Age-related alterations in the genetics and genomics of the male germ line

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Paternal aging is associated with increased risk of genetic disease transmission to the offspring. The changes associated with aging arise predominantly through formation of single nucleotide variation through DNA replication errors, as well as possibly chronic exposure to environmental toxins and reactive oxygen species exposure. Several age-related reproductive factors are also contributory, including the systemic hormonal milieu, accumulation of environmental toxin exposure, aging germ cells, and accumulation of de novo genetic and genomic abnormalities in germ cells. In this article we review the age-related genetic and genomic changes that occur in the male germ line. (Fertil Steril® 2017;107:319–23. ©2017 by American Society for Reproductive Medicine.)
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Over the last 6 decades, couples have delayed marriage and reproduction because of various socioeconomic factors and shifting gender roles in the work force. During this time the median age of fathers at the time of first marriage increased by 25% to the current median age of 29 years (1). Similarly, from 1980 to 2010 the number of men fathering children between the age groups of 35–39 and 40–44 years rose by 48% and 51%, respectively (2). Although the reproductive effects of advancing maternal age are well known, the effects of advancing paternal age are less well studied. However, as increasingly more babies are born to older fathers, interest in studying the implications of advancing paternal age on reproductive outcomes and offspring health has similarly risen.

Multiple studies investigating the association between paternal age and reproductive outcomes concluded that increasing age is associated with impaired semen parameters; fivefold longer time to pregnancy; and reduced fertilization rates, embryo quality, implantation rates, pregnancy rate, and live-born deliveries (3–9). Furthermore, increased paternal age is linked to a broad range of developmental abnormalities (Table 1), such as congenital birth defects and neurologic disorders, and a statistically significant increase in 5-year offspring mortality related to the severity of the congenital malformations, malignancies, and other external causes (11, 12). Several age-related reproductive changes drive these impaired outcomes, including changes to the systemic hormonal milieu, accumulation of environmental toxin exposure, aging germ cells, and accumulation of de novo genetic and genomic abnormalities in germ cells. In this article we review the age-related genetic and genomic changes that occur in the male germ line.

REACTIVE OXYGEN SPECIES AND DNA FRAGMENTATION

For fertilization to take place, spermatozoa require a certain amount of reactive oxygen species (ROS), which are the byproducts of oxygen metabolism and consist of reduced oxygen molecules with chemically reactive unpaired electrons, to undergo biologic functions such as capacitation, hyperactivation, acrosome reaction, and oocyte fusion (13). In addition, ROS modulate nuclear maturation and facilitate nuclear condensation in spermatozoa by oxidizing nuclear proteins (14). Although a certain amount of ROS is

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TABLE 1

Offspring genetic conditions associated with advanced paternal age.

Condition	Paternal age (y)	Relative risk	Population risk	Adjusted risk
Achondroplasia	>50	7.8	1/15,000	1/1,923
Apert syndrome	>50	9.5	1/50,000	1/5,263
Pfeiffer syndrome	>50	6	1/100,000	1/16,666
Crouzon syndrome	>50	8	1/50,000	1/6,250
Neurofibromatosis I	>50	3.7	1/3,000–1/4,000	1/810–1/1,080
Retinoblastoma	>45	3	1/15,000–1/20,000	1/5,000–1/6,667
Down syndrome	40–44	1.37	1/1,200[a]	1/876[a]
Klinefelter syndrome	>50	1.6	1/500 men	1/312 men
Epilepsy	40–45	1.3	1/100	1/77.0
Breast cancer	>40	1.6	1/8.5	1/5.3
Childhood leukemia	>40	1.14	1/25,000	1/21,930
Childhood central nervous system tumor	>40	1.69	1/36,000	1/21,302

Note: Adapted with permission from Ramasamy et al. (10).
[a] Maternal age 20–29 years.

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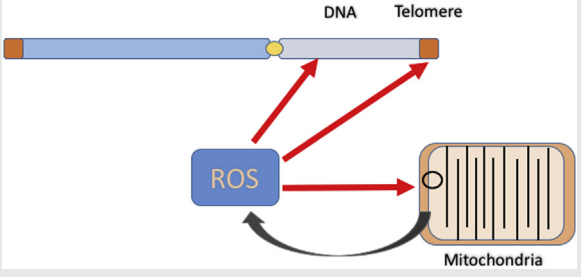
necessary for normal sperm function, excess ROS can place a detrimental oxidative stress on spermatogenesis and fertilization via damage to sperm DNA and proteins and are associated with poor semen quality and function. Studies comparing ROS levels of healthy fertile men aged <40 years vs. those aged >40 years found significantly lower ROS levels in the seminal ejaculate (15). Reactive oxygen species harm sperm by entering the nucleus, binding to DNA, and inducing double-strand breaks (16). The relationship between age and DNA fragmentation is well established, with higher levels of DNA damage more often found in older men. Even when matched comparisons are made between young and old subjects who are normozoospermic, a statistically significant correlation ($P<.001$) remains between age and percent sperm DNA fragmentation (17). Using the sperm chromatin structure assay, Das et al. (17) compared 107 normozoospermic young men (<40 years of age) with 41 normozoospermic older men (≥41 years of age) and found higher DNA damage levels in the older cohort (17% ± 13% vs. 12% ± 18%). Moskovtsev et al. (18) also used sperm chromatin structure assay to compare DNA fragmentation values in a cohort of men ≥45 years of age with a cohort of men <30 years of age and found that damage levels were twice as high in the ≥45 years cohort (32.0% ± 17.1% vs. 15.2% ± 8.4%). These findings were corroborated by a large meta-analysis of 10,220 patients by Johnson et al. (19), who identified a statistically significant age-dependent increase in DNA fragmentation.

Although the mechanism for elevated DNA fragmentation in older men remains unclear, several factors may contribute, including a higher incidence and prevalence of varicoceles (the incidence of varicoceles increases by 10% with each decade of life [20]), environmental exposure to pollutants, and comorbidities such as obesity, diabetes, infections, and other lifestyle issues (reviewed by Sabeti et al. [21]). Coupled with age-related reduction in antioxidant enzymatic activity (reviewed by Aitken and De Iullis [22]), higher ROS levels in the semen of older men increase the oxidative stress, resulting in impaired sperm DNA integrity via creation of double-strand DNA breaks, mutations of genomic and mitochondrial DNA, perturbation of DNA repair enzymes, and the accumulation of single nucleotide variants with each mitotic and meiotic replication (Fig. 1). Defective DNA repair in turn may result in greater numerical and structural chromosomal abnormalities, increasing the risk of aneuploidy by twofold among fathers aged >50 years compared with fathers aged 25–29 years in one study by McIntosh et al. (23). This oxidative stress–mediated DNA damage has been linked with IVF/intracytoplasmic sperm injection failure and abnormal offspring development, particularly with learning disorders and impaired cognition (24–26), although some studies were not performed with the rigor required for evidenced-based medicine.

STRUCTURAL AND NUMERICAL CHROMOSOMAL ABNORMALITIES, DNA MUTATIONS, AND PATERNAL AGE

Genomic instability is characterized as a higher frequency of spontaneous genetic and genomic mutations. Genomic instability associated with aging is a multifactorial, complex process that represents the cumulative effects of chronic ROS

FIGURE 1



Reactive oxygen species generated from the mitochondrial electron transport chain (*black arrow*) damage DNA and mitochondrial DNA and disrupt telomerase activity, causing germ cell senescence.

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