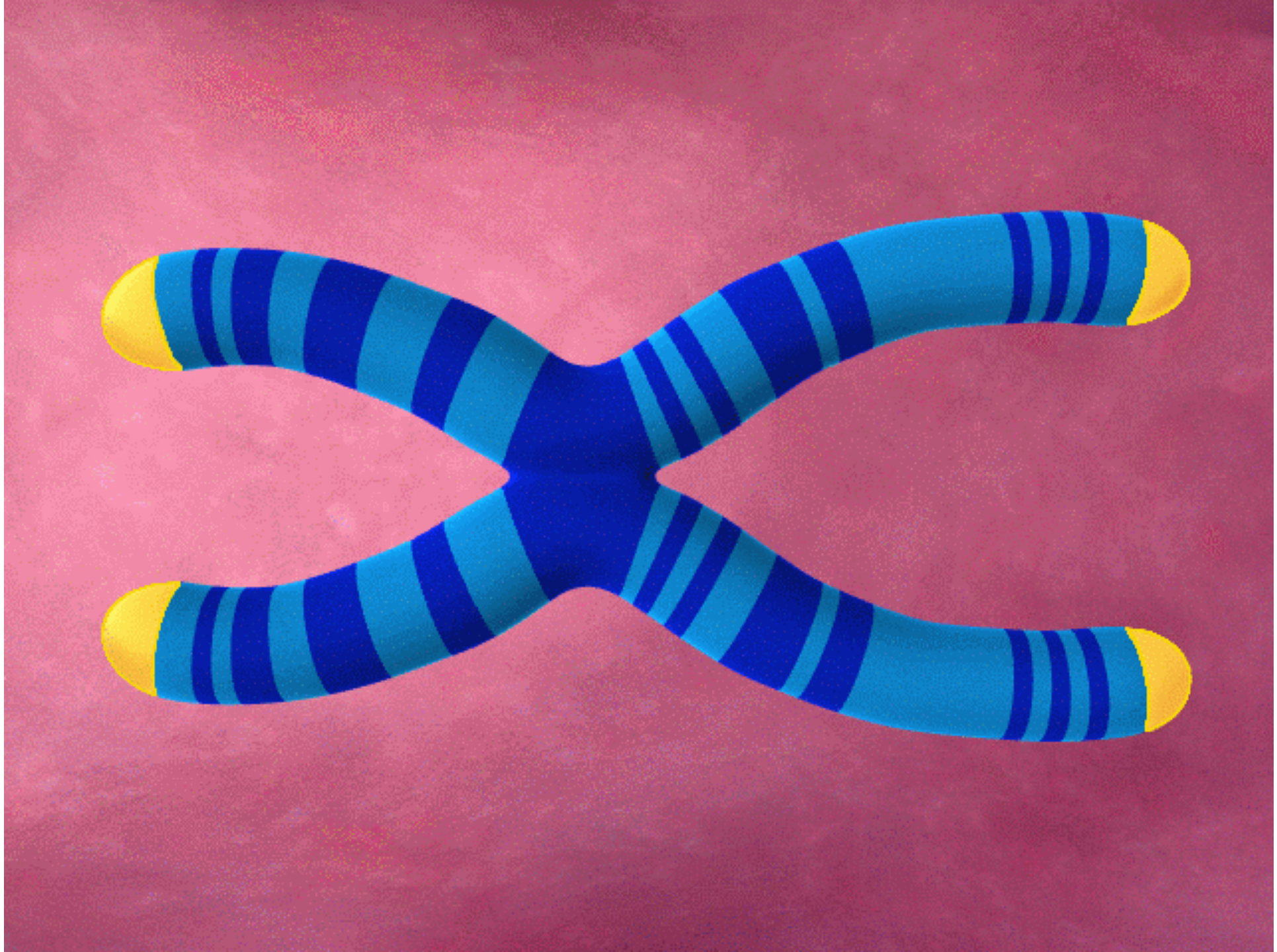
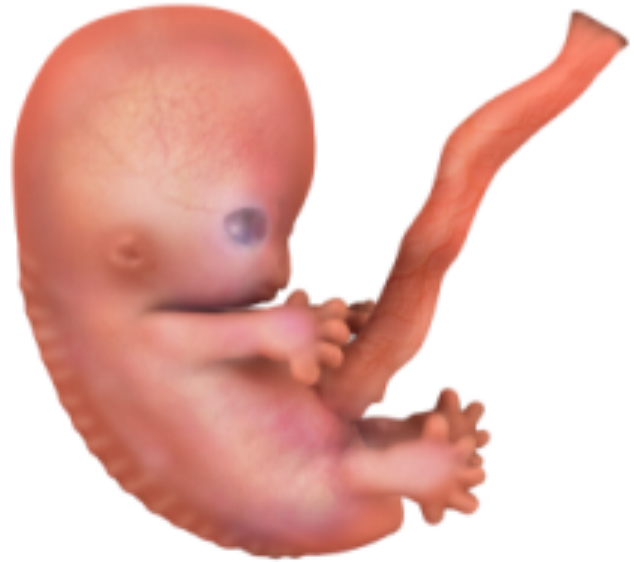


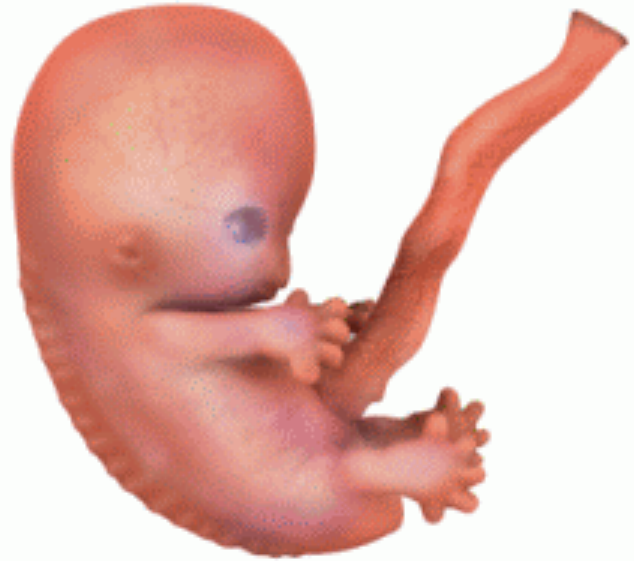




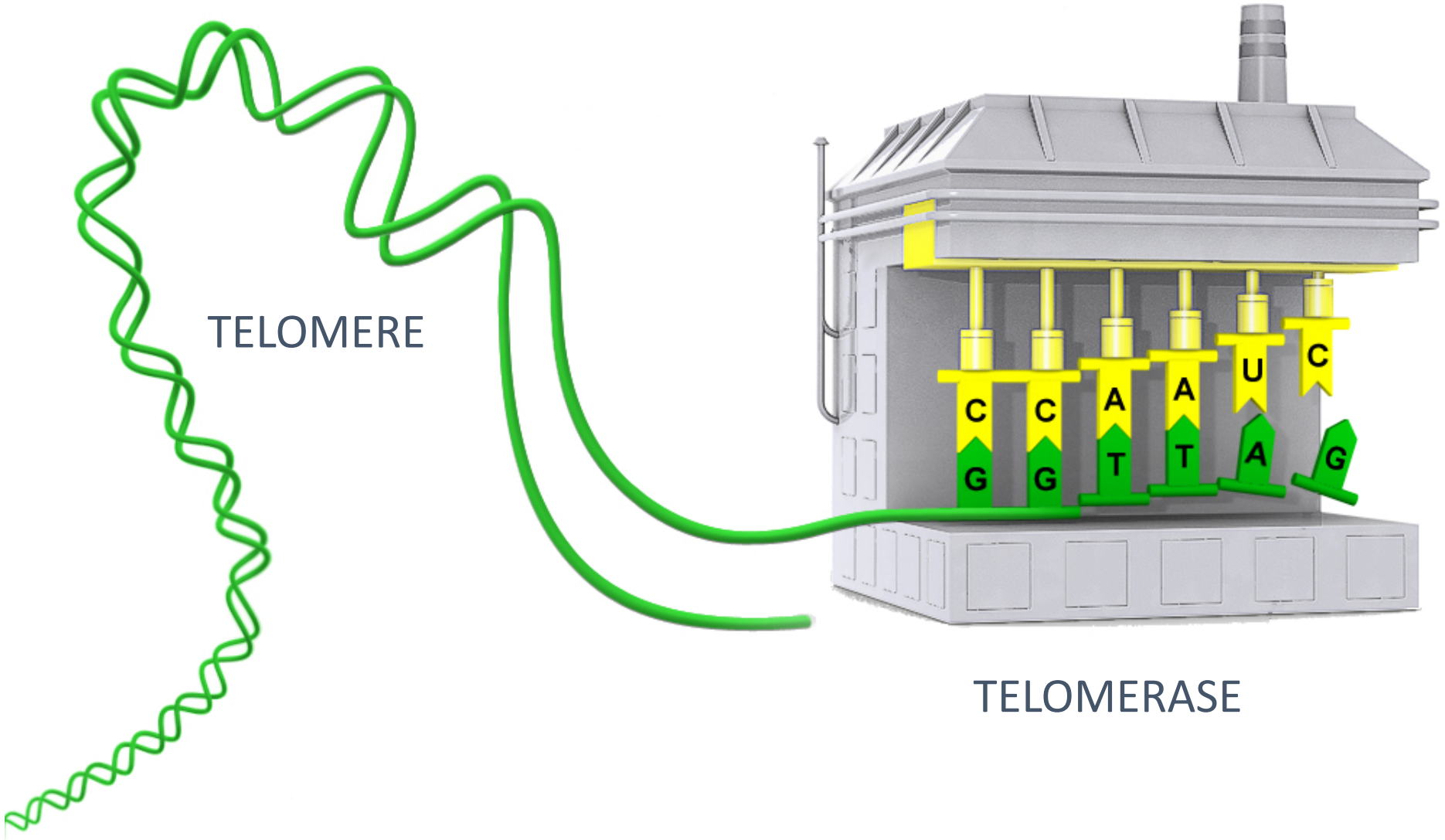
Telomere



Telomere



Telomerase Lengthens Telomeres



Confirmed by 100's of Subsequent Peer Reviewed Studies

Scientific Peer Reviewed Studies

Confirmed by Zero Subsequent Peer Reviewed Studies

Immortalization of Human CD8$^+$ T Cell Clones by Ectopic Expression of Telomerase Reverse Transcriptase[1]

Erik Hooijberg,[2]* Janneke J. Ruizendaal,[2]* Peter J. F. Snijders,† Esther W. M. Kueter,* Jan M. M. Walboomers,† and Hergen Spits[3]*

Replicative senescence of T cells is correlated with erosion of telomere ends. Telomerase plays a key role in maintaining telomere length. Therefore, it is thought that telomerase regulates the life span of T cells. To test this hypothesis, we have over-expressed human telomerase reverse transcriptase in human CD8$^+$ T cells. Ectopic expression of human telomerase reverse transcriptase led to immortalization of these T cells, without altering the phenotype and without loss of specificity or functionality. As the T cells remained dependent on cytokines and Ag stimulation for their in vitro expansion, we conclude that immortalization was achieved without malignant transformation. ***The Journal of Immunology,*** **2000, 165: 4239–4245.**

The ends of linear eukaryotic chromosomes, which are called telomeres, consist of DNA-protein complexes ending in a large duplex loop (1). They serve to maintain chromosomal integrity and prevent end-to-end fusion of the chromosomes. Telomere length is not constant over time. The telomeric ends have a length of 5–15 kb in humans and shorten by 50–100 bp per cell division in normal somatic cells (2, 3). When telomeric ends get too short, cells will enter a state of replicative senescence followed by crisis and cell death. Thus, telomere shortening may prevent unlimited proliferation of human somatic tissues. Telomere shortening is counteracted by the ribonucleoprotein enzyme complex called telomerase, which has two key components, the telomerase reverse transcriptase (TERT)[4] and telomerase RNA, which is used as a template to elongate telomeric ends (for reviews see Refs. 4–6). The crucial role of human (h)TERT in maintaining telomeric length and subsequently of the replicative life span of cells has been demonstrated recently. It has been documented that ectopic expression of hTERT, in cell types without endogenous expression of hTERT, led to elongation of the telomeres and to an increased life span of foreskin fibroblasts, retinal pigment epithelial cells, and endothelial cells (7–9), indicating that hTERT by itself regulates the life span of these cell types. In other cases, however, ectopic expression of hTERT was not sufficient and had to be accompanied by an inactivated Rb/p16^{INKa} pathway to give similar effects in human mammary epithelial cells and foreskin keratinocytes (10)

A correlation between telomere shortening and life span has also been found in cells of the immune system. It was reported that the average telomeric length and the replicative potential are higher in naive T cells as compared with memory T cells from the same donor, in both CD4$^+$ cells (11, 12) and CD8$^+$ cells (13, 14). These findings are consistent with two ex vivo studies with peripheral blood leukocytes, indicating a correlation between the loss of telomere repeat fragments and the age of the donor (15, 16). Ongoing shortening of telomeres and subsequent induction of replicative senescence in cells of the immune system occur despite the presence of endogenous hTERT in T and B cells (17, 18). The levels of telomerase activity in peripheral blood T and B lymphocytes are regulated at the level of hTERT transcription (19–22), but post-transcriptional mechanisms may also play an important role in the control of the function of the enzyme (23). Activation of T cells by strong stimuli like PMA and ionomycin (20), but also milder stimulation by a combination of CD3 and CD28 Abs (19, 24) or by the cognate Ag presented by the appropriate target cell (25), can induce a transient expression of telomerase. Recently, it was shown that telomerase is up-regulated and telomere length is preserved after virus-induced clonal expansion of CD8$^+$ T cells (26). Despite the endogenous expression and activation induced up-regulation of hTERT in subsets of human T cells, presumably resulting in maintenance of replicative potential in vivo (18), Ag-specific T cell clones cannot be expanded in vitro beyond 20–25 population doublings (PD; reviewed in Ref. 17). This finding raises the question whether the replicative life span of T cells is solely regulated by

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Meta-Analysis of Scientific Peer Reviewed Studies Versus Hearsay Analysis

For More

Watch

People Unlimited's Spring Celebration 2016

Dr. Bill Andrews: "What's Real and What's Not" - YouTube

Hearsay:	Human Stem Cells Produce Telomerase
Meta-Analysis:	Only Human Embryonic Stem Cells Produce Enough Telomerase to Affect Telomere Length

Hearsay:	Aging Works the Same in All Life Forms
Meta-Analysis:	Only Humans, Some Non-Human Primates, Dogs, Cats, Horses, Sheep, Pig, and Deer have been Shown to Age by Telomere Shortening. All Rodents and Lemurs Age by Different Means. Some Animals have No Detectible Aging.

Hearsay: PAPD5 Inhibitors Cure Human Aging

Meta-Analysis: PAPD5 Inhibitors Cure a Type of Human Aging that Only 9 People in the World Suffer From.

Why All the Hearsay????

Hearsay:

If You Have a Telomeropathy it is Because You Have a Defective Telomerase

Telomeropathy

An Unhealthy Consequence of Short Telomeres

Aging is the most common Telomeropathy,

But not the only Telomeropathy

Telomeropathies

- AIDS
- Alzheimer's
- Cancer
- Cardiovascular
- Cell & Tissue Transplants
- COPD
- Cri du Chat syndrome
- Degenerative Disc Disease
- Down's Syndrome
- Dyskeratosis Congenita
- Fanconi's Anemia
- General Immunity
- Idiopathic Infertility
- Idiopathic Pulmonary Fibrosis
- Liver Cirrhosis
- Macular Degeneration
- Muscular Dystrophy
- Osteoarthritis
- Osteoporosis
- Progeria
- Recurrent Pregnancy Loss
- Rheumatoid Arthritis
- Skin Aging
- Tuberous Sclerosis
- Werner's Syndrome
- And, Aging Itself

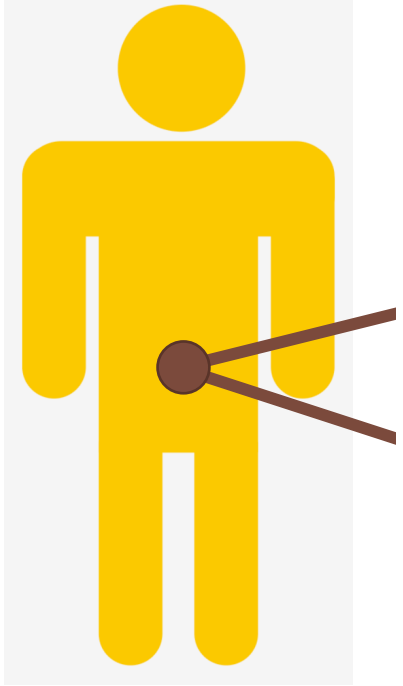
Hearsay:	If You Have a Telomeropathy it is Because You Have a Defective Telomerase
Meta-Analysis:	If You Have a Telomeropathy it is Because One of Your Parents Had a Defective Telomerase

When is Telomerase Active?

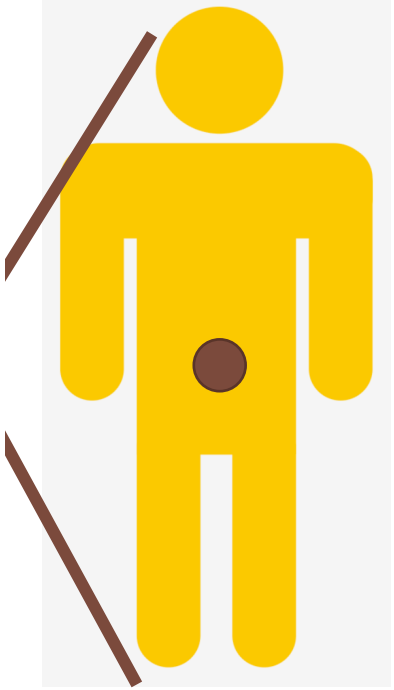
Telomerase^{+}

Telomerase^{-}

A Defective Telomerase Here



Causes Short Telomeres Here

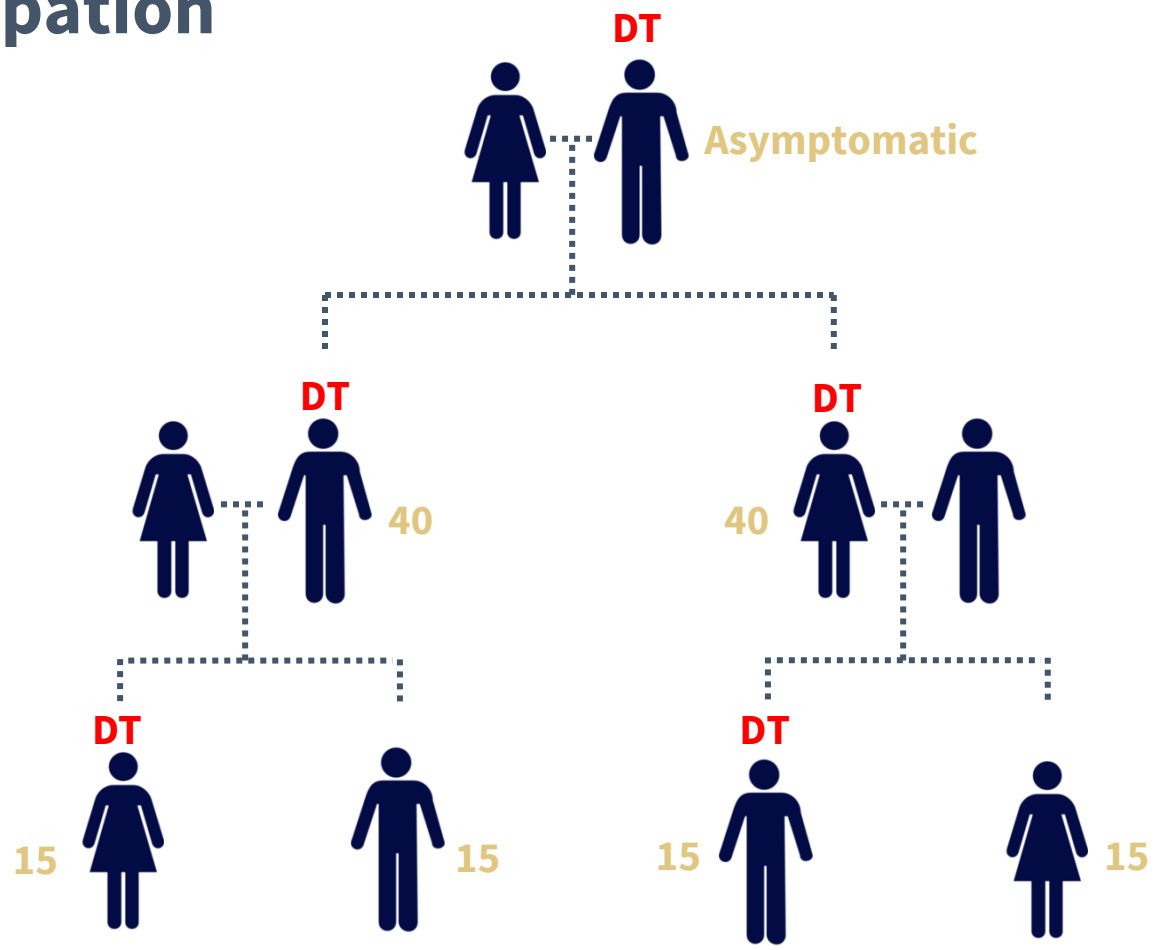


Primordial Germ Cells

Telomerase^{+}

Telomerase^{-}

Diseases of Anticipation



DT = Defective Telomerase

Research in The Netherlands

PULMONARY FIBROSIS AND A TERT FOUNDER MUTATION
WITH A LATENCY PERIOD OF 300 YEARS.

van der Vis JJ, van der Smagt JJ, Hennekam FAM, Grutters JC, van Moorsel CHM

Chest. 2020 Apr 18. pii: S0012-3692(20)30712-1


Jan Grutters
Joanne van der Vis
Coline van Moorsel

Chest. 2020 Apr 18. pii: S0012-3692(20)30712-1

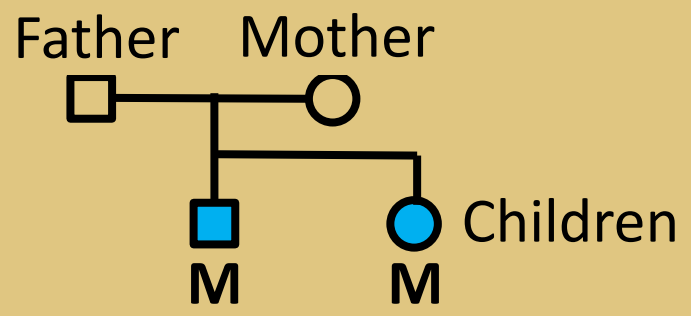
Disease of Anticipation

300 Years Ago

<-M->

Blue = Idiopathic Pulmonary Fibrosis
M = Telomerase Mutation

Parents did not have Idiopathic Pulmonary Fibrosis
It's unknown if they had the Telomerase Mutation



Chest. 2020 Apr 18. pii: S0012-3692(20)30712-1

To Understand an Inherited Disease Scientists Need to Look at More than Just the Patient's Genetics

A Patient Can Have Ideal Genes
But Still Suffer from a Disease
Because an Ancestor
Had a Genetic Mutation

Such Diseases are Called "Diseases of Anticipation"

And, Lengthening Telomeres is the Cure

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Thank you