VIEWPOINT

Aging fathers, selfish testes and neurocognitive disorders

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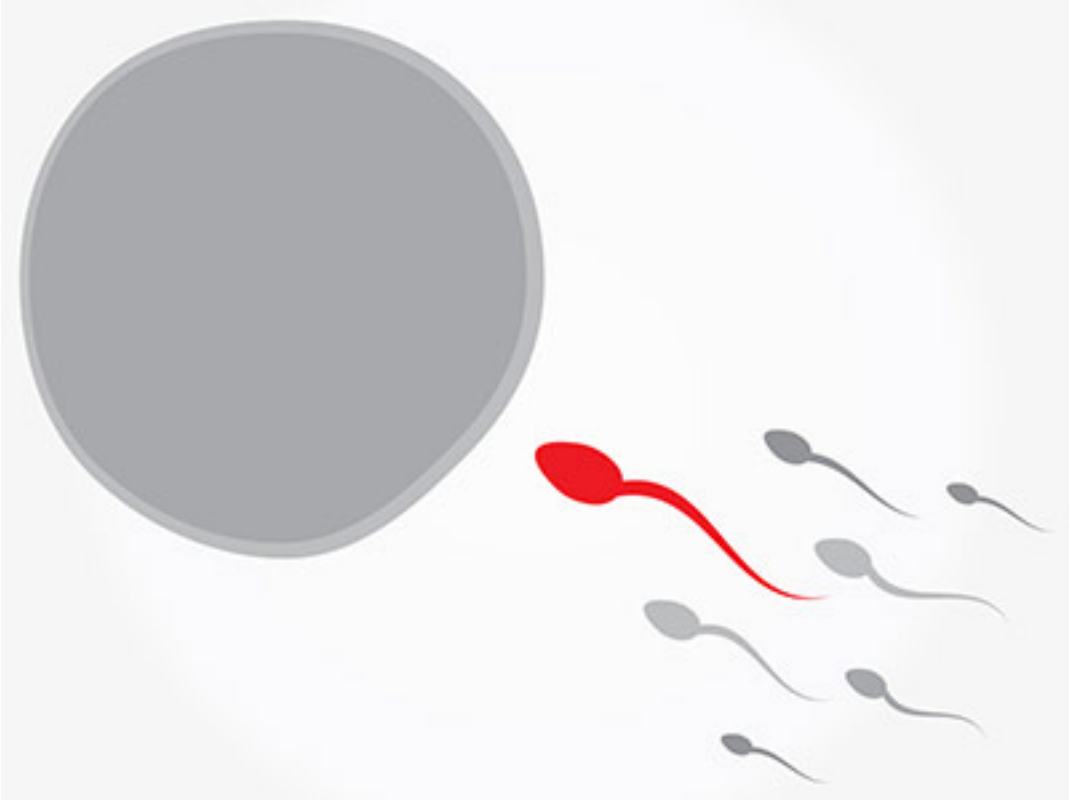
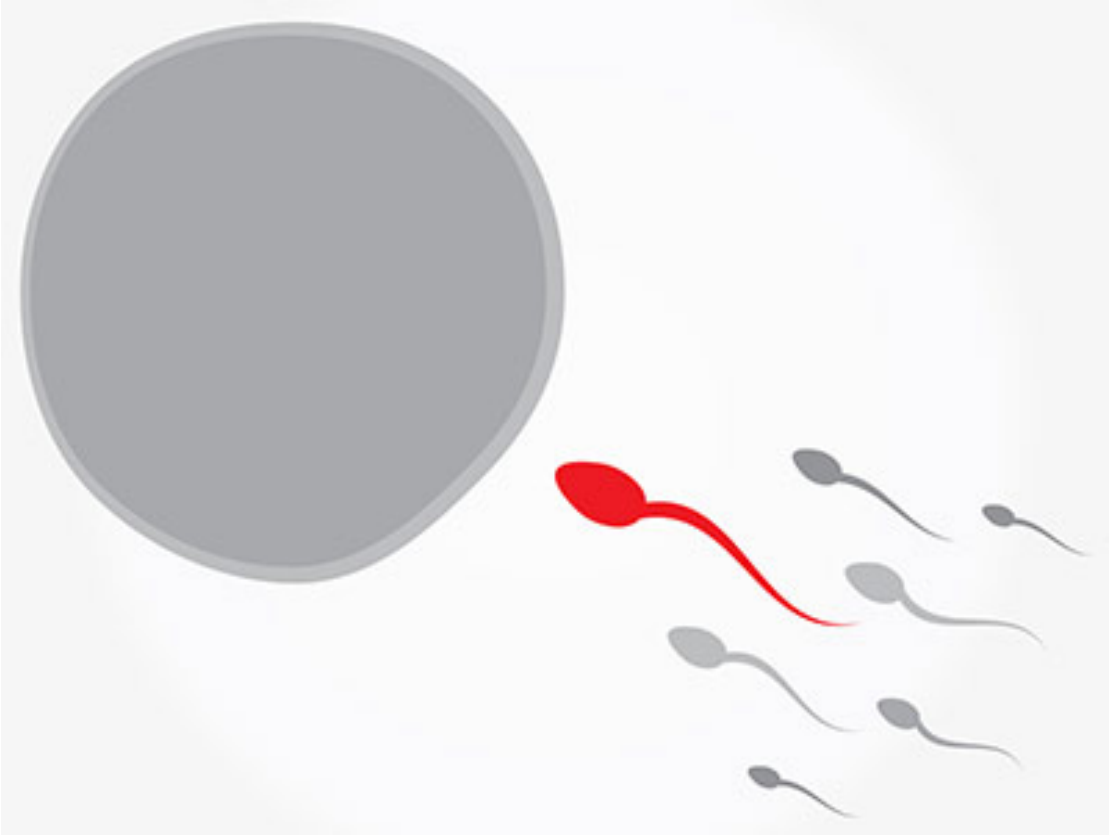
24 SEPTEMBER 2013





Copy errors: The likelihood of an error, or mutation, in sperm DNA rises steadily with age, but this may not fully explain the increased risk of certain disorders.

There is robust evidence from epidemiological studies that the risk of developing neurocognitive disorders, including autism and schizophrenia, increases with the age of the father at the time of conception.

Among others, a 2011 Swedish study describes a **two-fold increase in relative risk** of autism for a child born to a father over 55 years of age compared with a father younger than 29 years[1]. Studies have consistently reported similar risk factors for schizophrenia[2].

Despite this well-documented paternal-age effect, the biological basis for the association remains poorly understood. The prevailing explanation is that this effect is mediated by an increase in *de novo*, or spontaneous, mutations in the sperm of aging men.

An additional mechanism may be at play in the testes of men as they age: This process, known as ‘selfish selection,’ predicts that certain mutations may ‘hijack’ the normal mechanisms of sperm

production to their own advantage. This enriches for sperm that carry harmful mutations[3].

It is well established that the production of mature sperm relies on regular divisions of specialized stem cells called spermatogonia, at a rate of about 23 divisions per year. As men age, the sperm they produce derives from spermatogonia that have undergone many more cell divisions than when they were younger.

Remembering that each cell division requires copying the entire 3.3 billion base pairs that constitute the human genome, it is almost unavoidable that copy errors in the form of point mutations (just like random spelling mistakes) will occur. Aging spermatogonia are thus believed to slowly accumulate random *de novo* mutations over time.

Copy errors:

Studies published in the past few years that are based on sequencing the whole genomes of family trios (in which the father's and mother's sequences are compared with that of their child) have allowed a direct evaluation of this copy-error phenomenon.

These studies reveal that every one of us has about 30 to 100 point mutations that were not present in our parents — confirming that the estimated *de novo* mutation rate in people is around 1×10^{-8} per generation.

Interestingly, the authors of one study also showed that not only do about 85 percent of *de novo* point mutations arise during spermatogenesis but also that about one or two new mutations occur for each additional year of the father's age. This leads to a **doubling of the total mutational load** for every additional 16.5 years of paternal age[4].

Although this finding clearly demonstrates an association between the total number of *de novo* mutations and paternal age, it is important to recognize that it does not necessarily imply a causal link between these age-related paternally derived *de novo* mutations and neurodevelopmental disease risk. Indeed, as the human genome is large, the vast majority of these mutations are unlikely to affect the coding part of the genome, and few will be associated with disease.

There are other plausible hypotheses explaining the paternal-age effect observed in neurocognitive disorders that rely not on genetic but rather on social or behavioral factors. For example, men who have some autism traits — and so a genetic predisposition to the disorder — may have a tendency to delay fatherhood until later in life[5].

About ten years ago, we and others tested the association between *de novo* mutations, paternal age and disease risk by studying a group of rare, spontaneous genetic conditions that we collectively called 'paternal-age-effect disorders'[6].

Although the best-known disease in this class is probably achondroplasia, the most common form of short-limbed dwarfism, we originally studied a related condition called Apert syndrome.

Children with Apert syndrome — which arises in about 1 in 65,000 births and involves malformations of the skull, face, hands and feet — are born to healthy parents who do not have any history of the condition. However, their fathers tend to be significantly older than the population average.

In Apert syndrome — unlike in autism and schizophrenia, for which the genetic cause of the disease is likely to be different in each individual — virtually all affected people have one of two paternally derived dominant point mutations in a gene called FGFR2. This has allowed us to look at what is going on in the sperm of men of different ages at the genomic site where the mutation takes place.

We found that virtually all men carry the Apert mutation in their sperm at rates elevated by 100- to 10,000-fold above those for other sites in the genome and that the levels of this mutation increase significantly as men age[7]. It became apparent that the levels of the Apert mutation observed in sperm are far too high to be accounted for by the accumulation of recurrent copy errors alone.

Selfish selection:

The data instead point to another mechanism, which we termed ‘selfish selection:’ Once a rare mutation occurs, it confers a selective growth advantage to the mutant spermatogonia. This leads to their clonal expansion and relative enrichment of mutant sperm over time.

This process shares many of its characteristics with tumor growth in cancer. In fact, all known genes linked to the paternal-age effect have been associated with cancer in different cellular contexts[6].

The obvious question the selfish selection hypothesis raises is whether the paternal-age effect described epidemiologically for neurocognitive disorders could be associated with the same phenomenon. And, if so, what are the implications for our understanding of these complex disorders[3]?

Despite many genetic studies performed over the past few years, the causes of neurocognitive disorders have remained elusive. This is puzzling, and perhaps even paradoxical, considering that these disorders are both highly heritable and fairly common. The current picture that emerges from large genetic screens suggests that these disorders are highly heterogeneous: There is a rapidly **growing list** of more than 300 candidate genes for autism and **around 1,000 for schizophrenia**.

Most of the mutations isolated so far are unique to a given family. Still, it appears that many of the candidate genes interact with one another and **cluster within a small number** of molecular pathways[8, 9]. Unexpectedly, these genes show a significant overlap with gene networks involved in cancer, as well as with those linked to selfish selection in the testes.

Studies of paternal-age-effect disorders have established that selfish selection is mediated through the dysregulation of the **RAS-MAPK signaling cascade**[3, 6]. As RAS is required in many cellular contexts, including brain development, learning, memory, cognition and neuronal adaptation to experience, subtle alterations of this pathway may also be relevant to the pathology of neurocognitive disorders.

In other words, the mechanism of selfish selection, which is predicted to be universal and to affect all men as they age, may favor the propagation of harmful *de novo* mutations that preferentially affect signaling pathways relevant to brain disorders.

This selfish process is appealing. Not only does it offer a parsimonious explanation for the association between advanced paternal age and neurocognitive disorders, but it may also provide insights into the complex genetic architecture of these disorders. It also points to the importance of *de novo* mutations that affect specific molecular pathways.

From a more provocative standpoint, this hypothesis also suggests that mutations associated with autism and schizophrenia are part of a ‘normal’ process that produces functional genetic variation at each generation — an essential prerequisite to the evolution of a species. As such, these complex disorders might be seen as the unavoidable consequence of a selfish mechanism originating in the aging testes.

Before we can reach this conclusion, it will be necessary to establish formally whether a proportion of the mutational burden associated with neurocognitive disorders is caused by selfish selection in the testes of aging men. This will undoubtedly require a better understanding of the genetics of autism and other complex disorders, as well as the mechanisms controlling human spermatogenesis.

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