

Paternal Sperm Telomere Elongation and Its Impact on Offspring Fitness ^[1]

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Telomeres are structures at the ends of DNA strands that get longer in the DNA of [sperm](#)^[2] cells as males age. That phenomenon is different for most other types of cells, for which telomeres get shorter as organisms age. In 1992, scientists showed that [telomere](#)^[3] length (TL) in [sperm](#)^[2] increases with age in contrast to most cell of most other types. Telomeres are the protective caps at the end of DNA strands that preserve chromosomal integrity and contribute to DNA length and stability. In most cells, telomeres shorten with each cell division due to incomplete replication, though the enzyme telomerase functions in some cell lines that undergo repetitive divisions to replenish any lost length and to prevent degradation. Cells, and therefore organisms, with short telomeres are more susceptible to mutations and genetic diseases. While TL increases in a subset of [sperm](#)^[2] cells and longer telomeres may prevent early disintegration of DNA, it may also prevent natural mechanisms of [apoptosis](#)^[4], or cell death, from occurring in abnormal [sperm](#)^[2].

Research on telomeres started in the 1980s, with Elizabeth Blackburn, Carol Greider, and Jack Szostak, who contributed to a wide array of fields, ranging from [senescence](#)^[5], or aging, to cancer studies and prenatal development. During that time Blackburn and her team researched telomeres and telomerase at the Sidney Farber Cancer Institute in Boston, Massachusetts, at the Harvard Medical School in Boston, and at the University of California Berkeley in Berkeley, California. For their research on telomeres, Blackburn and her team earned the 2009 Nobel Prize in Physiology or Medicine.

Since then, scientists have used embryonic and prenatal experiments to study how telomeres preserve chromosomal integrity. When cells replicate, telomeres shorten because of DNA synthesis, which requires short strands of nucleic acids called RNA primers. Enzymes lengthen the RNA primers to form Okazaki fragments, or short strands of DNA, which enzymes combine to become one continuous strand. The RNA primers, however, occupy a certain space on the DNA template and once they are removed, there is a gap at the end of the DNA. This phenomenon, called the end-replication problem, creates loss of genetic material that cells counteract by producing telomerase to repair [telomere](#)^[3] ends.

If a male sires offspring via those of its [sperm](#)^[2] cells that have long telomeres, then those offspring will inherit DNA with long telomeres. Scientists hypothesized that TL's heritability, demonstrated initially through studies of twins, relates to the role of telomerase in counteracting the end-replication problem of DNA. While researchers in the late twentieth and early twenty-first centuries studied maternal influences on developing oocytes, paternal effects of [sperm](#)^[2] on development remained unclear. For example, scientists found that mRNA, a molecule that conveys genetic information through the cell, comes from the [egg](#)^[6], and not from the [sperm](#)^[2]. But some scientists began to study how non-genetic factors in [sperm](#)^[2] cells affected the [viability](#)^[7] of fertilized eggs.

In 1992, Richard Allsopp and his research team at McMaster University in Hamilton, Canada, found that [sperm](#)^[2] telomeres do not decrease with age like their somatic (body) cell counterparts. That research indicated that a mechanism involving telomerase or some other substance protects germ-line cells. Scientists said that heredity, age, and gender can influence TL, but significant variability in [telomere](#)^[3] length across the human population indicated that some other factors could be involved. In 2005, Brad Unryn and colleagues at the University of Calgary in Calgary, Canada, further demonstrated that there is a positive correlation between TL and increased paternal age. They hypothesized that such a phenomenon could account for the large range of TL observed throughout the human population, especially if paternal contribution to TL is cumulative over generations.

As a genetic mechanism, the specifics behind [sperm](#)^[2] TL elongation remained elusive into the second decade of the twenty-first century, even as its implications in development were established. In 2007, Tim De Meyer and his colleagues in Ghent, Belgium, further corroborated the results of Unryn and his team by analyzing 2,433 volunteers, half male and half female. De Meyer and his team compared information on the volunteers' [telomere](#)^[3] lengths to statistical information of their parents' ages at [conception](#)^[8] and the current ages of the volunteers. De Meyer showed that older fathers' ages at [conception](#)^[8] were positively associated with longer TL in their children. De Meyer's study provided a quantitative gain of seventeen additional base pairs in TL for each additional year of age in the father. Furthermore, differences in TL between daughters and sons were insignificant, contradicting earlier hypotheses that TL varied with gender. The results confirmed the hypothesis that [sperm](#)^[2] contributed to TL variance and demonstrated that TL is not completely reset during embryonic development in the [zygote](#)^[9], but rather it can be inherited from father to child.

Later in 2008, Masayuki Kimura from New Jersey Medical School in Newark, New Jersey, and his team later confirmed De Meyer's work, by demonstrating that a father's age positively correlates with his children's leukocyte (white blood cell) TL. Kimura's study was conducted in four distinct populations, and the researchers found that children's leukocyte TL increased

anywhere from half-fold to twofold with each additional year of their father's age. Some hypothesized that [sperm](#)^[2] [telomere](#)^[3] elongation in older men and its potential effect on offspring's leukocyte TL potentially increased longevity and lessened age-related disorders in offspring of older fathers.

In 2010, Katarina Nordfjäll and her colleagues at Umeå University in Umeå, Sweden, further demonstrated that a child's TL correlated more with his or her father's TL than with his or her mother's TL. In Nordfjäll's study, there appeared to be no statistical difference in TL length due to the gender of the father's offspring, and the researchers observed correlations in TL length between grandfathers and grandchildren. Those associations over multiple generations supports the hypothesis that [sperm](#)^[2] TL contributes to population-wide TL variability due to paternal inheritance. The 962 individuals examined in Nordfjäll's study also demonstrated diminishing father-child correlations over time, which indicates that environmental or non-genetic factors such as oxidative stress can influence TL fluctuations throughout an organism's lifetime.

While scientists largely accepted the correlation between a father's [sperm](#)^[2] TL and his child's TL after those studies, the implications of a longer TL for biological fitness of the child remained unclear. Longer TL is often a positive trait in most cells. However, aging can negatively affect genomic stability when mutations accumulation and other lifestyle factors counteract the positive benefits of having longer telomeres. In 2009 Silvia García-Palomares and colleagues demonstrated that older paternal ages at [conception](#)^[8] have negative effects on offspring [viability](#)^[7] in mice. The scientists individually housed male mice at a variety of different ages with female mice that were all the same age. They monitored the resulting offspring for two generations, which they respectively called F1 and F2. F1 females from older fathers had longer intervals between births indicating reduced fertility, and F2 generation mice had lower weaning weights overall. F1 mice also displayed shorter lifespans accompanied by a lower incidence of tumor development due to early death, and decreased body weights at death.

In 2010, Gideon Sartorius and Eberhard Nieschlag at the University of Domagkstrasse, in Muenster, Germany, published a literature review in which they concluded that older paternal age at [conception](#)^[8] negatively influences the overall fitnesses of offspring. Beyond [telomere](#)^[3] interactions, increased age in males correlates with decreased sexual activity, [infertility](#)^[10], increasing [miscarriage](#)^[11] rates, and deflated male [hormones](#)^[12], such as testosterone, in the body. Sartorius and Nieschlag state that if paternal TL's effect on offspring TL does contribute somehow to offspring fitness, researchers must consider that other factors might be involved in the impact paternal [sperm](#)^[2] age has on [conception](#)^[8]. According to the authors of the study, if researchers specify whatever positives there are for offspring that have longer than normal TL, they may increase longevity for those of future generations and provide a better quality of life in a society that is gradually having children at older ages.

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