The emerging fragile X premutation phenotype: Evidence from the domain of social cognition

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Abstract

Fragile X syndrome is a neurodevelopmental disorder that is caused by large methylated expansions of a CGG repeat (>200) region upstream of the FMR1 gene that results in the lack of expression of the fragile X mental retardation protein (FMRP). Affected individuals display a neurobehavioral phenotype that includes a significant impairment in social cognition alongside deficits in attentional control, inhibition and working memory. In contrast, relatively little is known about the trajectory and specificity of any cognitive impairment associated with the fragile X premutation (“carrier-status”) (approximately 55–200 repeats). Here, we focus on one aspect of cognition that has been well documented in the fragile X full mutation, namely social cognition. The results suggest that premutation males display a pattern of deficit similar in profile, albeit milder in presentation, to that of the full mutation. However, little evidence emerged for a correlation between CGG repeat length and severity of phenotypic outcomes. The findings are discussed in the context of functional neuroimaging and brain-behaviour-molecular correlates. We speculate that the deficiencies in social cognition are attributable to impairment of neural pathways modulated by the cerebellum.

1. Introduction

Fragile X syndrome is the most common form of heritable mental retardation, affecting approximately 1 in 4000 males and 1 in 6000 females (Turner, Webb, Wake, & Robinson, 1996). In recent years, it has become one of the most widely researched and well-documented of genetic conditions. In nearly all cases, the syndrome is caused by an expansion of the CGG repeat at the beginning of the FMR1 gene on the X chromosome. This expansion leads to methylation of the promoter sequence and loss of the “fragile X mental retardation protein” (FMRP) (Verkerk et al., 1991). In normal individuals, there are 7–60 repeats, with 30 repeats found on the most common allele (DNA sequence at FMR1 gene site). Alleles with between 55 and 200 repeats are called “premutations” and generate some protein. When 200 or more CGG repeats are present, there is hypermethylation and a subsequent silencing of the FMR1 gene. This is commonly referred to as the FMR1 full mutation. However, unlike females affected by the mutation, full mutation males are hemizygous and therefore often display a more pronounced phenotype that is characterised by significant developmental delay. In contrast, individuals with a premutation (an expansion of 50–200 CGG repeats) possess

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unmethylated versions of the \textit{FMR1} gene and therefore have normal or near-normal levels of FMRP (Devys, Lutz, Rouyer, Bellocq, & Mandel, 1993). The frequency of the fragile X premutation in the general population is estimated at 1 in 250 females (Rousseau, Rouillard, Morel, Khandjian, & Morgan, 1995) and 1 in 813 males (Dombrowski et al., 2002) and has generally been associated with normal intellectual functioning. Although the various phenotypic effects of the premutation are likely to be subtle in comparison with the full mutation, the greater effects of the premutation are likely to be subtle in comparison with the full mutation, the greater prevalence of this condition warrants investigation of possible neurocognitive and neurobehavioral effects.

In terms of the neurological expression of the full mutation, studies have revealed decreased size of the posterior vermis of the cerebellum in males and females (Mostofsky et al., 1998; Reiss, Aylward, Freund, Joshi, & Bryan, 1991). Other structures affected by \textit{FMR1} status include the caudate nucleus (Eliez, Blasey, Freund, Hastie, & Reiss, 2001) and the hippocampus (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997; Reiss, Lee, & Freund, 1994). In addition, several studies reported a correlation between neuroanatomical abnormalities and the degree of functional impairment in the full mutation. For example, posterior vermis volumes are positively correlated with performance on specific measures of intelligence, visual–spatial ability, and executive function suggesting a putative functional role for this structure (Mostofsky et al., 1998). Taken together the purely structural and combined structural/functional studies implicate the cerebellum, caudate nucleus, and hippocampus as potential sites for phenotypic effects from abnormal \textit{FMR1} gene expression.

Another source of valuable information regarding vulnerable candidate brain structures comes from the expression profile of FMRP in the unaffected brain. For example, Kogan et al. (2004) showed a relationship between local higher basal FMRP expression levels in the magnocellular pathway of the thalamus—a pathway associated with visual deficits in full mutation individuals. Identified areas with relatively higher \textit{FMR1} gene expression include in the mouse, the hippocampus and cerebellum (Hinds et al., 1993), in human embryos, differentiating neurons of the nucleus basalis magnocellularis, the hippocampus, discrete cortical areas, and to a lesser extent the cerebellum (Abitbol et al., 1993). Such findings are consistent with imaging studies showing structural abnormalities in the same brain regions of individuals with the full mutation. However, it is important to stress that abnormal structures form part of widely distributed networks and that deficits may be observed across a broad range of activities. For example, in addition to motor control and the acquisition of complex motor sequences, the cerebellum in its connection with the frontal lobes has more recently been implicated in higher order processes, including social cognition (Riva & Giorgi, 2000).

Recent work by Hagerman and colleagues indicate that a subgroup of older males (>50 years) with the premutation may have an increased risk of developing a progressive cerebellar ataxia and tremor (Berry-Kravis et al., 2003; Jacquemont et al., 2003). Associated neurobiological findings in this subgroup include generalised brain atrophy, elevated FMR1 messenger RNA levels and autopsy findings of widespread eosinophilic nuclear inclusion bodies in CNS neurons and glia (Greco et al., 2002). Such findings suggest that that brain regions compromised in full mutation males and females may be susceptible in some carriers.

At the \textit{cognitive level}, there are relatively few studies that have examined the pattern of any deficit in the fragile X premutation—fewer still have defined the premutation male phenotype. In contrast, the profile of males with the FMR1 full mutation is now well documented and there is an abundance of evidence showing that fragile X is not a syndrome characterised by global mental retardation. Instead, the profile can be characterised by uneven abilities within and across cognitive domains. Relative strengths in vocabulary (Dykens, Hodapp, & Leckman, 1987), verbal working memory (Jakala et al., 1997), and long-term memory for meaningful and learned information (Freund & Reiss, 1991) are accompanied by relative weaknesses in attentional control (Cornish et al., 2004; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004; Wilding, Cornish, & Munir, 2002), executive functions (Cornish, Munir, & Cross, 2001; Estevez-Gonzalez, Roig, Piles, Pineda, & Garcia-Sanchez, 1997), and linguistic processing (Ferrier, Bashir, Meryash, Johnston, & Wolff, 1991; Sudhalter, Cohen, Silverman, & Wolf-Schein, 1990).

In the domain of social cognition, recent findings indicate that individuals with the full mutation demonstrate deficits in mentalising (“theory of mind”) abilities, (Cornish, Burack, Rahman, Russo, & Grant, in press; Garner, Callias, & Turk, 1999) alongside impairments in basic face recognition and emotion perception (Cornish, Munir, & Cross, 1998; Turk & Cornish, 1998). Although these studies did not report comparable levels of impairment to those typically associated with autism, strong similarities between the two syndromes exist. Commonalities include echolalia, repetitive speech, social avoidance, and hand flapping in response to anxiety and excitement (Ferrier et al., 1991; Turk & Graham, 1997).

1.1. The present study

Here, the main objective was to examine whether the FMR1 premutation has a phenotypic effect in adulthood and, in particular, whether there are subtle abnormalities in the social cognition of this group. In contrast to previous studies, we aimed to use a sample with sufficient power to examine the relationship between CGG repeat size and postulated cognitive deficit. By looking
across a wide age range, we could also establish whether, as with the motor control results discussed above, there may be a trajectory moving from subtle to more obvious impairment over the years.

Perhaps particularly for social cognition tests, variability may arise from cultural factors in addition to more individual differences in ‘basic’ perceptual, semantic and intellectual capacities. Selecting an appropriate control group is therefore crucial. Here, we adopted two. The first was recruited from genetically normal (6–39 CGG repeats) male relatives of our index group who, in general, would share socio-economic and cultural backgrounds with the premutation participants. A slight drawback of this approach is that, if the premutation is associated with subtle impairments in intellectual as well as social function, this group may not be well matched to the experimental population on general factors such as IQ. A second possibility is that the control group—through having an affected relative or through showing subtle problems themselves—may under-represent the difficulties faced by the premutation group in any comparison. Accordingly, we recruited a second control group from members of the general population with no family history of fragile X who were matched on age and IQ with the premutation group.

We used two measures designed to tap “mentallising abilities” (see below) and facial expression recognition—both capacities known to be compromised in males with the full FMR1 expression. In addition, given the evidence of communication difficulties in boys with full mutations (Turk & Graham, 1997), boys with premutations (Aziz et al., 2003) and girls with the full mutation (Keysor & Mazzocco, 2002; Mazzocco, Baumgardner, Freund, & Reiss, 1998) we employed the self-report Autism Spectrum Quotient instrument.

2. Methods

2.1. Participants

Group 1 comprised 22 adult males with a fragile X premutation (“carrier”) who were recruited through the UK Clinical Genetic Service Centres and the UK Fragile X Society. Participant’s ages ranged from 18 to 69 years with a mean age of 47.91 years (SD 15.79). Group 2 comprised 22 non-affected adult males from FXS families (familial controls) who were age matched (within a 5 year window) to the premutation males. Their ages ranged from 20 to 67 years, with a mean age of 40.8 years (SD 12.9). Group 3 comprised 22 non-affected adult males with no family history of FXS (non-familial controls) who were recruited from the local area and matched individually on age to the premutation group. Ages ranged from 20 to 68 years, with a mean age of 44.6 years (SD 14.8).

Table 1
Mean CA (SD) and IQ scores across the three groups: Premutation males, familial and non-familial controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Premutation</th>
<th>Familial</th>
<th>Non-familial controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>47.91 (15.8)</td>
<td>40.8 (12.9)</td>
<td>44.6 (14.8)</td>
</tr>
<tr>
<td>IQ</td>
<td>105.18 (10.5)</td>
<td>114.82 (12.8)</td>
<td>114.00 (10.5)</td>
</tr>
</tbody>
</table>

All participants were tested (individually) on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). This test provides a composite IQ score based on four subtests tapping both verbal and performance domains. Table 1 shows a summary of mean chronological age (CA) and IQ across the three groups.

The three groups were well matched on age ($F(1.306) = 0.278, \text{ ns}$). There were significant differences between the groups for IQ ($F(4.960) = 0.010$). Post hoc analysis (Scheffe) revealed that the Premutation group had a lower mean IQ than the familial ($p = .025$) and non-familial control groups ($p = .043$). There was no significant difference in IQ between the two control groups.

2.2. Fragile X DNA testing

Direct PCR was carried out using primers F5'CACGACGTGTAAACGACGAGGAGGCGCCGGCTGC, CAGG, R5'GAGAGGTGGGCTGCGGGCGCTG, modified from Wang, Green, Bobrow, and Mathew (1995) at 0.5 pmol final concentration. Conditions were as follows: Final concentration 1 mM MgCl₂, dATP, dCTP, and dTTP at 0.2 mM, 7-deazaGTP (Amersham Pharmacia Biotech) at 0.4 mM supplemented with 5% DMSO in a total volume of 20 μl. Cycling conditions were 32 cycles at 67 °C annealing. Products were separated on PAGE gels and visualised by silver staining according to standard protocols. Where the premutation was visible on PCR the repeat size was calculated according to size markers and by electrophoresing the products in size order and aligning the stutter bands. Southern blotting was carried out according to standard protocols on genomic DNA using a double digest of EcoR1 (NEB) and the methylation sensitive enzyme Eagl (NEB) and probed with Ox1.9 (Knight et al., 1993).

Sizing was relative to a female control of known repeat size. Where possible, repeat sizes derived from SB were compared to those obtained from direct PCR. Repeat sizes of those individuals who gave a result on direct PCR and on SB were congruent. Blots were overexposed to detect any evidence of mosaicism against a known mosaic control. A premutation was an allele between 55 CGG repeats up to approximately 200 repeats without any evidence of abnormal methylation. Mosaicism was considered present when there was evidence of a methylated cell line as well as an unmethylated premutation cell line.
2.3. Test materials

In the present study, tasks that tapped both simple and complex mental states were administered to participants. These tasks were chosen because they had been developed for use with normal adults and are powerful enough to detect subtle individual differences in social sensitivity.

2.4. Facial expression recognition test (Ekman & Friesen, 1971)

To test for the ability of judging simple mental states in human faces, the present study used the well-known and cross-cultural concept of seven basic emotional states by Ekman and Friesen (1971). This test consists of 70 black and white photographs of actors’ faces posing happy, sad, fearful, angry, surprised, disgusted, or neutral emotional expressions. Participants were required to look at each photograph and choose the verbal label that best described the emotion. All pictures were shown for 3 s, followed by a 5-s pause for the subject to give his response. The maximum score was 70.

2.5. Revised eyes test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001)

The Revised Eyes Test is a more extensive version of the original test developed by Baron-Cohen, Jolliffe, Mortimore, and Robertson (1997) and comprises items related only to complex mental states. The stimuli for this test consist of 35 black and white photographs taken from larger photographs in popular magazines. Each pair of eyes is digitised and cropped such that the remaining image was black and white and measured 2 by 5 in, showing the eye region of faces, from just above the eyebrows to the bridge of the nose. Baron-Cohen, Wheelwright, Skinner, Martin, and Clubley (2001) and Baron-Cohen, Wheelwright, Hill et al. (2001) asked two judges to generate target words and foils for each picture in open discussion. These target words were then tested with their semantic opposites as foils on groups of eight judges (four male and four female). The criterion adopted was that at least five out of the eight judges agreed that the target word was the most suitable description for each stimulus and that no more than two judges picked any single foil.

Participants were asked to look at each photograph one at a time and to choose the word (from a choice of 4) that best describes what that individual may be thinking or feeling. For example, the correct response of “panicked” needed to be selected from three foil terms, “jealous”, “arrogant,” and “hateful”. All pictures were shown for 3 s, followed by a 5-s pause for the participants to give his response. Immediately before the test, participants were asked to read through the glossary and indicate any word meanings of which they were unsure (in practice, none of the participants asked for clarification). The maximum score was 35.

2.6. Autism spectrum quotient (AQ) (Baron-Cohen et al., 2001)

The AQ is a self-assessment screening instrument developed by Baron-Cohen, Wheelwright et al. (2001) to measure the degree to which an individual of normal intelligence shows autistic traits. Participants were presented with 50 statements about different aspects of social functioning: social skill, attention switching, attention to detail, communication, and imagination. Each subscale comprised 10 statements, with participants being asked to either agree, slightly agree, slightly disagree, or definitely disagree with each. In addition to individual subscale scores, an overall score can be derived.

2.7. Procedure

With approval from regional and local ethical committees, and after receiving informed consent, the participants were tested in a quiet setting, generally their own homes. Feedback was not given on individual performance.

3. Results

3.1. Revised eyes test

To examine whether premutation was associated with difficulties in reading emotions from the eyes, the performance of the three groups on the Revised Eye Test was compared using ANCOVA. To establish whether any difference was greater than one would expect based on the observed IQ differences, both IQ and age were covaried out. There was a statistically significant group effect \( F(2,64) = 5.27, p < .005 \). Post hoc Scheffé tests confirmed that the FXS premutation group performed significantly worse \( (p < .001) \) than either of the control groups. There was no significant difference between the premutation and familial control group or between the familial and non-familial control groups. The percentage of errors across groups is shown graphically in Fig. 1.

3.2. Facial expression recognition test

Performance of the three groups on the Facial Expression Recognition task was again compared using ANCOVA with age and IQ covaried out. There was a statistically significant effect of group \( F(2,64) = 4.23, p = .02 \). Scheffé post hoc analysis revealed that the difference between the premutation group and the non-familial controls was statistically significant \( (p < .05) \), whilst
3.3. Autism spectrum quotient

There were no significant group differences in the total score from this self-report measure \(F(2, 64) = 1.928, p = .2]. However, analysis of the five categories showed a significant group difference for the Attention Switching subscale \(F = 4.068, p < .02\). The statements in this category refer to a preference for rather fixed routines, emotional distress at changes in routine, and a tendency to focus on details (for example, “I tend to have very strong interest, which I get upset about if I can’t pursue”, and “I prefer to do things the same way over and over again”). Scheffé tests revealed a similar pattern to that reported above, with the critical difference in performance between the premutation group and non-familial controls \((p < .012)\). There were no other significant group differences across the categories.

3.4. Relationship between chronological age and performance on the Revised Eyes task, Facial Expression task, and the AQ

Previous research examining motor function in males with the premutation has suggested an exaggeration of relative impairment with increasing age. Here, we examined relationships with age across this measures using correlation within the premutation group. With IQ co-varied out, a robust relationship with age emerged on the Facial Expression task \((r = -.63; p = .002)\), with older participants experiencing more difficulty on this measure. A similar pattern emerged for familial controls \((r = -.44; p = .05)\). Previous research has shown normal ageing effects on a similar test of facial recognition that particularly compromise the recognition of fear and, to a lesser extent, anger expressions (Calder et al., 2003). In the premutation group here, the relationship between fear recognition and age was minimal \((r = -.164 \ p = .466)\), and indeed no single face category–age relationship reached statistical significance in isolation. The results therefore suggest a general decline in sensitivity to emotional expression with age that cannot be explained purely on the basis of general intellectual decline. There were no other significant correlations.

3.5. Relationship between the premutation CGG repeat length and performance on the revised eyes task, facial expression task, AQ, and IQ

There were no significant correlations between number of CGG repeats in the premutation range and performance on the Revised Eyes task \((r = .27; p = .34)\), the Facial Expression task \((r = -.14; p = .63)\), or on the AQ \((r = -.04; p = .88)\). There was no also no correlation between IQ and CGG repeats \((r = 19; p = .52)\).

4. Discussion

To date, this is the first study to investigate social cognition in FMR1 premutation adults and one of the few studies to incorporate a population-based, non-clinical sample together with age-matched familial and non-familial controls. Our primary aim was to establish...
whether individuals with the FMR1 premutation show subtle impairments on tasks of social cognition, tasks that are typically impaired in individuals with the full mutation. In addition, we sought to identify the trajectory and specificity of any such impairment—in particular, whether phenotypic effects become more severe with age. Finally, we assessed the extent to which variability in performance might be explained by the size of the expansion in the FMR1 gene.

The results may be summarised as follows:

1. Males with the premutation performed significantly more poorly than males without the premutation on a task requiring recognition of complex emotions/inference of mental state from photographs of eyes. This relative impairment was over and above that which might be anticipated on the basis of general ability, as indexed in IQ. A similar pattern was observed on a task requiring recognition of emotion from the whole face. Notably, the difficulties experienced by the premutation group were most apparent when categorising neutral expressions. As these were not the most difficult for the control group, it suggests that task difficulty per se cannot account for the finding. Similarly, the adequate performance of the premutation group on some but not all expressions suggests that basic perceptual problems are unlikely to account for the effect. Importantly, this finding is consistent with previous research reporting similar but more severe problems in individuals with the FMR1 full mutation (Cornish et al., in press; Garner et al., 1999; Turk & Cornish, 1998). This suggests that social perception difficulties may lie on a continuum. Although this idea is not supported by the correlation analysis between CGG repeat expansion size and performance on the Revised Eyes Task, the somewhat limited range of expansion sizes (78–164) of the premutation males in the present study may preclude establishing such a relationship.

2. On a self-report questionnaire of social difficulties, the strongest difference between the premutation and the non-familial control group lay in the attention switching factor. At a cognitive level, problems in attention switching and control have been reported as a fundamental deficit in the FMR1 full mutation (Munir, Cornish, & Wilding, 2000; Wilding et al., 2002). It is has been suggested that this control requires a balance of excitation and inhibition, to enable switching from one attentional focus to another, or from one emitted response to the next response in a sequence. In the present study, premutation males may display a subtle yet similar profile to that of full mutation males. At the behavioural level, this may result in problems in over focusing and a fixation on details, whilst at the cognitive level, our preliminary analysis of attention and executive functioning in this group is strongly suggestive of executive dysfunction (Cornish, Manly, James, Mills, & Hollis, 2003). Although speculative, it is possible that the subtle impairments in executive functioning can be accounted for by disturbances in the cerebellum, which can modulate executive functions subserved by frontal cortex. Such deficits have been described previously for patients with cerebellar atrophy (Grafman et al., 1992), impairments normally attributed to damage of the frontal lobe. Schmahmann and Pandya (1997) have demonstrated that there are indeed corticopontine pathways from prefrontal areas suggesting that the cerebellum contributed to the network of brain areas critical for higher-order cognitive processes.

3. Previous research has demonstrated that, for motor abilities, there is an interaction between premutation status and age—with abnormalities becoming marked in older age. There was a remarkably strong relationship between worsening performance in categorising emotional expressions and increasing age in the premutation and—to a lesser degree—in the familial control group. The direction of the relationship in the Revised Eyes Test was consistent with this finding for both groups, although insufficient to reach statistical significance. Unlike normal ageing effects that disproportionately compromise the recognition of fear and anger expressions (e.g., Calder et al., 2003); the decline in the premutation group appeared to be more general. This effect is unlikely to be explicable on the basis of more general intellectual decline with age and, given the relatively good performance of many members of this group on some aspects of this task, unlikely to result from basic perceptual processing problems.

4. A notable trend across the emotional cognition tasks employed here is that, although differences between the relatives of participants with the FMR1 premutation and non-related controls were not sufficient to reach statistical significance, often the performance of this group fell somewhere between the premutation and non-familial groups. This occurred despite the “unaffected” relatives being well matched in terms of general ability. This raises the question of whether, across a large sample, there are subtle effects of having one or more relatives affected with full mutation fragile X, whether there are other social factors that interact with fragile X prevalence, or whether indeed these relatives may themselves show very subtle problems with no currently obvious cause.

Our finding of a selective deficit in social cognition in premutation carriers raises the interesting possibility that the cerebellum might serve as a neurobiological locus for these abilities. Evidence from aging premutation carriers indicates that abnormal FMR1 mRNA levels in this population have their greatest impact on cerebellar functioning (Berry-Kravis et al., 2003; Hagerman et al., 2001; Jacquemont et al., 2003; Jacquemont et al., 2004). Although premutation status does not appear to guarantee development of ataxia and tremor in later life,
there seems to be a significant increased vulnerability of this brain structure with increased CGG repeat number. Moreover, one of the most consistent findings from research into the neuroanatomical abnormalities associated with autism, a condition where similar deficits in social cognition have been reported, (e.g., Baron-Cohen, Wheelwright, Hill et al. (2001)), indicates that there are structural abnormalities of the cerebellum. Furthermore, mounting evidence implicates the cerebellum, as being critical for non-motor functions, including language, thought modulation, and social behaviour. Riva and Giorgi (2000), for example, observed that children with lesions of the cerebellar vermis involving the posteroinferior lobules had autistic-like disruptions of social and communicative behaviour. Finally, the expression pattern of FMRP in the brains of mouse embryos and to a lesser extent in human embryos reveal relatively higher levels of the protein in the cerebellum, suggesting that alterations in the function of FMRP might have a detrimental impact on this brain structure (Abitol et al., 1993; Hinds et al., 1993). Future research should examine the contribution of the cerebellum to the social cognition deficits in fragile X syndrome. Specifically, these studies should investigate the relationship among mutation status, neuroanatomical variations in the cerebellum, and performance on neuropsychological measures of social cognition.

In conclusion, the findings of the present study provide evidence of a subtle yet measurable effect of the FMR1 premutation on aspects of social cognition, namely for skills that require accurate social perception. Consistent with previous research, the pattern of deficit is similar in profile, albeit milder in presentation, to that of the full mutation, indicating that the premutation does not come without some degree of cognitive risk. Future research will need to address whether there is an increased risk of impairment to individuals who have CGG repeat sizes in the higher premutation range (>150), whether the effects generally worsen with age. It is possible that the severe clinical profiles of ataxia and tremor reported in previous studies included males in the upper premutation range and that the potential of developing such pathology is directly related to FMR1 repeat size. Finally, it is crucial that future research address the phenotypic consequence of premutation status in childhood as well as the developmental timing of any impairment. This will allow interventions to be targeted more appropriately and prior to the development of irreversible neuropathology. Furthermore, it may allow for identification of at risk premutation individuals for the development of more serious pathology later in life. A longitudinal study of premutation males may assist in our understanding of the impact of the repeat expansion on the neurobiology as well as the unique features of perception, cognition, emotion, and behaviour in this population.

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References


