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The Effect of *de novo* Mutations on Human Fitness and Timing of Reproduction

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Many studies have been performed to evaluate the effects of *de novo* mutations. These studies are achieved by examining genotypes of probands whose parental genotypes are known, and discovering new onset mutations. The results of these studies can have great implications for genetic research and its possible applications to medicine. Important factors to be considered are the rate of *de novo* mutations and from which parental individual they are primarily derived. These *de novo* mutations are frequently evident phenotypically through conditions like autism and schizophrenia.[5] This microreview addresses these considerations and provides new insight to today's knowledge about the role of parental age and risk of genetic mutation.

Introduction

In recent generations, parents have been waiting to have children until they attain stability in their career and financial situation. This means couples are having children at later ages than previous generations did. In addition, divorce rates continue to rise as do the number of marriages between older men and younger women. These men often start a family with their new wife as well, even though they are past the typical paternal childbearing age. Studies show that as the father increases in age, his mutation rate increases as well.[1] This means that the offspring of parents reproducing later in life are put at a greater risk for mutation. This creates a provoking question: by what age should we fulfill our reproductive capacities?

Recent Progress

Recent progress has been made in the discovery of genes that typically undergo mutation and lead to the aforementioned diseases. It also gives us the ability to identify important biomarkers. Biomarkers are simply mutations found in a gene, which indicate a strong potential to develop a specific condition in the future. This is useful to physicians, as it better educates them in the conditions to which a patient is predisposed. This work could potentially have dramatic effects on health insurance companies and the amount of coverage they offer patients. Like most areas of science, there is still much more information to be discovered regarding *de novo* mutations. There is little data on mutation rate for older ages. In addition, no studies have been conducted to weigh the effects of environmental hazards and distress. Research in this area would further teach us the cause of *de novo* mutations along with how individuals phenotypically respond to different mutant forms.

Until recently, many scientists were under the impression that the risk of genetic mutation in offspring was highly dependent on maternal age at time of conception. This was proven to be a less important variable when compared to paternal age at conception.[1] Research definitively concluded that there is an increased risk for *de novo* mutation from the paternal genome rather than the maternal genome.[1] In fact, they found that there is an increase of 2.01 mutations per year the father ages.[1] The rate of mutational increase is at 4.28% per year, and after 16.5 years the mutational rate doubles.[1] There is in fact some correlation to maternal age and mutational rate, but in comparison to paternal age, it is not significant.[1] In addition, there has been a great push to determine which loci mutate most frequently. Two types of chromosomal sites have been studied in depth: CpG and non-CpG

chromosomal sites. CpG chromosomal sites are where adult somatic cells are methylated, while DNA methylation occurs at non-CpG chromosomal sites for embryonic stem cells. There is a clear difference between the mutation rates of CpG and non-CpG chromosomal sites. First of all, CpG sites often form dinucleotides. It appears that spontaneous oxidative demination of methylated cytosines can increase the amount of mutations on CpG dinucleotides. Secondly, unmethylated CpG sites cluster together to form islands. These islands may then undergo hypermethylation, an indication of disease processes such as cancer. This trait is heritable among daughter cells. Additional research has been conducted on the type of mutation that occurs. Other studies have found that most *de novo* mutations are due to deleterious alleles and insertions.[2] Deleterious mutations do appear to be more prevalent, which is concerning when considering human fitness. In any other species, deleterious mutations would likely lead to their demise. However, with the manifestation of modern science technology and an environment where our needs are easily met, there is less selective pressure on humans now than ever.[2] It is then argued that the majority of deleterious mutations are rarely evident phenotypically and have little to no affect on human fitness. Scientists argue that these mutations are found as disruptive non-sense mutations and at splice sites.[5] In addition, these non-sense mutations are highly correlated with the development of autism.[5]

Discussion

Overall, the data reflects progress in our knowledge of mutations and their rate relative to parental age. We have determined that the mutational rate increases more rapidly for the father than the mother in relation to age. This makes sense, considering each egg containing the females gametes are formed by birth. However, a father continues to produce gametes as he ages; if his replicative machinery functions more poorly with increased age, his mutation rate will also increase with age. In fact, by the time the father is 35, his mutational rate has more than doubled from what it was when he was 16 years of age. The mutational rate needs to be better studied for individuals over the age of 45 in order to obtain a complete picture of mutational importance. One might wonder, if the mutation rate is so high, what keeps the human population so prosperous and able to reproduce? In any other species, the high mutation rate would allow natural selection to diminish the species. While the high accumulation of deleterious alleles is concerning, it is comforting to know that modern luxuries are, so far, keeping natural selection at bay. It is worth evaluating though whether these mutation accumulations are increasing the amount of disease and hastening the onset of their effects. It is exciting to see where further research takes us and how it will guide our ability to counsel adults on timing of procreation.

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