An Evolutionary Genetic Framework for Heritable Disorders

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Natural selection is expected to drive the frequencies of heritable, fitness-harming states to very low levels, yet many heritable disorders – and especially mental disorder – are common in the human population. These two statements are sometimes interpreted to imply that disorders have not been under natural selection, but this need not be the case. Evolutionary genetics provides three broad classes of models, none of them mutually exclusive, for understanding why disorder risk alleles have persisted in the human population despite natural selection.

Advanced article

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Introduction

It is a question that anyone who understands evolution eventually ponders: given the optimizing power of natural selection, why do so many humans suffer from debilitating disorders? Why do people die from cancers, infections or heart disease? Why do they suffer through arthritis, fever or nausea, or spend their youth depressed or anxious? Why do so many people need their vision to be corrected or their wisdom teeth removed? In short, why is not the body better designed?

It is a testament to the field of Darwinian Medicine that we now have satisfying explanations for many of these questions. Unpleasant symptoms such as fever, diarrhoea and nausea are not defects. They are the body's defences, crafted by natural selection to fight infections (fever) and expel noxious toxins or parasites (nausea and diarrhoea). Many diseases and inconveniences associated with senescence and aging exist because selection acts much more strongly on the young than the old: genes that benefit those of reproductive age but that increase risk of a disorder later in life tend to fixate (reach 100% prevalence) in the population (Williams, 1957). Other diseases and inconveniences, such as obesity, impacted wisdom teeth and poor vision are side effects of living in environments much different than those that our bodies' were designed to deal with. In sum, a core tenet of Darwinian Medicine is that many conditions that modern medicine deems to be disorders – which may cause a great deal of suffering and that we might rather live without – are nevertheless adaptive when one considers *what* natural selection optimizes (fitness rather than subjective well-being) and *when* this optimization took place (eons ago, under conditions quite different than modern environments). **See also**: Darwinian Medicine; Evolutionary Thinking in the Medical Sciences

However, some conditions – those that strike during peak reproductive years, are debilitating, and have high rates across many cultures – appear to be simply deleterious, even from a strict evolutionary perspective. Even more puzzling, many such disorders are highly heritable, which is to say that differences between people in the genetic variants (alleles) that they harbour in their genomes influence the risk of developing the disorder. If they were truly deleterious, it would seem that natural selection should have eliminated such risk alleles from the gene pool long ago. Why do risk alleles that cause heritable variation in common, harmful disorders persist in the population?

Most generally, what is required is a framework for understanding why genetic variation – which is caused by the existence of alternative alleles at loci affecting a trait – would ever exist for disorders and other fitness-reducing conditions in nature. Since natural selection should drive one most-fit allele at a given locus to fixation and all less-fit alternatives to extinction, loci that have a net effect on fitness should not contribute to genetic variation. Put another way, there should be little or no genetic variation in fitness-related traits, but empirical observations suggest otherwise (Houle, 1992). This issue has been the topic of years of investigation in the field of evolutionary genetics, and several robust theories have emerged from that field that can help us form and test explanations for why risk alleles persist in humans.

Because they account for such a large percentage of the total disability among reproductively aged persons, I focus here on common, heritable mental disorders such as mental retardation, schizophrenia and severe depression, but the types of explanations I will cover are equally relevant to any

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kind of heritable ailment, from heart disease to endometriosis to lower back pain. It is likely that only a few basic evolutionary processes can explain most of the genetic variation underlying both physical and mental conditions.

Common, Heritable Mental Disorders

Heritable mental disorders are highly prevalent in modern industrialized societies. In the United States, for example, approximately 4% of people suffer from a severe mental disorder such as autism, schizophrenia or mental retardation and nearly 50% of people will meet criteria for a less severe mental disorder, such as depression or an anxiety disorder, during their lifetime (Kessler *et al*., 2005). From an evolutionary perspective, the rates of common mental disorders are astronomically high – orders of magnitude higher than thousands of fitness harming disorders with simple inheritance patterns such as Apert syndrome or Achondroplastic dwarfism. Moreover, the heritability estimates for these common mental disorders range from approximately 30–40% (for panic disorder, depression) to 80–90% (schizophrenia, autism).

Together, the high heritability and prevalence rates of mental disorders imply that mental disorder risk alleles are cumulatively very common in the population. Indeed, psychiatric genetics has largely moved towards a view of common mental disorders as being the quantitative extreme of 'normal' variation. By this view, risk alleles are also ubiquitous, albeit at lower doses, in unaffected individuals (Plomin and McGuffin, 2003). Given that natural selection quickly weeds out alleles that have even a slightly negative effect on fitness, this might seem to imply that common mental disorders are not actually evolutionarily deleterious. Indeed, as discussed earlier, a basic tenet of the Darwinian Medicine approach is to question whether conventional disorders, as defined by the medical establishment, truly harmed ancestral fitness.

However, this traditional Darwinian Medicine approach does not seem adequate to fully explain the paradox of common, heritable mental disorders. Mental disorders typically have onsets anywhere from childhood to the early thirties – before and during the period when ancestral humans were reproducing (Bailey *et al*., 1996). Furthermore, some of the severest of these mental disorders (mental retardation, schizophrenia and bipolar disorder) are observed at high levels the world over, including in nonindustrialized societies, and thus do not fit the profiles of other maladies that are products of modern industrialized environments. Finally, severe mental disorders such as schizophrenia and mental retardation are associated with profound reductions in fertility in modern environments. Whereas the effects of these disorders on fertility in ancestral environments is unknown, based on their disability, it is fair to posit that severe mental disorders would also have harmed fitness in ancestral environments.

Three Explanations for the Persistence of Risk Alleles in the Population

Several researchers in evolutionary psychology and Darwinian Medicine have argued that the commonality and heritability of mental disorders implies that they were not disadvantageous to fitness (see commentaries in Keller and Miller, 2006). Implicit in such arguments is the notion that genetic maladaptation should be rare in nature, but we now know that this is not the case. Indeed, a principle focus of the field of evolutionary genetics is in understanding why maladaptive alleles are so ubiquitous in nature. I will discuss three hypotheses, each drawn from evolutionary genetics, that were originally intended to understand genetic maladaptation in nature, but that can be profitably extended to help us understand the existence of alleles that increase the risk of disorders in humans. None of these hypotheses are mutually exclusive – each may play important roles depending on the disorder. Fortunately, several lines of evidence, reviewed at the end of the chapter, can help clarify the relative importance of these processes. **See also**: Genetics and Variation in Survival and Reproduction

Mutation-selection

The human genome contains some three billion base pairs, each of which comes in one of four varieties (A, adenine; T, thiamine; C, cytosine and G, guanine). Through the production and regulation of proteins and (increasingly it is realized) strands of ribonucleic acid (RNA), an individual's sequence of base pairs controls much about how its cells and organs develop. Each of the three billion base pairs must be replicated with extraordinary fidelity every time a new cell is created. However, as with any copying process, errors do sometimes occur; when they do, the new base pair sequence is called a mutation. Mutations that occur during sperm or egg cell replication are relevant to the evolutionary process because these are potentially passed on to every cell in an offspring, every cell in an offspring's offspring, and so forth. This is how a new mutation is 'introduced' into the population. **See also**: Mutations and the Genetic Code

Most mutations have no effect on fitness simply because most regions of the genome have no effect on the phenotype. Very rarely, mutations occur in important regions of the genome and actually increase fitness, and these can go on to fixate in the population, serving as the genetic substrate for new adaptations. However, among mutations that occur in regions important to fitness (perhaps 5% of the genome, based on studies of conserved deoxyribonucleic acid, DNA), the vast majority reduce the fitness of their carriers. Generally, the reduction in fitness from a new mutation is very small and hardly noticeable within a lifetime, but over evolutionary time, these mutations statistically decrease their carrier's average number of offspring and, thereby, their frequencies gradually decrease in the population – natural selection in action. Nevertheless,

slightly deleterious mutations tend to persist in the population for a number of generations before going extinct. For example, a mutation that decreases its carriers' fitness by 1% will exist in 100 different individuals on average (García-Dorado *et al*., 2003). Thus, at any given time, populations are laded with old, slightly deleterious mutations, each of which slightly degrades organic functioning. It should be noted that whether or not a mutation is deleterious depends on its genetic and environmental background in which it finds itself. For example, certain disease-causing mutations in humans are harmless – indeed are actually the predominant (wild-type) allele – in nonhuman primates (Azevedo *et al*., 2006).

Mutation-selection models describe an equilibrium that occurs when the number of newly arisen mutations affecting a trait in a given generation equals the number of old mutations affecting that trait that are driven to extinction in a generation. It has long been understood that mutation-selection maintains a very small and calculable amount of maladaptive genetic variation in traits affected by single genes, and that this simple process accounts for the majority of the thousands of harmful single-gene disorders. However, it is increasingly clear that some traits must be affected by hundreds or even thousands of genes, and the cumulative amount of genetic variation maintained by mutations in such traits can be quite high, perhaps high enough to fully account for their heritability (Houle, 1998). **See also**: Mutation–Selection Balance

The best current estimates are that the typical human inherits at least 1000 slightly deleterious mutations (Fay *et al*., 2001), the majority of which are expressed in brain tissue. Researchers have recently argued that mental disorders (Keller and Miller, 2006; Yeo *et al*., 1999) and complex disorders in general (Wright *et al*., 2003) may be, in part, the phenotypic manifestations of the cumulative effect of these slightly deleterious mutations. Humans born with a particularly large number of mutations that disrupt the performance of particular constellations of neurocognitive systems are at risk for developing aberrant behaviours that, in turn, have been categorized as discrete mental disorders by the medical establishment. Mutational models imply that such disorders are not 'natural kinds' with clear boundaries and common causes, but rather are umbrella concepts covering a heterogeneous constellation of similar-appearing phenotypes. Mutational models also imply, by the way, that mental disorders – or at least behavioural disorders – exist in all animals, but that their specific manifestations depend on the pre-existing cognitive architectures and behavioural patterns of the specific species.

Balancing-selection

Balancing-selection describes an equilibrium process whereby natural selection actively maintains two or more alleles at a locus – thereby maintaining genetic variation on a given trait. This typically occurs when the marginal fitness effects of the alternative alleles (the fitness effect of each allele averaged across every genome it might find itself in) are exactly equal. It might seem that this is an unlikely occurrence, and indeed it is. In most situations, the marginal fitness effects of one allele is slightly higher than any other alternative allele, and this allele tends to spread through the population until practically everyone carries it. There are special situations, however, when the marginal fitness effects of alternative alleles are exactly equal and when the two or more alternative alleles are each maintained by natural selection.

The best-known type of balancing-selection, called overdominance, occurs when the heterozygote has higher fitness than either homozygote. In this situation, allele frequencies will increase or decrease until both alternative alleles have precisely the same marginal fitness effects. Importantly, neither allele will 'win out' over the other allele given this dynamic – both will be maintained. For example, if heterozygotes (*Aa*) have the highest fitness, and *AA* confers half the fitness of *Aa* whereas *aa* confers zero fitness (it is lethal), the equilibrium frequencies will be 66% for *A* and 33% for *a*. At these frequencies, the marginal fitness effects of the *A* allele and the *a* allele are exactly equal (33% lower than the most-fit heterozygous state). If either allele drifts by chance away from this equilibrium, selection against the homozygotes will return the alleles to the stable equilibrium frequencies. In this way, natural selection actively maintains even a lethal disorder in the population at a stable frequency of 11% (0.33^2) – a byproduct of the fact that heterozygotes cannot reliably produce heterozygote offspring. The persistence of sickle-cell anaemia, endemic to equatorial regions of Africa and Asia, is attributable to this process (Allison, 1954). **See also**: Heterozygous Advantage; Sickle Cell Disease as a Multifactorial Condition

A more general type of balancing-selection, frequency-dependent selection, maintains genetic variation in much the same way – indeed, overdominance can be considered a special case of it. Frequency dependent selection occurs when the fitness of an allele or some genetically influenced morph *decreases* as its frequency *increases*. Again, this might seem to be a very unlikely occurrence, but because frequency-dependent selection can maintain a large amount of variation indefinitely, the dynamic need arise only very rarely for it to play an important role in maintaining the genetic variation of traits. **See also**: Selection: Frequency-dependent

As an example, Mealey (1995) has argued that psychopathy – a condition characterized by social manipulation and a lack of empathy – may be a psychological morph maintained by frequency dependent selection. At low frequencies, psychopathy successfully exploits social emotions of trust and cooperativeness. As its frequency increases, however, its fitness decreases due to higher levels of vigilance and distrust in populations with higher levels of psychopathy. The equilibrium state, according to Mealey, is for natural selection to maintain a small but nevertheless steady number of psychopaths in human populations.

A final type of balancing-selection is antagonistic pleiotropy. Pleiotropy refers to the situation when an allele has

an effect on more than one trait; antagonistic pleiotropy occurs when one of these effects increases fitness whereas the other decreases fitness. This could in principal maintain two or more alternative alleles at the same locus if the fitness effects of these alleles turn out to be equal. For example, if one allele increases mental disorder risk but also increases creativity, while the other decreases mental disorder risk at the cost of creativity, both alleles might be maintained in the population. This would maintain genetic variation in both creativity and mental disorder risk. However, recent mathematical models have questioned the likelihood of this type of situation to maintain alternative alleles (Hedrick, 1999). In most situations, one allele or the other would have a slight advantage over the other and would fixate. Even if the two alleles had precisely the same marginal fitness effects, it is likely that one or the other allele would eventually fixate by chance. Nevertheless, antagonistic pleiotropy may make the fitness effects of alleles much closer to neutral than they would otherwise appear, and may substantially slow down the march to fixation.

Time-lags and neutral evolution

As discussed earlier, several conditions such as obesity and poor vision are side effects of living in evolutionarily novel environments. These conditions exist at much reduced levels in societies where food is not abundant or where reading rates are low, respectively. The prevalence rates of certain mental disorders, such as depression, also show a high level of cross-cultural variability, suggesting that perhaps depression rates in western industrialized societies do not reflect ancestral rates. This conjecture has some intuitive appeal – the protective effects of social support, for example, may be much lower in modern environments – but such a hypothesis has not yet been systematically tested. Nevertheless, this hypothesis for the high rates of depression only serves as a partial explanation. It offers a hypothesis to explain the high rates of depression, but still required is an explanation for the genetic variation of depression – why do depression risk alleles exist in the population?

One possibility is that alleles that today increase risk for certain mental disorders did not have this same effect in ancestral environments, and were essentially neutral with respect to fitness. Although neutral alleles also tend to fixate or go extinct by chance, the drive towards fixation is much slower among neutral alleles, and as a class, they are much more likely to be variable in the population than are deleterious alleles. For example, it is possible that alleles that increase or decrease shyness had little effect on fitness in ancestral environments. Fast forwards to modern environments and large cities, where shyness may well place one at risk for being lonely and, by extension, becoming depressed. In such modern environments, these ancestrally neutral shy alleles now would increase the risk for depression, and contribute to the genetic variation underlying the disorder.

Another way that evolutionary time-lags might help explain the genetic variation underlying mental disorders has to do with the eternal struggle waged between pathogens and their hosts (Gangestad and Yeo, 1997). Throughout evolution, the bodies of animals have served as tempting hosts for various life stages of bacteria, viruses, fungi and animals such as worms and flies. These parasites typically reduce the fitness of hosts, and so hosts have evolved defences against them. Pathogens, however, rapidly evolve new adaptations to overcome such defences. A side effect of this pathogens–host conflict is genetic variation in host defences: as pathogens adapt to the existing defence alleles, new ones arise in the hosts and begin spreading through the population. At any given time, many different defence alleles exist in the population. If mental disorder risk is in any way affected by either pathogens themselves or by a side effect of defence alleles, host–pathogen coevolution can maintain genetic variation in mental disorder risk.

For example, the neurotropic Borna disease virus and childhood *Streptococcal* infections are risk factors for affective disorders and adult obsessive-compulsive disorder, respectively. Given that resistance to these viruses is likely to be heritable (Vogel and Motulsky, 1997) – a consequence of new defence alleles risking and old defence alleles falling in frequency – part of the genetic variation underlying these disorders must also be a byproduct of host–parasite coevolution.

Standards of Evidence

Each of these three hypotheses are plausible explanations for genetic variation in mental disorder risk. However, it is not adequate to merely have plausible explanations; hypotheses for the genes underlying mental disorders must make testable predictions that can allow us to distinguish between them. Later, I briefly summarize some of the most important of such predictions and discuss relevant data. The first of these is the most direct way to test these hypotheses, but several indirect lines of evidence are currently more feasible to collect.

Identification of the locations and sequences of the causal alleles

The most direct way to assess why risk alleles persist in the population would come from actually identifying such alleles. Knowledge of the frequencies and geographic distributions of both the risk alleles and the genomic regions surrounding them would allow for tests of the type of selection maintaining the alleles (Bamshad and Wooding, 2003). Nearly all models of balancing-selection predict that the alleles causing the variation will be common in the population – for example, 20% of the population may have one variant and 80% the other. Moreover, balancing-selection predicts a good deal of genetic diversity in nearby regions (as reflected by a high score on a measure of genetic diversity, such as Tajima's D), and a high level of within-population genetic diversity compared to between-population genetic diversity. Mutation-selection, however,

predicts that the alleles causing variation will be individually rare in the population – for example, 99% of the population may have one variant and 1% may have many different, rare variants, each increasing risk of a disorder. Mutation-selection also tends to reduce genetic diversity in nearby regions (reflected by a low Tajima's D) and predicts high levels of between population genetic diversity. Neutral evolution generally makes predictions between mutation-selection and balancing-selection. **See also**: Neutrality and Selection in Molecular Evolution: Statistical Tests

In the future, as more and more risk alleles are identified, and as new methods that allow for complete sequencing of the genome become available, this type of evidence will be increasingly used to more directly test evolutionary hypotheses for the persistence of risk alleles. Unfortunately, we do not as yet have reliable knowledge on which alleles increase mental disorder risk. Twenty years of studies so far have produced meagre and inconsistent results, with suspected risk alleles typically explaining little population risk. One interpretation of such a pattern of findings is that a large number of loci, each harbouring many different risk alleles, affect mental disorder risk, and that each risk alleles has a relatively small effect on overall population risk. This itself is a necessary condition for mutation-selection to have much role in mental disorder risk, but it does not directly test the hypothesis.

Despite our imperfect knowledge of where mental disorder risk alleles are located, some studies have begun to investigate the genetic patterns of *suspected* risk loci. Recently, Crespi *et al*. (2007) investigated 76 loci suspected of influencing schizophrenia risk. Crespi *et al*. found that this group of loci was more likely to show signatures of having been under directional selection compared to a control group of loci. One interpretation of this finding is that recently selected loci, when disrupted by mutations, are more likely to lead to schizophrenia than loci that have not been under recent selection. However, some previous studies have also found that some of these 76 genetic loci (APOE, apolipoprotein E and CCR5, chemokine (C-C motif) receptor 5) show signs of having been under balancing-selection (Crespi *et al*., 2007). Future research may help clarify the relative importance of these processes.

Inbreeding depression

Inbreeding depression refers to the observation that offspring of genetic relatives tend to be less fit, and tend to score lower on fitness related traits, compared to offspring whose parents are unrelated. There are two basic reasons why inbreeding depression may occur – mutation-selection and balancing-selection – but both point to a common conclusion: traits that increase following inbreeding have been selected against across evolutionary time. Inbreeding has been associated with increased risk of several mental disorders, including mental retardation, schizophrenia and affective disorders (reviewed in Keller and Miller, 2006), which suggests that these disorders existed in ancestral environment, or at the very least that their risk alleles were deleterious to ancestral fitness.

However, as mentioned earlier, two different processes might lead to the genetic underpinnings of inbreeding depression. The first is overdominance: inbreeding increases homozygosity and decreases heterozygosity, thereby reducing fitness. The second process is mutation-selection: selection quickly removes from the gene pool mutations that have the most dominant effects, leaving the pool of existing mutations at any given time enriched with those that are partially recessive. By increasing homozygosity, inbreeding reveals the full negative effects of these partially recessive deleterious mutations. Although evidence from the 1940s to the 1980s seemed to support the overdominance hypothesis of inbreeding, evidence over the last 30 years from experimental organisms favours the mutation-selection cause of inbreeding depression (Bürger, 2000). **See also**: Inbreeding

Agents that increase mutation risk

There are several predictions that are unique to the mutation-selection hypothesis of mental disorder risk. One is that mental disorders should increase with paternal, but not maternal, age. This is because the number of replications that occur in sperm cells increases with the age of the male, whereas females are born with their full contingent of 400 or so eggs which do not require any additional replications as females' age. Importantly, each replication of sperm or egg cells carries with it a small chance of a copying error (i.e. mutation), meaning that the chance of new mutations in offspring increases with paternal but not maternal age. There is now strong evidence that paternal but not maternal age increases the risk of mental retardation, autism and schizophrenia (reviewed in Keller and Miller, 2006). This implies that new mutations (which tend to be more harmful than older mutations that have already been circulating in the population over many generations) increase the risk of these mental disorders, and by extension, also suggests that the more common but less harmful older mutations can do so as well.

Similarly, there is evidence that chromosomal abnormalities (translocations, inversions and so forth) can cause behavioural syndromes that mimic symptoms of bipolar disorder, autism, affective disorders, mental retardation and schizophrenia – indeed, except for the telltale physical signs associated with these chromosomal abnormalities, it is likely that patients with such chromosomal abnormalities would simply be diagnosed with a mental disorder. Chromosomal abnormalities are, in a sense, mutations of very large effect, except that rather than disrupting a single gene they tend to disrupt a large number of them. Again, the fact that large-effect mutations can increase mental disorder risk suggests that many small-effect ones could do the same.

A final line of evidence unique to the mutation-selection hypothesis of mental disorder risk comes from studies of radiation exposure, such as that following the Chernobyl

disaster. Radiation can cause mutations in normal cells (increasing the risk of disorders in those directly exposed to the radiation) as well as in reproductive cells (increasing the risk of disorders in the offspring of those exposed to radiation). In fact, both types of mutational risk – to those exposed to it and to the offspring of those exposed to it – have been linked to an increase in mental disorder rates.

Together, these lines of evidence strongly support the hypothesis that mutations play a role in the aetiology of mental disorders. Of course, such evidence does not imply that mutations are the sole – or even the primary – factor. Careful modelling and better data are necessary to understand the relative importance of mutations to mental disorder risk.

Fitness effects in relatives of those with mental disorders

Having just discussed an evidentiary standard unique to the mutation-selection hypothesis, we now turn to one that is unique to certain forms of balancing-selection. One consequence of antagonistic pleiotropy and overdominance is that the unaffected relatives of those suffering from a disorder or people premorbid for a disorder should manifest some compensatory fitness benefit. If, for example, an allele increases both the risk of schizophrenia and creativity, then unaffected people who carry this allele (schizophrenia patients investigated before onset and/or relatives of those with the disorder) should show higher creativity and higher reproductive success.

Indeed, such a link has been found: relatives of schizophrenics and those scoring highly on traits thought to be related to schizophrenia (schizotypal personality styles) appear to have a more creative cognitive style (Nettle and Clegg, 2006). This may well indicate some advantage to 'low doses' of schizophrenia risk alleles, but other explanations are possible. For example, with regard to the schizophrenia-creativity link, Nettle (2006) hypothesized that being highly creative in the context of a high-mutation background increases schizophrenia risk whereas it does not increase schizophrenia risk in a low-mutation background. According to this explanation, it is creativity alleles that are maintained by balancing-selection, and the cost of high creativity is only manifested when it occurs in a high-mutation background. This interesting hypothesis shows how mutational models and balancing-selection models need not be mutually exclusive.

Summary

Darwinian Medicine has mostly focused on understanding why *universal* capacities for disorders exist, such as the capacity for fever or depression. Until recently, there have been few attempts to use modern evolutionary genetics to understand the evolutionary persistence of genetic variation underlying mental disorder risk. Three models from evolutionary genetics – mutation-selection, balancing-selection and neutral evolution – provide an evolutionary framework for understanding the persistence of mental disorder risk alleles and, more generally, the genetic variation underlying any human disorder. As knowledge of the human genome grows, it is likely that genetic locations and the risk alleles of mental disorders will be identified, which will allow for more stringent tests of evolutionary genetic hypotheses. Until this point, however, several indirect tests of these hypotheses are available. Currently, this evidence suggests that mutation-selection accounts for at least some portion of the genetic variation underlying mental disorders, but such evidence does not preclude the possibility that future research will reveal important roles of balancing-selection and neutral evolution/time-lags.

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