Does genetic testing for ERα gene polymorphisms provide new possibilities of treatment for cognitive function disorders in postmenopausal women?

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Abstract

It is commonly considered that cognitive abilities decrease with age, especially with respect to processing and psychomotor speed. It is an interesting issue whether, apart from the ageing process, the undergoing of menopause itself deteriorates cognitive functions, compared to women at reproductive age. Hopes for improvement of cognitive functions were pinned on the use of menopausal hormone therapy. However, the results of studies concerning the effect of hormone replacement therapy on cognition proved to be contradictory. It seems that the essence of the problem is more complicated than only estrogen deficiency. It is suggested that estrogen receptor α (ERα) polymorphism may be responsible for the differences in the effect of estrogens on cognitive processes. The article presents current knowledge concerning the effect of estrogens on the central nervous system, especially the role of ERα polymorphism, with respect to foreseeing benefits from the use of exogenous estrogens for cognitive functions. At the present stage of research, ERα appears to be poorly specific; nevertheless, it may be an important instrument for the classification of peri- and post-menopausal patients in the group where therapy with the use of estrogens may bring about benefits in terms of prevention and treatment of cognitive disorders. It also seems necessary to conduct prophylactic, screening examination of cognitive functions in post-menopausal women, in order to identify those at risk of the development of dementia.

Key words: estrogen receptor α polymorphism, cognitive functions, menopause.

Introduction

Cognitive functions are mental processes which enable the processing of information from the external and internal environment of the body. They constitute a basis for the functioning of an individual by the acquisition of knowledge and its appropriate use in daily life. The processing of information taking place by way of cognitive processes consists in the reception of information from outside and inside, its storage and transformation, as well as its retrieval from the brain and deployment in the

environment in the form of a specified response or behavior. Basic and complex cognitive functions are distinguished. Among the basic cognitive functions are classified perception, attention and memory. Complex cognitive functions are reasoning, imagination, executive functions, linguistic functions and cognitive control [1, 2].

Numerous reports in the field of neuropsychology have confirmed that many cognitive functions deteriorate with age. Consideration concerning the theory of age-related cognitive functions disorders, which have been described in the literature over the years, presents concepts according to which: 1) speed of information processing clearly diminishes with age; 2) resistance to interference and local switching between tasks, considered as indicators of selective attention, are maintained in ageing, if basic differences in speed are taken into account; 3) coordination and global switching between tasks, processes traditionally associated with divided attention, deteriorate with age more than the expected effects of the general slowdown; 4) switching attention is an age-sensitive process, and may be the basic process underlying both the effect of conditions and age-related differences in coordination tasks [3, 4].

Cognitive capacity decreases with age, and especially concerns such processes as the speed of processing, and psychomotor speed. However, some abilities may remain at a stable level, or may even improve until a certain age, e.g. verbal memory [5]. There is a large variety of cognitive changes related to ageing [6]. The understanding of this cognitive aspect of ageing (pertaining to so-called cognitive reserve) may lead to seeking ways for strengthening cognitive functions and prevention of their deficits [4, 7].

Considering the importance of menopause in the life cycle of a woman, researchers have for a long time been interested in whether these are only brain ageing processes that affect cognitive functions, or a menopausal transition that deteriorates the cognitive functions of women after menopause, compared to those at reproductive age. A significant difference is manifested in some tests evaluating cognitive functions. An acceleration of the deterioration in functioning after menopause was found in such tests as reaction time, psychomotor speed and visual-spatial tests. It is also suggested that the decline in the acceleration of cognitive functions after menopause may be related to the lack of sex hormones or other factors related to reproduction, which may play a protective role against age-related damage of some cognitive functions in women. Nevertheless, there are still no unequivocal results confirming any of the existing hypotheses [8–10].

Further observations, made in the search for causes of cognitive dysfunctions, result from the fact that Alzheimer's disease (AD) more often afflicts females than males [11, 12]. It usually develops in postmenopausal women, i.e. during the period when the level of estrogens decreases.

During the menopausal period, many women complain of changes of cognitive functions with respect to concentration and attention, and the majority describe the deterioration of verbal memory. Cognitive disorders more frequently occur during early menopause – the deterioration of memory is primarily most evident within 12 months after the last period [13]. Despite the fact that cognitive functions return to normal after menopause in 80% of women, the conversion to dementia remains higher than in the general population [11, 14, 15].

Biological and epidemiological evidence indicates a beneficial effect of exogenous estrogens on cognitive functions of postmenopausal women [16, 17]; however, nearly all long-term clinical studies have not shown such benefits [18–20]. Observation studies of the level of exogenous estrogens and cognitive functions are also not unequivocal. Some of them confirm a hazardous effect [21, 22], others a protective effect [23, 24], while others do not indicate any clinically observed relationship between estrogens in serum and cognitive functions [25].

Estrogens exert an effect on the central nervous system through, among other things, estrogen receptors. Thus, at present, researchers focus their attention on the molecular mechanisms of estrogens' effect on various functions, including cognitive functions.

The objective of the present study is to present the current knowledge concerning the effect of estrogens on the central nervous system, especially the role of estrogen receptor α polymorphism, to foresee benefits from the use of exogenous estrogens for cognitive functions.

The PubMed database and other databases were searched in order to find publications based on high quality clinical studies, and reports concerning problems related to cognitive function disorders during the period of menopause. The key words were: ERα polymorphism, estradiol, cognitive functions, and hormone replacement therapy (HRT). The article was compiled based on publications from the years 1994–2015.

Estrogen receptors – types, function, polymorphisms

Estrogens exert an effect through 2 independent steroid receptors, ERα and ERβ, which differ structurally and functionally. These receptors are encoded by various genes, play different signaling roles, and are located in various tissues. The ERα gene is located on the long arm of chromosome 6

(6q24-27), whereas the ERβ gene is located on the long arm of chromosome 14 (14q22-24). Estrogen receptors (ER) are stimulated by estrogens, and in their absence, by tissue growth factors [26]. Both receptors, upon binding a ligand, may form homo- and heterodimers [27, 28]. Estrogen receptor are cytoplasmic proteins which, when bound to a hormone, move into the nucleus. Upon binding by the hormone, the receptor is transformed, i.e. it undergoes biochemical and structural changes. On the cellular membrane there is an additional sub-fraction of estrogen receptors, which may be responsible for the extranuclear, non-genomic action of estrogens. Non-genomic action of estrogens (an instant effect) is related to the stimulation of the release of nitric oxide (NO) with omission of receptors, and a direct effect on L-type ion calcium channels (blockade) and potassium channels – a vasodilatory effect. Activation of the steroid receptor depends on the concentration of free hormone in serum, its affinity to the receptor, the total number of receptors, and changes produced after the previous receptor activation. The biological action of steroid depends on its concentration. A positive correlation is observed with low concentrations, while a negative correlation is observed with high concentrations. The receptor response also depends on the exposure time. Prolonged exposure to a high concentration of hormone results in diminished receptor sensitivity [27].

The presence of ER has been found in many tissues and organs. Their prevalence in organs, which has been considered to date as non-typical of estrogens, proves their great systemic importance. In the central nervous system (CNS), estrogen receptors are present in the hypothalamus, olfactory lobe, amygdala, hippocampus, cerebral cortex, cerebellum, and pituitary gland [27].

It was found that a decrease in the ERα number and expression in the hippocampus region is associated with the impairment of hippocampus-dependent cognitive functions. This decrease is observed in some neurological diseases related to memory, including AD [29], while ERβ expression in AD may increase [30]. Thus, it seems that the weakening of the ERα function, and not the reduction in the number of estrogen receptors, may be associated with a weaker response to estrogen therapy at an older age. The degree of the weakening of receptor function may depend on ERα polymorphisms. The degree of expression of particular ERα polymorphisms is related to the weakening of the ERα function to a varying degree, which may lead to the necessity of modification of the estrogen dose in order to improve memory [31–34].

The genes encoding ERα have many polymorphic variants (there are approximately 9,000). Among the most important and most frequently examined are two single nucleotide polymorphisms (SNP) – Xba1 and PvuII. The Xba1 (A/G rs9340799) polymorphism is located in intron 1 of the *ER* α gene 351 bp 5′ end upstream of exon 2, also known as IVS1-351. It is induced by A/G transition [35]. Xba1 is located approximately 50 bp away from the PvuII polymorphism site (T/C, rs2234693), known as IVS1-397T/C [28]. It is caused by T/C transition in intron 1, 397 bp 5′ end upstream of exon 2. Despite the location of the PvuII polymorphism in the intron, it plays a major role in the regulation of ERα protein expression. Due to the presence of C allele at location 397, the restrictive enzyme PvuII does not recognize the restrictive site and does not cut the DNA strand between locations 399 and 398, which happens when the T allele is in this location. It is considered that the C allele is related to the presence of a functional site binding the b-myb transcription factor, which may enhance ERα transcription [28, 36].

Effect of estrogens on the central nervous system and cognitive functions

The presence of estrogen receptors in the CNS evidence that the nervous system is subject to the action of estrogens. Estrogens affect neural functions and the development of neurological diseases by, among other things, the strong effect on synaptogenesis, protection against oxidative stress, inflammatory reactions, induction of growth factor synthesis, effect on blood supply and immune system of the CNS. Estrogens while regulating neurotransmission in the brain (serotonin, acetylcholine, noradrenaline, dopamine) affect mood and cognitive functions [37, 38]. The decrease in the level of estrogen after menopause may cause neurons sensitive to estrogen to become more susceptible to the ageing processes and various neurodegenerative changes manifested as dementia, including AD [39].

Estrogens affect the CNS by exerting a genomic and extra-genomic effect in various well-recognized aspects, such as an effect on verbal abilities, coping with spatial tasks, efficiency of verbal and non-verbal memory, motor skills, as well as mood and emotional phenomena [40, 41]. A direct administration of estrogens to the prefrontal cortex or hippocampus improves spatial memory and object recognition memory [42].

Many reports indicate a protective function of estrogens with respect to neurotoxicity, including amyloid β peptide (Aβ) related neurotoxicity. It is considered that the essence of AD is the deposition of amyloid-β in the brain in the form of plaque [43]. Estrogens affect metabolism of tau protein and amyloid-β – proteins participating in the development of AD. In addition, they reduce

synthesis and deposition of amyloid-beta in the structures of the brain [44].

According to Ryan *et al.*, estrogen deficiency accompanying menopause leads to the deterioration of the results of visual memory and verbal fluency in later life. The study was conducted in a group of women who had undergone premature menopause, i.e. at the age 40, following ovariectomy and premature ovarian failure (POF). Premature menopause was associated with a 30% increase in the risk of deterioration of psychomotor speed and NCI within 7 years after menopause. The researcher indicated that these results should also be referred to the natural menopause [45]. Henderson showed the presence of the relationship between the concentration of estradiol and verbal memory [46]. Woods and Mitchell paid attention to the relation between perimenopausal period and cognitive functions efficacy, reporting the fact of the deterioration of recent memory during this period. In a study which covered 205 menopausal women, 72% of respondents reported certain subjective problems with memory. According to the researchers, the perception of one's memory as functioning worse, to a great extent was related to decreased mood caused by the sole fact of being in the perimenopausal period [47]. Kampen and Sherwin observed an effect of estradiol concentration on the efficacy of verbal memory; however, they did not confirm any effect on the concentration of attention [48].

In the Rancho Bernardo Study, it was found that a higher level of estradiol was related to worse memory outcomes in the examined women [39, 49]. A similar relationship was noted in the Rotterdam Scan Study [22]. Barrett-Connor and Goodman-Gruen reported that in postmenopausal women a higher concentration of exogenous estrogens is not at all combined with better outcomes in cognitive functions [25].

Studies carried out in Finland showed that a high intensification of vasomotor symptoms, the relation of which with a decrease in estradiol level, is not to be contested and does not disturb the course of cognitive processes [50]. In the studies by Bojar *et al.*, women with very intense vasomotor symptoms obtained the same results with respect to reaction time, attention concentration, and pace of information processing as those with a low intensity of symptoms [51].

Hormone replacement therapy and cognitive functions

According to the recommendations of the International Menopause Society of 2011, HRT used by younger women during the perimenopausal period is related to a lower risk of AD [52]. These recommendations are based on the results of the recent observation studies which support the concept of a 'therapeutic window'. This suggests that HRT is beneficial with respect to dementia only at middle age, while starting HRT in a later period of life is hazardous [53–55].

Nevertheless, according to the NAMS study of 2014, the available data do not contain adequate indications to ascertain whether the use of HRT shortly after menopause increases or decreases the speed of development of cognitive disorders, or increases the risk of dementia. Considering the risk of ultimate findings, HRT cannot be recommended at any age for the prevention of treatment of cognitive ageing or dementia [56].

Thus, it seems that based on the above-mentioned data, the essence of the problem is more complicated than merely a progressing estrogen deficiency which, most probably, only initiates the cycle of negative phenomena in the CNS. A decrease in the level of estrogens during the menopausal period does not fully explain the fact of occurrence at that time of clinically evident cognitive disorders or mood disorders. Similarly, there are insufficient data to explain an increased incidence of AD noted in this period by only a decrease in the level of estrogens. Estrogens affect neural functions and the development of neurological diseases through exerting an effect on neurons and glial cells, as well as on oxidative stress, inflammatory reactions, blood supply, and the immune system of the CNS [52]. In the light of the above-presented data, benefits in the area of cognition should be expected from the use of HRT in peri- and postmenopausal women. The reports presented below demonstrate the ambiguity of results.

Hogervorst reported benefits from using HRT with respect to the improvement of cognitive functions in women with and without dementia – although, importantly, only in the case of its short-term application (2–4 months). In contrast, the researcher reported that the results of several comprehensive studies confirmed that long-term use of estrogens, especially with progesterone, exerts a negative effect on cognitive functions, especially in women aged over 65, leading to a cumulated risk of cognitive disorders and dementia [57].

Considering the effect of HRT on cognitive functions, the moment of introduction of this supplementation seems to be extremely important [58, 59]. According to Ryan *et al.*, hormone replacement therapy introduced immediately after menopause has, on the one hand, a beneficial effect on the outcomes of visual memory in the future; however, on the other hand, it negatively affects verbal fluency [45]. Sherwin found that in order to benefit with respect to the improvement of memory outcomes, the critical moment of introduction of HRT is the perimenopausal period, or

during the first several months after menopause. According to the researcher, the use of exogenous estrogens at a later time does not have any effect on memory [60–62]. Supporting this thesis, Smith *et al.* explained a favorable effect of early estrogen therapy on memory by the effect on an increase in the number of synapses and improvement of their function in the hippocampus – an effect which does not seem to occur later [58].

Synaptic connections are critical for the memory process, and their decrease is related to the deterioration of memory, manifested already at middle age [63–65], and even more, as early as in the initial stages of AD [66]. Therefore, in recent years, HRT has been proposed in order to reduce the risk of development of AD and decrease cognitive disorders in patients with AD [67]. According to some researchers, the loss of synaptic connections may be reversible if estrogen therapy is implemented during the peri-menopausal period [68]. As mentioned before, estrogens induce changes in synaptogenesis and the maintenance of the normal functions of synapses. In a study conducted in rats, estrogen therapy led to an increase in the number of dendrites in the hippocampus [69]. However, this ability of estrogens decreased in rats with age, and was related to the reduction in the number of ERα receptors in neurons, especially at the site of synapses. The result of this study was an opinion that the background of reduction in synaptogenesis dependent on estrogen therapy in older animals is the loss of the number of ERα [70]. Foster expanded this scope of problems by stating that earlier introduction of a low-dose estrogen therapy has a protective effect with respect to the ageing of the brain, and that in order to obtain the same effect in humans at an older age, a higher dose of estrogen is required, which may be associated with many undesirable effects [61].

According to many scientific reports, women who applied hormone replacement therapy prior to the occurrence of the last period had better outcomes in tests evaluating memory compared to those who started treatment after menopause [13].

Other authors also reported that the dose of exogenous estrogen is important in the determination of the results of therapy with respect to selected aspects of memory [61, 62, 71]. They described the relationship between the dose of estrogen and memory in the form of a graph presenting a reversed letter U, and explained that by increasing the estrogen dose up to a certain value an improvement of memory is obtained, but its further increase results in progressive deterioration of this cognitive function. This relationship is true in mice [72], rats [73], primates and humans [61].

Taking into account the fact that HRT did not exert a positive effect on cognitive processes in all respondents, the importance of molecular mechanisms is considered, which may modulate the hormone-receptor reactions to the use of HRT.

Cognitive functions according to ERα polymorphisms – effect of hormone replacement therapy on cognitive functions in carriers of particular ERα polymorphisms

Researchers' reports on whether an individual allele in the estrogen receptor gene, as well as polymorphisms themselves, increase or decrease the risk of cognitive function disorders still remain unequivocal. Ryan *et al.*, in a study which covered 3,800 older women without features of dementia, did not observe any relationship between XbaI and PvuII ERα polymorphisms, or a decrease in the outcomes of the examined cognitive functions, i.e. visual memory, psychomotor speed, executive functions, global functions, and verbal fluency [74]. Similarly, other researchers also reported the lack of a relationship between XbaI and PvuII polymorphisms and the risk of development of AD [75, 76]. In addition, they stated that none of the polymorphisms was related to the development of forms of dementia other than AD: vascular dementia, alcohol-related dementia, or dementia related to Parkinson's disease [31, 77, 78].

However, many researchers mentioned that the presence of some PvuII and XbaI polymorphisms is associated with the risk of development of cognitive disorders and dementia, including AD, and that these disorders could become a marker of genetic predisposition to AD [79]. Bousman, in a study of 80 postmenopausal women (age range: 56–67), noted that the carriers of the T allele of PvuII were characterized by considerably lower memory outcomes (logical memory) compared to the carriers of the C allele. Homozygous women with PvuII CC obtained the best results in the evaluation of memory. The results obtained depended on demographic factors, concomitant diseases, presence of APOE e*4, cigarette smoking and alcohol consumption. In the researcher's opinion, they are also evidence indicating the need for further studies to confirm that the presence of the T allele of PvuII is a genetic marker of the risk of memory disorders among postmenopausal women [80]. Sundermann conducted a comprehensive meta-analysis including 14 studies of this issue. Based on literature data from 1995 to November 2009 from the databases PubMed, Embase, and PsychINFO, the author found a strong relationship between XbaI GG and PvuII CC ERα polymorphisms, and risk of the development of dementia, especially AD. A relationship was also observed for ERα polymorphisms possessing alleles Xba1 G and/or PvuII C, and anxiety and/or depressive disorders of the perimenopausal age [81].

Yaffe observed an effect of XbaI A and/or PvuII T polymorphisms on the development of AD and worse outcomes of cognitive functions measured by means of the Modified Mini-Mental Status Examination (3MS). The researcher drew attention to the fact of a more rapid deterioration of cognitive functions within 4 years in older individuals who were the carriers of Xba1 AA and/or PvuII TT [32–34, 82]. The relationship between XbaI A and PvuII T polymorphisms and the risk of development of dementia was also confirmed by Luckhaus *et al.*, although only among the Asian and not the European population [78].

Many researchers have drawn attention to the fact that ethnic variation seems to be a very important issue. The expression of DNA genes characteristic for an individual race leads to the fact that the results of the action of ERα polymorphisms may differ. Some authors indicate the fact of ethnic variation with respect to the frequency of occurrence of single alleles, as well as entire genotypes of XbaI and PvuII. In the Asian population, the CA genotype occurs twice as frequently as among the Caucasian population. The researchers also suggest that ethnic variation may, through various ERα expression, result in different levels of sex hormones, which is associated with changeable intensity of menopausal symptoms [83].

Cheng conducted a meta-analysis of 18 studies including 13,192 participants. The result of the analysis was finding a significant relationship between ERα PvuII polymorphism and the risk of AD in a Caucasian population (CC + CT vs. TT), while this relationship was not observed in the Asian population. Also, no relationship was found between XbaI polymorphism and increased risk of AD in Caucasian and Asian populations [84]. Isoe reported that in patients with AD in an Asian population, the PvuII C and XbaI G alleles occur more frequently (49%). The researcher also noted that the prevalence of the G allele, apart from patients afflicted with AD, was higher among patients with dementia in the course of Parkinson's disease (PD) (63%), compared to healthy individuals [85]. Ji *et al.*, in his study which included 223 patients with AD, 66 patients with vascular dementia, 17 with alcohol-related dementia, and 134 healthy individuals, observed that in patients with AD with late onset of the disease XbaI G and PvuII T alleles occurred more often, compared to the remaining groups. The presence of the T allele and TT genotype was also significantly more frequent in patients with AD with late onset who were carriers of the allele APOE e*4 than in individuals without this allele [31]. Monastero *et al.* reported that the presence of XbaI AA genotype was related to a higher risk of AD. This risk was additionally higher in women and was associated with a greater probability of the development of AD with late onset [86].

In 2 prospective studies, Yaffe *et al.* suggested that the presence of PvuII T or XbaI A alleles was related to a higher risk of development of cognitive disorders measured by means of the Mini-Mental Status Examination (MMSE). Compared to women with XbaI GG and PvuII CC genotypes, those with the A or T allele were characterized by greater deterioration of cognitive functions. The greater emotional arousal was produced by the researcher's statement that women with the genotype PvuII TT or XbaI AA are at 3 times higher risk of the development of AD or other forms of dementia compared to those with the genotype XbaI GG or PvuII CC [32, 33]. In an Italian study, Corbo observed that a higher prevalence of PvuII CC and XbaI GG genotypes, and the combined genotype CCGG, occurs in patients with sporadic AD with late onset (22%), compared to the control group (9%). In women afflicted with AD, the presence of genotypes CC and GG was associated with worse MMSE results and a quicker loss of cognitive functions [34] (Table I).

Many years ago, while implementing the first HRT preparations for treatment, great hopes were placed in them. It was considered that hormonal drugs containing estrogen would be a panacea for all menopausal women's complaints, including disorders of cognitive functions. Today, we know that not all women should use HRT; therefore, attempts are being undertaken to find women especially sensitive to this type of therapy and who would benefit from its use.

According to Myśliwska, enhanced ERα transcription encoded by the PvuII C allele leads to its stronger expression on the surface of the cells. This may result in stronger binding of estradiol to ERα in homozygous women with PvuII CC. A higher dose of bound estradiol means its stronger action, which indirectly indicates that homozygous women with PvuII CC considerably more effectively respond to HRT than those possessing the T allele of PvuII [28]. Moreover, has been confirmed that among postmenopausal women the lowest concentration of exogenous estradiol is found in carriers of the T allele of PvuII, and the highest in homozygous women with PvuII CC [28, 87], although the mechanism of the development of this relationship has not yet been finally recognized.

Considering the fact that 20% of Caucasian women are PvuII CC homozygous, slightly over 20% TT homozygous, and the reminder are PvuII TC homozygous, only a small group of homozygous women with PvuII CC have the chance to benefit from the use of HRT. Scarabin-Carre considered that in women with Xba1 AA genotype, a high concentration of endogenous estradiol is associated with unfavorable vascular changes;

Table I. ERα polymorphism and cognitive functions disorders

Author	ERα Xba1/PvuII polymorphism	Type of cognitive function disorders
Bousman *et al.*, 2012	PvuII T	Logical memory
Sunderman *et al.*, 2010	Xba1 GG and/or PvuII CC	Dementia – especially related to AD
Yaffe *et al.*, 2002, 2009	Xba1 A and/or PvuII T	Cognitive functions disorders measured by MMSE
	Xba1 AA and/or PvuII TT	3-fold increase in the risk of AD or other forms of dementia
Cheng *et al.*, 2014	CC and/or CT PvuII	AD in Caucasian population
Isoe *et al.*, 1997	Xba1 G and/or PvuII C	AD in Asian population
		PD in Asian population
Ji *et al.*, 2000	Xba1 G and/or PvuII T	AD with late onset
Monastero *et al.*, 2006	Xba1 AA	AD
Corbo *et al.*, 2006	Xba1 GG and/or PvuII CC	AD
		Worse MMSE results
		Quicker loss of cognitive functions

therefore, these women, too, would not benefit from the use of HRT in order to prevent dementia and other cognitive functions disorders [88].

In conclusion, prophylactic screening of cognitive functions in women after menopause is certainly necessary in order to identify those threatened by the risk of development of dementia. Despite the fact that at the present stage of research, ERα polymorphism is poorly specific, it may be a very important instrument for the classification of patients at peri- and post-menopausal age in the group in which therapy using estrogens may bring about benefits in terms of prevention and treatment of cognitive function disorders. Further studies need to be planned to evaluate benefits from the use of particular schemes of HRT with respect to cognitive functions in women who are carriers of individual ERα polymorphisms.

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Conflict of interest

The authors declare no conflict of interest.

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