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Review

Causes & Prevalence

The origins of *de novo* gene mutations in genetic syndromes with high autism spectrum disorder risk

RA Jensen*

Abstract

Introduction

The advanced technological achievement of fluorescent in situ hybridisation (FISH) has allowed evolutionary biology to directly examine the locations and frequency of specific sperm mutations in male donors with a minimum of 10,000 sperms per donor. Reviews of the literature suggest that all males produce sperm mutations associated with genetic syndromes with high autism spectrum disorder risks throughout their lives. The frequency of sperm mutations increases with advancing age and the production of sperm mutations may be operating via environmental risk factors. Autism spectrum disorder is a complex multifactorial condition. Rutter has proposed the existence of broader autism phenotype candidate genes. This review discusses the interplay between proposed broader autism phenotype genetic influences and a *de novo* gene mutation known as Down syndrome. When both independent mechanisms are present, a developmental trajectory towards an autism spectrum disorder diagnosis is followed.

Conclusion

There are increasing reports of germline mutations being as a contributing risk factor in ASD. *De novo* gene mutations arise from reproductive errors (sperm or egg mutations). Mostly, the role of *de novo* gene mutations is recognized in genetically determined syndromes with high risk of ASD and an unambiguous medical diagnosis. Males generate sperm mutations (deletions and duplications) associated with specific genetically determined syndromes throughout their lives. Environmental risk factors are associated with the production of sperm mutations and increasing levels of exposure; increasing paternal age also increases the frequency of sperm mutations. Have we reached to the point where the general population's rapidly expanding mutation rate has reached the point of no return? Stephan J. Gould's theory of punctuated equilibrium states that the mutation rates in natural history are stable for millennia, punctuated by periods of rapid evolutionary change. Thus, we may well be entering a period of punctuated equilibrium.

Introduction

Autism (Autistic Disorder, pervasive developmental disorder-not otherwise specified [PDD-NOS], and Asperger Syndrome) is a strongly genetically influenced disorder and at the same time, it is also a complex multifactorial condition. The relative contribution of genetics and environmental risk is subject to heated debate and argument that has been exacerbated by the California Autism Twin Study (CATS) group's finding that environmental risk factors may be far more important than previously recognised[1]. ASD has been typically described as the most heritable of the developmental disorders; thus, genetic research has focused on the consequences rather than the origins of gene mutations in ASD. *De novo* gene mutations in simplex families has generated all the excitement in research work of ASD, but a great deal of insight into understanding the mechanisms involved in *de novo* gene mutations in idiopathic cases can be gained by studying the genetic syndromes, with an unambiguous medical cause[2–4].

The advanced technological achievement of fluorescent in situ hybridisation (FISH) has allowed evolutionary biology to directly examine the locations and frequency of sperm mutations in healthy male donors. The FISH methodology requires examining a minimum of 10,000 individual sperm per donor and as such does not permit the technology to be used in examining the frequency of *de novo* egg mutations, although these mutations are also likely to be involved in the genetic syndromes associated with high ASD risk. Both increased paternal and maternal ages are associated with increased ASD risk. The average *de novo* mutation rate is 1.20×10^{-8} per nucleotide per generation with the paternal effect of an increase, doubling every 16.6 years. The increase in the *de novo* mutation rate of single nucleotide polymorphisms is significantly dominated by the age of the father at conception of the child[5,6]. The aim of this review is to discuss the origins of *de novo* gene mutations in the genetic syndromes with high ASD risk.

Sperm mutations in general population studies

Molina's laboratory studied sperm mutations in 10 healthy male volunteer donors focusing on mutations, deletions and duplications, identified in individuals diagnosed with a genetic syndrome associated with high ASD risk[10]. The chromosome regions specifically examined for sperm mutations in healthy donors were as follows: 7q11.23 (Williams syndrome), 15q11–13 deletions

* Corresponding author
Email: rajensen088@aol.com

6100 N Brookline Ave #27, Oklahoma City OK, 73112 USA

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(Prader–Willi syndrome), 15q11–13 duplications (Dup15 syndrome) and 22q11 (22q11 deletion syndrome) and most genetic and epigenetic cases of Williams syndrome, Prader–Willi syndrome, Dup15 syndrome and 22q11 deletion syndrome primarily were caused by *de novo* gene mutations in contrast to being inherited events. Sperm mutations (deletions and duplications) in all the three regions were found in the sperm of all the volunteer healthy donors. The frequency of the sperm deletions was higher than the estimated general population prevalence for Williams syndrome, Prader–Willi syndrome and 22q11 deletion syndrome suggesting the following:

1. increased foetal loss due to the gene mutation,
2. reduced motility of sperm mutations and/or
3. underestimates of population prevalence for Williams syndrome, Prader–Willi syndrome and 22q11 deletion syndrome.

Paternal age effect was not observed in this study[7–11].

The paternal age effect in girls with ASD may be associated with *de novo* gene mutations in simplex families[4]. Several groups have tested the hypothesis that advancing paternal age may be associated with increased frequency of sperm mutations in volunteer donors. The frequency of chromosome 9 sperm mutations was found in all healthy donors segregated by age groups and increased with advancing age[12]. Structural aberrations in chromosome 1 were present in the sperm of all volunteer donors and the frequency of sperm mutations significantly increased with advancing age[13]. The frequency of XY sperm mutations increased with advancing age in karyotype normal fathers of boys diagnosed with Klinefelter syndrome (KS)[14].

KS and XYY syndrome are among the most common genetic syndromes affecting 1 in 500–1,000 males. KS is always caused by an extra X chromosome (47, XXY) and XYY syndrome is always caused by an extra Y chromosome (47, XYY). KS and XYY syndrome are not inherited. Mosaic KS and Mosaic XYY syndrome are rarely inherited[15,16]. KS is associated with autism risk and may involve the interplay of neurexin–neuroligin genes[17]. Bishop's group found that in their sample, 11% of KS males met the diagnostic criteria for ASD and 19% of XYY syndrome males met the diagnostic criteria for ASD[18]. Several studies have examined for the presence of XY and YY sperms in karyotype normal fathers of KS boys, subfertile males and in healthy volunteer controls using the FISH assay. XY and YY sperms were found in all groups suggesting that all males may produce XY and YY sperm throughout their lives and the production of XY sperm increases with advancing paternal age. The parent of origin for the extra X chromosome in KS is paternal in 53% of the cases; hence, the implication for this is that where the parent of origin is maternal, KS is transmitted via an XX egg mutation. The parent of origin for YY sperm is always 100%, which is paternally derived. Unlike XY sperm, the paternal age effect has not been observed in the production of YY sperm[19,20,14].

McAuliffe and colleagues discovered that increasing levels of environmental exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT) congeners, as measured in blood, is associated with increased production of XY and YY sperms in volunteer donors recruited from fertility clinics[21]. Persistent organic pollutants (POPs), including PCBs and polybrominated diphenylethers (PBDEs) have been found in post-mortem brain tissues in samples with maternal Dup15 syndrome or deletion (Prader–Willi syndrome). POPs, PBDEs and PCBs may predispose to genetic copy number variation of 15q11–q13, in most cases, likely via sperm or egg mutations[21,22].

The Chinese–Benzene and Sperm Study (C-BASS) group examined the frequency of sperm mutations in workers, who were exposed to benzene in manufacturing plants in China. The study recruited 30 exposed workers employed for more than a year and divided the workers into three groups as follows: a low exposure group, a moderate exposure group and a high exposure group. A control group of 11 unexposed workers from the same town was also recruited. Every participant in all the four groups was found to have sperm mutations including 1p36 sperm deletions. The frequency of the 1p36 sperm deletions was lowest, but present in the unexposed group, higher in the low exposure group, higher still in the moderate exposure group and highest in the high exposure group. The authors concluded that workplace exposure to benzene induces 1p36 sperm deletions and is a risk factor for *de novo* 1p36 deletion syndrome. The 1p36 deletion syndrome estimated population prevalence is 1 in 5,000 to 10,000 males and may be associated with ASD via the deletion of the ASD susceptibility MTHFR (methylenetetrahydrofolate reductase) gene that maps to chromosome 1p36[16,23–25].

Male exposure to antidepressants, obesity, diabetes and workplace exposure to benzene produces damage to sperm deoxyribonucleic acid (DNA) and sperm mutations. These studies are required to be replicated using the more advanced FISH assay targeting specific chromosome regions for sperm copy number variations associated with ASD risk in genome and genome-wide association studies[25–27].

Maternal exposure to antidepressants, obesity, metabolic conditions and diabetes, and living in close proximity (> 307 m) to heavily congested freeways in densely populated California urban areas is associated with

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ASD risk. The environmental risk factors that produce sperm mutations in males are also frequently seen in females suggesting that pre-conception exposure to these environmental risk factors may also produce egg mutations in females; however, there is no technology that can test this hypothesis[28–30].

Autism is a multifactorial disorder. The genetic syndromes associated with high ASD risk result in risk for multiple congenital anomalies, multiple medical complications and risk for a broad spectrum of neurodevelopmental and neuropsychiatric conditions. There is no single causal mechanism that is predictive of ASD in the genetic syndromes. ASD in this group, likely involves multiple contributing risk factors that cumulatively may increase total risk in any individual case. The genetic syndromes are associated with high risk for narrowly defined autistic disorders (AD) or broadly defined ASD. The majority of cases do not meet the diagnostic criteria for AD or ASD suggestive of additional independent risk factors, such as the familial clustering of the broader autism phenotype (BAP) in unaffected first degree relatives that may distinguish ASD cases from non-ASD cases[31,32].

Rutter has proposed the existence of narrowly defined BAP candidate genes as follows:

"In other words, what is required for autism 'proper' to develop are the susceptibility genes and some other risk factor that could be either genetic or environmental in origin. The implication, if it is a two hit process is that the genes underlying the broader autism phenotype may not be exactly the same as those involved in the transition to the handicapping disorder"[33].

Ghaziuddin tested the Rutter hypothesis in Down syndrome with and without co-occurring ASD, featuring the interplay between a *de novo* genetic mutation and a history of BAP genetic effect that when both component parts are present, a developmental trajectory to an ASD diagnosis is followed. In Down syndrome with ASD, there was an excess of unaffected first degree relatives (parents and siblings), who exhibited an increased family loading of BAP features compared with the first degree relatives in Down syndrome children without ASD who did not exhibited an increased family loading of BAP features. ASD was not present in first degree relatives, parents and siblings, and the genes underlying the BAP component part were independent of and were a background genetic effect, secondary to the disruption of early brain development in Down syndrome and the transition to ASD, as predicted by the Rutter hypothesis[34,35].

Discussion

De novo gene mutations are the building blocks of human evolution. The lesson to be learned from evolutionary biology is that all males produce sperm mutations associated with genetic syndromes with an identified medical cause and high risk for co-occurring ASD throughout their lives. Sperm mutations increase with increase in paternal age, and environmental influences are central to understand the complex mechanisms involved in the production of sperm mutations in males and by inference, egg mutations in females. Given the high rates of *de novo* gene mutations in idiopathic ASD, these findings may also represent in part, a contributing risk factor to the larger group of individuals diagnosed with ASD, who remain without an unambiguous medical cause.

Conclusion

There are increasing reports of germline mutations being a contributing risk factor in ASD. *De novo* gene mutations arise from reproductive errors (sperm or egg mutations). Mostly, the role of *de novo* gene mutations is recognized in genetically determined syndromes with high risk of ASD and an unambiguous medical diagnosis. Males generate sperm mutations (deletions and duplications) associated with specific genetically determined syndromes throughout their lives. Environmental risk factors are associated with the production of sperm mutations and increasing levels of exposure; increasing paternal age also increases the frequency of sperm mutations. Have we reached to the point where the general population's rapidly expanding mutation rate has reached the point of no return? Stephan J. Gould's theory of punctuated equilibrium states that the mutation rates in natural history are stable for millennia, punctuated by periods of rapid evolutionary change. Thus, we may well be entering a period of punctuated equilibrium.

Abbreviations list

AD, autistic disorders; ASD, autism spectrum disorder; BAP, broader autism phenotype; Dup15, 15q11–13 duplications; FISH, fluorescent in situ hybridisation; KS, Klinefelter syndrome; PBDE, polybrominated diphenylether; PCB, polychlorinated biphenyl; POP, persistent organic pollutants.

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