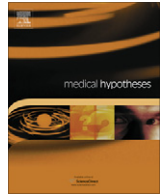




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## Unstable genes unstable mind: Beyond the central dogma of molecular biology

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### ABSTRACT

Schizophrenia has a polygenic mode of inheritance and an estimated heritability of over 80%, but success in understanding its genetic underpinnings to date has been modest. Unlike in trinucleotide neurodegenerative disorders, the phenomenon of genetic anticipation observed in schizophrenia or bipolar disorder has not been explained. For the first time, we provide a plausible molecular explanation of genetic anticipation and pathophysiology of schizophrenia, at least in part, with supporting evidence. We postulate that abnormally increased numbers of CAG repeats in many genes being expressed in the brain, coding for glutamine, cumulatively press for higher demand of glutamine in the respective brain cells, resulting in a metabolic crisis and dysregulation of the glutamate–glutamine cycle. This can adversely affect the functioning of both glutamate and GABA receptors, which are known to be involved in psychosis, and may also affect glutathione levels, increasing oxidative stress. The resulting psychosis (gain in function), originating from unstable genes, is described as an effect “beyond the central dogma of molecular biology”. The hypothesis explains genetic anticipation, as further expansions in subsequent generations may result in increased severity and earlier occurrence. Many other well described findings provide proof of concept. This is a testable hypothesis, does not deny any known facts and opens up new avenues of research.

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### Background

Schizophrenia and bipolar disorder are very highly debilitating mental illness with over 80% heritability risk [1], afflicting approximately 1.1% population around the world. Despite very intense efforts for the last two decades, and nearly 150 additional genetic association studies being reported every year, it is very frustrating that we are repeatedly coming up blank [2]. Over 150 genes and loci and genes have been proposed in human genome, to be associated with the disease and many later refuted. Observed high genetic risk has not been possible to be explained. The phenomenon of anticipation in psychoses has been pointed out since the 19th century and there are several reports of evidence for anticipation in schizophrenia [3]. Despite the strong evidence for a genetic component, very little is understood about the underlying genetic and molecular mechanisms for schizophrenia and BPAD [4]. It is well established that unstable trinucleotide repeat DNA is the biological basis of the clinical phenomenon of genetic anticipation observed in several neurodegenerative disorders like Huntington disease and therefore it was thought that the genetic anticipation observed in schizophrenia and bipolar affective disorders, could also be ex-

plained as unstable genes, unstable mind [5]. However, despite promising findings in the mid-1990s, no trinucleotide repeat expansion has yet been identified as a cause of idiopathic schizophrenia or bipolar disorder [4].

To us the clue for the hypothesis presented here, came from the observation that the frequency of longer CAG repeats in hSKCa3, was significantly higher in schizophrenic and bipolar patients than the ethnically matched control [6].

Francis Crick proposed central dogma of molecular biology (CDMB) in 1970, and today we know that all the phenotypes in an organism are governed by proteins constructed from DNA information. Herein we propose that there can also be phenotypic effects beyond CDMB, which may be of special significance in schizophrenia pathophysiology. Indirect metabolic effects of expression of expanded CAG repeats (unstable genes), causing unstable mind, is here described as an effect beyond CDMB.

The schizophrenia literature is very vast and encompasses many disciplines. We do not intend to review the literature, but present a very selective literature that we considered to be pertinent to validate the hypothesis. There is no intended omission of any literature contradicting the hypothesis, as we regard the hypothesis to accept all proven schizophrenia facts [7], in its fold. Proof of concept already exist, it is only the question of seeing them from a different window, which the hypothesis, presented here attempts to provide.

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## The hypotheses

The hypothesis (Fig. 1) states that

Expanded CAG repeats in many genes in the human genome, exceeding disease threshold, confers schizophrenia heritability. These CAG repeats, while getting translated into longer polyglutamine stretches, would press demand for abnormally high amount of glutamine in the respective brain cells.

Up regulation of glutamine, upsets the glutamine glutamate ratios, which in turn results in the of glutamate and GABA receptor dysfunction.

Depletion of glutamate can also lower the reduced glutathione levels, resulting in oxidative stress.

Metabolic crisis resulting in psychosis is in itself a toxic “gain in function”, further expansion of CAG repeats, in subsequent generations resulting in increase severity and earlier occurrence of the disease, are both characteristics of genetic anticipation phenomenon, for which molecular explanation is provided by the hypothesis.

We evaluate and present below evidence to validate the hypothesis.

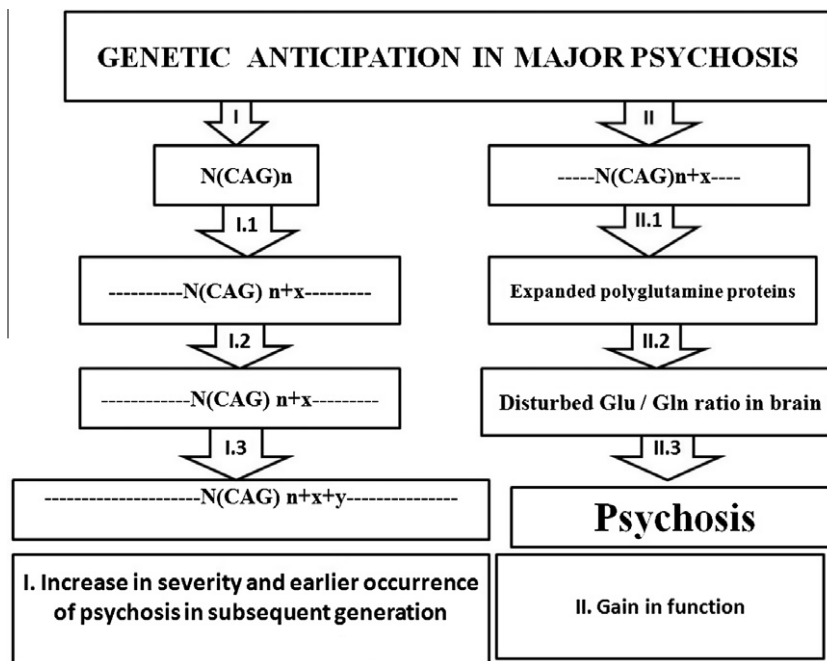
## CAG repeats

For the hypothesis to be valid there has to be a large number of expandable CAG repeats being expressed in human brain. Length distribution study of CAG-Q tracts, for the entire human genome in healthy individuals, has identified 64 CAG repeats in 62 genes. Size of CAG-Q tracts in these genes, ranged from 5 to 39.8 [8]. It is also evident that large number them are expressed in the brain

as earlier large scale screening for CAG repeats in human brain reference cDNAs, selected 124 CAG repeats [9]. Further DNA polymerase slippage has been proposed as primary mechanism for instability of trinucleotide and it is also suggested that slippage shows a bias toward expansion for short repeats, shortening of longer repeats [10].

It is intriguing that patients suffering from most of the established neurodegenerative CAG repeat disorders, more frequently show association with schizophrenia and bipolar disorder, indicating that CAG triplet expansions may underlie neuropsychiatric conditions. Increased incidences of schizophrenia-like symptoms in Huntington's disease (HD), has been reported [11]. Four patients with DRPLA, confirmed by genetic identification of an expanded CAG repeat, have been shown to develop schizophrenia-like psychosis [12]. The gene for spinocerebellar ataxia type1 (SCA1) is a potential candidate gene for schizophrenia because of previous positive linkage findings in this region (6p22-24), and significant association between the frequencies of alleles of this gene and schizophrenia [13]. SCA17 is caused by an expanded polyglutamine tract in the TATA box-binding protein (TBP) gene. Higher frequency of alleles with greater than 35 CAG repeats in patients with schizophrenia compared with that in controls has been reported [14]. Higher prevalence of psychotic conditions in CAG repeat neurodegenerative disorders provides further credence to the concept.

Similar to the observation in hSKCa3 gene [6], the findings that in certain population, in TBP gene also CAG repeats longer than the modal value is over-represented in schizophrenic patients [14], validates the hypothesis. Further the observation regarding hSKCa3 gene in schizophrenia [6], could not be replicated in Japanese population [15]. Hypothesis does not expect a uniform CAG polymorphism pattern though out the world. However over representation of longer CAG repeats in hSKCa3 was seen in Serbian population [16]. This variation in polymorphic pattern of CAG re-



**Fig. 1.** Molecular explanation to the genetic anticipation observed in major psychosis. Increase in severity and earlier occurrence of the disease in subsequent generation (I), gain in function (II) are the two characteristics observed in genetic anticipation, herein explained by CAG repeat expansions. Normal individuals would have  $N(\text{CAG})n$  repeats, wherein 'N' is the total number of polymorphic expandable CAG repeats expressed in the brain. 'n' is the total length of all the repeats in a healthy individual. In an affected individual 'n + x' is the expanded number of CAG repeats, wherein 'x' is additional abnormal number of CAG repeats added to the CAG repeats during DNA replication (meiosis or mitosis), responsible for psychosis (I.1). This would be genetically transferred (I.2). In subsequent generation, CAG repeats may get further expanded to  $N(\text{CAG})n + x + y$ , where in 'y' is further expansion of 'n + x' that would result in increase in severity and earlier occurrence of psychotic conditions, in the subsequent generation (I.3).  $(\text{CAG})n + x$ , would produce poly glutamine proteins with longer stretches glutamine (II.1) in specific region of the brain. This would in turn result in disturbance of glutamine glutamate ratios (II.2), culminating in psychosis (II.3). Resulting psychosis is the gain in toxic function, another characteristic of phenomenon of genetic anticipation.

peats in different population and occasional reports of association of longer CAG repeats in different genes (e.g. hSKCa3/TBP), actually forms the basis of our hypothesis.

### Thinking glutamatergically

Recently, there are trends of changing concepts in schizophrenia, based on glutamatergic models [17]. Glutamatergic theories, now seem to open new potential approaches for treatment of schizophrenia [18]. Although schizophrenia was once seen as a disease affecting only a few key brain regions and regionally discrete neurotransmitter systems such as dopamine, more recent findings implicate widespread cortical and subcortical dysfunction, suggesting more generalized etiology. On a neurochemical level, antagonists of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors, such as phencyclidine or ketamine, uniquely reproduce the symptomatic, neurocognitive and neurochemical aspects of the disorder, suggesting that regardless of underlying etiology, NMDA dysfunction represents a final common pathway leading from pathogenesis to symptoms. NMDA dysfunction may also account for both the impaired dopaminergic regulation and the impaired GABAergic neurotransmission that has been documented in schizophrenia. Hypothesis presented here, is in line with this changing concept.

### In vivo evidence

Alterations in the ratio of glutamine to glutamate are reported in the cerebrospinal fluid (CSF) samples of first episode and drug naïve schizophrenic patients, suggesting an abnormality of the glia-neuronal glutamate glutamine cycle in the brain of patients with schizophrenia. The ratio of glutamine to glutamate in the CSF of first episode and drug naïve schizophrenic patients was significantly higher than that of normal controls, although each level of glutamine and glutamate in the CSF of patients was not significantly different from that of normal controls [19].

Some of the brain metabolites, including glutamine and glutamate, can now be quantified in vivo by proton magnetic spectroscopy. Many proton magnetic resonance (1HMRS) spectroscopic studies consistently report that in vivo levels of glutamine/glutamate ratios, particularly in drug naïve patients, are increased in different affected parts of the schizophrenic brain [20]. It is also observed that, medication lowers levels of glutamine and glutamate ratio perhaps by somehow facilitating glutamate availability [21]. Interestingly it has also been shown that the duration of illness was significantly related to glutamine/glutamate ratio [22]. Increased glutamine and glutamine/glutamate ratio in the schizophrenia group in CSF and brain is consistent with the glutamatergic hypofunction model, and validates the hypothesis.

According to the hypothesis presented here, to meet the demands of excessive CAG repeats being expressed in schizophrenic brain, the glutamine levels are up regulated with corresponding drop in the levels of glutamate. Levels of glutamate in the brain are primarily controlled by glutamine. Therefore glutamate levels drop and the glutamine glutamate levels get elevated, as seen in proton MRS in vivo studies of schizophrenic brain [20–22] and also seen in CSF of schizophrenic patients [19].

1HMRS study has also shown that there is no correlation between plasma levels of glutamic acid and glutamine with that of the levels found in the brain [23]. Therefore elevation of glutamine levels and depletion of glutamate levels by expressions expanded CAG repeats in schizophrenic brain can be expected to have a very serious consequences as external help is not readily available.

Eicosopentanoic acid treatment are known to significantly improve the disease outcome [24]. In a 1HMRS study it has been

shown that following E-EPA administration, glutathione and glutamate/glutamine increased in brain [25]. Omega-3 fatty acid supplementation seems to facilitate metabolite (glutamine, glutamate transport) exchange between the compartments. This links our concept with phospholipid and oxidative theories of schizophrenia.

A 3-T HMRS study, reports that glutamate/glutamine was significantly higher in the adolescents at high genetic risk for schizophrenia, than in the low-risk offspring [26]. The finding of glutamate/glutamine abnormalities in subjects at high genetic risk for schizophrenia, even before the disease actually sets in them, links our concept to the neurodevelopmental hypotheses of schizophrenia. It is worth noting here that in childhood onset schizophrenia, rare but more severe form of the disease, long polyglutamine stretches could be detected in a western blot by monoclonal antibody [27].

### Disregulations of genes

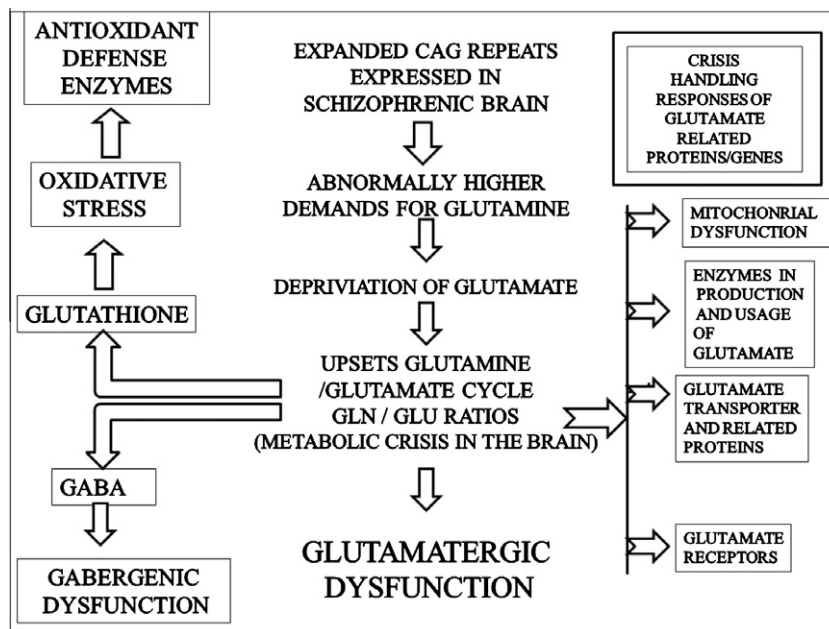
To get insight into the molecular mechanisms of schizophrenia, 160 schizophrenia candidate genes were prioritized by a multi-dimensional evidence-based gene ranking approach, glutamate ranked on the top of the neurotransmitters [28]. Many of the genes shown to be susceptible may seem, unrelated to glutamate receptors, but applying glutamate theory, seems to bring some order in the chaos [29].

As almost no glutamate crosses from blood to brain, it must be synthesized in the central nervous system. Glutamine is the main source for glutamate in the brain. There is compartmentation of brain glutamate metabolism in neurons and glia [30]. In order to keep the intrasynaptic glutamate low, rapid uptake glutamate into astrocytes and its conversion to glutamine, a non-neuroactive form has to be accomplished. Glutamine is then released to neurons via mitochondrial glutaminase form the glutamate used for neurotransmission. This pattern of metabolic compartmentation of glutamate–glutamine cycle, maintains low external glutamate and maximizes signal-to noise ratio upon depolarization.

According to the concept presented here, to meet the higher demand of glutamine forced by the expression of excessive CAG repeats in specific brain cells, glutamine levels are up regulated resulting in deprivation of glutamate resulting in glutamatergic dysfunction. The observed several up and down regulations of genes (Fig. 2), related to glutamate production and consumption [31], glutamate transport [32] and related proteins [33], GABA synthesis [34], glutathione synthesis [35].

Na<sup>+</sup>/K<sup>+</sup> dependant, Glutamate transporter (GLT) are found in neuronal and glial membranes. They rapidly remove glutamate from the extracellular space. Increased expression of GLT in schizophrenics has been reported [32]. The excitatory amino acid transporters (EAATs) are a family of plasma membrane proteins that maintain synaptic glutamate concentration by removing glutamate from the synaptic cleft. Increased expression of EAAT1 and 2 and JWA and KIAA0302, EAAT- interacting proteins, molecules that regulate EAAT3 and EAAT4 have been reported [33]. Less N-glycosylation of both EAAT1 and 2 has also been reported [36]. These findings suggest that genes/proteins associated with the regulation of glutamate levels by its synthesis, degradation, conversion to other metabolites such as GABA, glutathione, its transport across the membranes, may become abnormal in schizophrenia, and this deregulations may be a consequence of expanded CAG repeat expression (Fig. 2).

In schizophrenia there is a growing evidence base supporting dysregulation of mitochondrial energy generation and a parallel increase in oxidative stress [37]. Super oxide dismutase 2 (SOD2) and glutathione peroxidase 3 (GPX3) showed association with bipolar disease [38,39].



**Fig. 2.** Crisis handling responses of glutamate related enzymes/proteins gene expressions in the brain. To meet the unusual excessive demand for glutamine, glutamine levels need to be up regulated, perhaps at the cost of depletion of glutamate resulting in disturbed glutamine/glutamate ratio. Crisis handling responses of deregulations of related enzymes/proteins/genes, involved in glutamate synthesis and utilization, receptors, transport, GABA synthesis, glutathione synthesis, antioxidant defense enzymes, mitochondrial dysfunction, are observed, and provide proof concept.

Omega-3 fatty acids are essential for normal brain development, synaptic plasticity, to modulate membrane fluidity. Decreased omega-3 fatty acids levels have been found in blood. The underlying *in vivo* mechanisms of action of omega-3 fatty acids are still speculative, because treatment response have been associated with an increase in omega-3 fatty acids in blood and it correlates with improved disease outcome [40].

There is evidence that free radicals are involved in membrane pathology and may play a role in schizophrenia [40]. Being regions of high oxygen consumption, high lipid content, neuronal membranes are uniquely vulnerable to free radical damage. Elaborate antioxidant systems operate to protect against oxidative stress. In schizophrenia there is evidence for abnormal activities of antioxidant enzymes, and other lipid peroxidation indices in plasma, red blood cells and cerebrospinal fluid. Significantly lower levels of GSH, Glutathione peroxidase, and Glutathione reductase (GR) were found in schizophrenic group than in control groups. Concomitantly, a decreased GSH: GSSG ratio was also found in schizophrenic group. Moreover, both GSSG and GR levels were significantly and inversely correlated to age of schizophrenic patients, but not control subjects [35]. Almost half the altered proteins identified by proteomics were associated with mitochondrial function and oxidative stress responses [28]. This was mirrored by transcriptional and metabolite perturbations. Cluster analysis of transcriptional alterations showed that genes related to energy metabolism and oxidative stress differentiated almost 90% of schizophrenia patients from controls. It has been proposed that oxidative stress and the ensuing cellular adaptations are linked to the schizophrenia disease. It is suggested that impaired capacity to synthesize GSH under conditions of oxidative stress is a vulnerability factor for schizophrenia [41]. The gene of the key GSH synthesizing enzyme, glutamate cysteine ligase, modifier (*GCLM*) subunit, has been shown to be strongly associated with schizophrenia in two case-control studies and in one family study [42].

It is plausible therefore that several of the deregulations (Fig. 2), may very well be a compensatory, crisis handling gene re-

sponses, to meet the excessive glutamine demands, put up by expanded CAG repeats in schizophrenic patients.

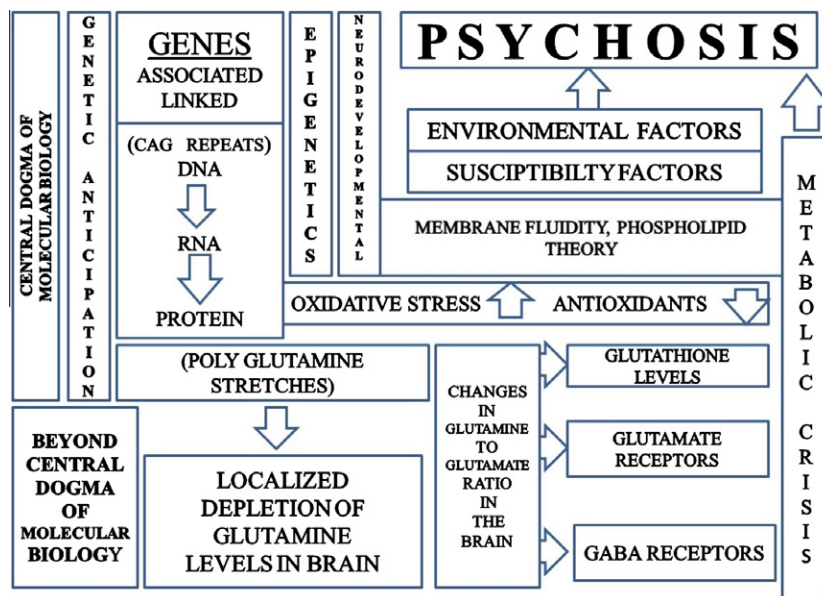
### Concluding remarks

The hypotheses provides molecular explanation to the familial nature of schizophrenia, and also perhaps to sporadic emergence of schizophrenia in a family, and most importantly to the phenomenon of genetic anticipation. The “unstable genes-unstable mind-beyond CDMB” is a very radical hypothesis, but seems very plausible with supportive evidence provided herein as proof of concept. Model is all inclusive as it accepts all known facts in its fold. (Fig. 3).

This is a testable hypothesis. Occasional observation of over representation of longer CAG repeats in hSKCa3 [6] or TBP [12] in schizophrenic patients in certain population forms the basis of the concept. It is surmised that polymorphic pattern of all the CAG repeat genes, may show closer similarity in a population. Further in a family, more closer resemblance of CAG polymorphic pattern, a characteristic CAG finger print, may be observed. The presence of unique longer CAG repeat length polymorphism in many CAG repeat genes may be characteristic of a schizophrenia patient and may also account for phenotypic variations in different schizophrenic patients, depending upon which part of the brain these expanded CAG repeats are being expressed.

This is a radical hypothesis if proved and accepted, opens up a new avenues of research. Further it suggests a very simple nutritional therapy. Omega-3 fatty acids along with antioxidants (vitamin C and E) [43] and N-acetyl cysteine [44] has been shown to have potential as a safe and moderately effective augmentation strategy for chronic schizophrenia.

Therefore, based on the hypothesis presented here and also on the favorable outcome reported in the literature for N-acetyl cysteine [44] and omega-3 fatty acid supplementation [24,43], we infer that glutamine, N-acetyl cysteine and omega-3-fatty acids, in conjunction with antipsychotic drugs if needed, that may be



**Fig. 3.** All inclusive model that accommodates all the confounding factors, associated and linked genes, neurodevelopmental, epigenetic, phospholipid theories etc. but at the same time, model, stipulates that CAG repeat expansion in multiple CAG repeat genes, as the main genetic basis of psychosis, as it explains genetic anticipation.

very effective. Glutamine supplementation may be helpful correcting the imbalance of glutamate/glutamine ratio in the brain. The precursors N-acetyl cysteine and glutamine acting synergistically can elevate glutathione levels to combat the oxidative stress. Omega-3 fatty acids may improve the functioning of receptors and transport of metabolites across the membrane in brain.

Although the disease prevalence is around 1% all over the world, significant differences in disease outcome are observed, possibly because of cultural socioeconomic differences in dietary intake of essential fatty acids and antioxidants [45]. David Horrobin proposed that the variation in phospholipid biochemistry may be responsible for both for schizophrenia and for our humanity [46]. It is very interesting that similar polymorphism is observed in CAG repeat genes in nonhuman primates, but the length of the repeat is smaller than present in human genes [47]. David Horrobin surmised from his phospholipid theory that schizophrenia is an illness that made us human, and it is very interesting that the expanded CAG repeat theory also arrives at the same conclusion.

### Conflicts of Interest statement

None declared.

### Acknowledgments

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