

REVIEW



Genetic risk factors for cancer-related cognitive impairment: a systematic review

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ABSTRACT

Background: Cancer-related cognitive impairment (CRCI) is a commonly reported complaint among non-CNS cancer patients. Even subtle CRCI may have detrimental effects on quality of life and identifying patients at increased risk for CRCI to improve survivorship care is important. In the present paper, we systematically reviewed available studies of possible genetic risk factors for developing CRCI.

Methods: Keyword-based systematic searches were undertaken on 24 July 2018 in PubMed, Web of Science, The Cochrane Library, and CINAHL. Three authors independently evaluated full-texts of identified papers and excluded studies with registration of reasons. Seventeen studies reporting results from 14 independent samples were included for review. Two authors independently quality assessed the included studies. The review was preregistered with PROSPERO (CRD42018107689).

Results: Ten studies investigated apolipoprotein E (APOE), with four studies reporting that carrying at least one risk allele (APOE4 (ε4)) was associated with CRCI, while six studies found no association. The remaining identified genetic risk variants associated with CRCI located in: *COMT*, four DNA repair genes, five oxidative stress genes, 22 genes related to breast cancer phenotype, and *GNB3*. No associations were found between CRCI and genes coding for interleukin-6 (*IL6*), tumor necrosis factor alpha (*TNF*), interleukin 1 beta (*IL1B*), and brain-derived neurotrophic factor (*BDNF*). With the exception of *APOE*, the genetic risk factors had only been investigated in one or two studies each.

Conclusions: Overall, the available evidence of possible genetic risk factors for CRCI is limited. While some research suggests a role for the ε4 allele, the literature is generally inconsistent, and the currently available evidence does not allow clear-cut conclusions regarding the role of genetic factors in the development of CRCI. Larger genetic studies and studies investigating additional genetic variants are needed to uncover genetic risk factors for CRCI.

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Introduction

Advancements in treatment regimens, including chemotherapy (CT), radiation therapy and endocrine therapy, have greatly improved cancer disease survival rates [1]. The treatments, however, often have substantial side effects. Cognitive impairment is a commonly reported side- or late effect among patients treated for non-central nervous system cancers [2]. While the available research has mainly focused on cognitive impairment following CT, emerging evidence suggests that the cancer disease itself, surgical procedures and endocrine therapy may also impact cognition [3], leading to the adoption of the term cancer-related cognitive impairment (CRCI).

Estimated prevalence rates of CRCI vary considerably, but longitudinal evidence suggests that up to 40% of cancer patients may exhibit CRCI already prior to treatment, up to 75% develop CRCI during treatment, and up to 60% exhibit CRCI after completion of treatment [4]. Patients who evidence CRCI prior to treatment may not necessarily be the

ones who subsequently evidence CRCI during or after treatment, which could indicate that the underlying mechanisms across treatment stages differ [4,5]. Although severity of CRCI is typically mild to moderate [5], even subtle impairment may have detrimental effects on daily functioning, including poorer occupational and social functioning, reduced ability to return to work, and impaired overall quality of life [6]. To improve survivorship care, promote well-informed treatment decisions, and optimize patients' ability to cope with CRCI, it is critical to identify patients at increased risk for CRCI.

Evidence suggests that cancer and cancer treatment may promote biological processes associated with neurological aging, including oxidative stress, inflammation, DNA damage, and compromised DNA repair [7]. Due to these shared pathways, CRCI has been conceptualized as an accelerated process of aging [2,8], and special interest has been directed toward genes involved in these biological pathways. Of genes relevant to neurological ageing, the most commonly investigated is perhaps apolipoprotein E (*APOE*), which encodes apolipoprotein ε,

a complex glycolipoprotein of importance to neuronal repair [9]. One *APOE* allele, the $\epsilon 4$, is strongly associated with late onset Alzheimer's disease and a well-known risk factor for age-related cognitive decline [10]. Other candidate genes include *BDNF* encoding brain-derived neurotrophic factor, which is important for neuronal repair [11], and *COMT* encoding catechol-O-methyltransferase, which is implicated in neurotransmitter degradation and regulation of prefrontal dopamine levels [12,13]. *BDNF* is the most widely distributed neurotrophin in the brain and has been studied extensively in relation to cognitive aging, neurodegenerative and mental disorders; however, it remains unclear whether genetic variants in the gene increase susceptibility or confers protection against cognitive impairment [14]. More is known about *COMT* for which functional outcomes of several single-nucleotide polymorphisms (SNPs) have been characterized. One example is the Val158Met polymorphism. It is known that Val carriers metabolize dopamine faster than Met carriers and therefore have less availability of this neurotransmitter, which could be associated with increased risk for cognitive impairment [11]. While several studies have investigated these and other candidate genes as potential risk factors for CRCI, no systematic review has yet been published. Our aim was therefore to systematically review and narratively synthesize the available evidence concerning genetic risk factors for CRCI.

Methods

The review was preregistered with PROSPERO [15] (registration number: CRD42018107689) and conducted and reported in accordance with the PRISMA-recommendations [16].

Search strategy and selection criteria

Keyword-based systematic searches were undertaken on 24 July 2018 in PubMed, Web of Science, The Cochrane Library and CINAHL (see [Supplementary Table S1](#)), using the following keywords: *Population*: cancer OR neoplasm OR oncol*, *independent variable*: genetic OR 'single nucleotide' OR 'polymorphism' OR 'genes' OR 'genotype' OR 'alleles' OR 'genomics', and *dependent variable*: 'cognitive impairment' OR cognition OR neuropsych*. When possible, search terms were included as MeSH-terms or MeSH-term equivalents in each database. No publication date restriction was applied. Study eligibility was determined using an adapted version of the PICO approach [17]: *Population*: Studies of adults (≥ 18 years) in treatment or previously treated for non-CNS cancer; *Independent variable*: Studies presenting data on genetic polymorphisms of hypothesized relevance to cognition/cognitive impairment; *Comparator*: Studies comparing data on the dependent variable according to variations in genotype; *Outcome*: Studies presenting pre- and/or post-treatment data on cognitive functioning as assessed with neuropsychological tests. Eligible study designs were randomized and non-randomized controlled trials, prospective and retrospective

controlled cohort studies, case-control studies, and cross-sectional studies. Only records written in English and published in a peer-reviewed journal were included. Case reports, narrative reviews, 'grey literature', e.g., conference abstracts, dissertations, and unpublished studies were excluded. Three authors (CRB, AA, RZ) independently evaluated full-texts of identified papers and excluded studies with registration of reasons. Additional records were identified through forward searches (citation tracking) and backward searches of reference lists (snowballing).

Data extraction and synthesis

Data extracted included: (a) study setting and design, (b) sample characteristics (number of patients, cancer type, gender, age), (c) comparison group characteristics, (d) assessment time points, (e) independent variable characteristics (assessed genotype(s)), and (f) dependent variable characteristics (neuropsychological tests used). Study quality was evaluated using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies [18]. Two authors (CRB, ERN) independently scored each included study and subsequently discussed and resolved discrepancies. Study characteristics and findings for each of the investigated genetic variations are summarized and reviewed narratively. When sufficient data were available, we calculated odds ratios (ORs) and associated confidence intervals (95% CIs).

Results

The study selection process is shown in [Figure 1](#). Following duplicate removal, a total of 913 records remained, of which 876 were excluded during title- and abstract screening. Thirty-seven records were left for full-text screening. Twenty records were excluded (see [Supplementary Table S2](#)) yielding 17 papers reporting results from 14 independent samples to be included in the review. The three authors agreed on all (100%) inclusion/exclusion decisions.

Study characteristics

The characteristics of the included studies are shown in [Table 1](#). Ten studies reported results on the influence of *APOE* genotypes on cognitive functioning in cancer patients. Six focused on breast cancer (BC) patients [19–24], one reported on both BC and lymphoma patients [25], and three reported on other patient groups [26–28]. The remaining seven studies reported results from studies investigating other genes than *APOE*, e.g., *COMT* [24,29] and *BDNF* [14,24], with five of these studies focusing on BC patients [14,29–32], one on prostate cancer patients [33], and one on patients with mixed non-CNS cancers [34]. See [Table 2](#) for overview of genotypes and patients.

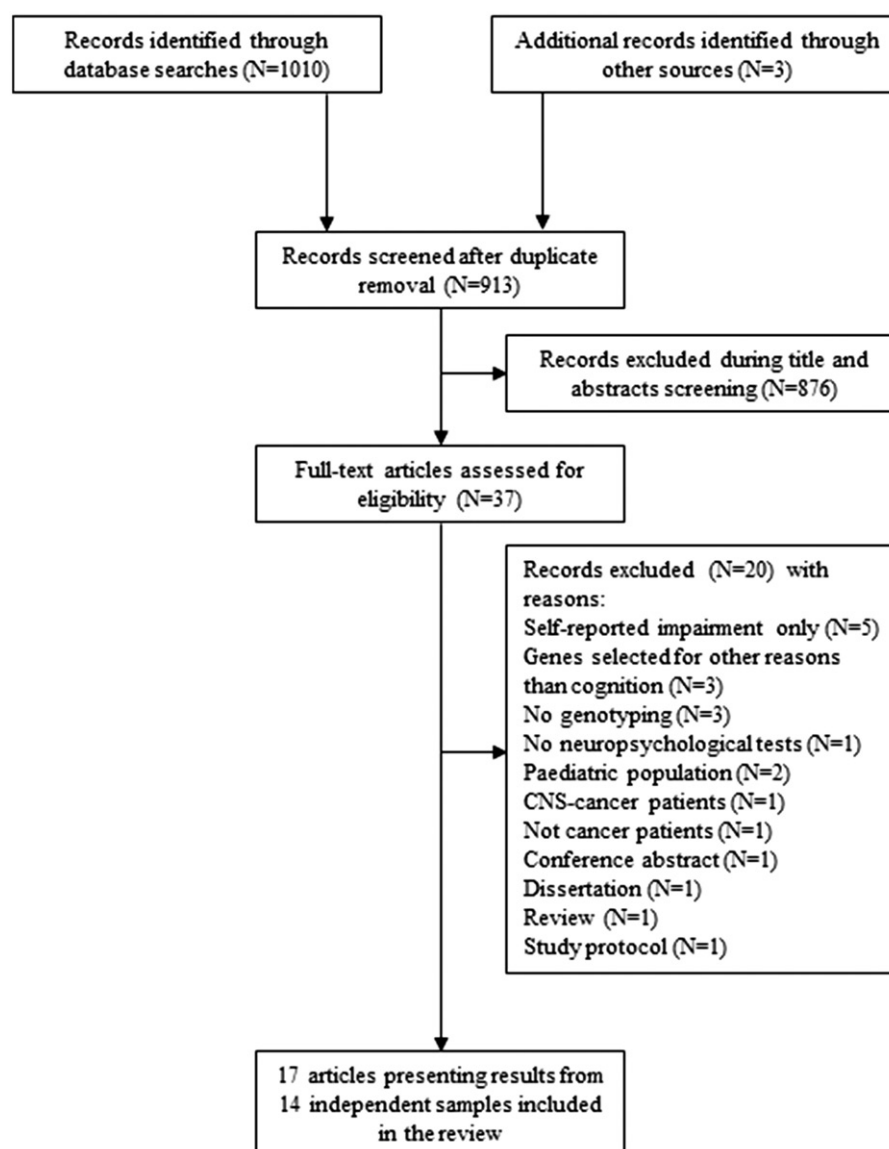


Figure 1. Flowchart for study selection.

Study quality assessment of included studies

Using the NIH Quality Assessment Tool [18], each study received a quality rating (range: 0–14). Eight studies [14,19,20,23,25–27,33] were rated ‘good quality’ (>9 criteria met), and the remaining nine studies [21,22,24,28–32,34] were rated ‘fair quality’ (5–9 criteria met). Study quality ratings are shown in [Supplementary Table S3](#). Eleven studies (65%) failed to provide information about the dates during which recruitment occurred and eight (47%) failed to specify the location of recruitment. Only five studies (29%) provided information about participation rates of eligible participants, of which only two met the criteria of 50%. With respect to a priori sample size justification, only two studies [27,28] provided this. Of the nine prospective studies, five failed to report follow-up rates, and two had dropout rates greater than 20%. The remaining criteria were generally met in most studies.

APOE genotypes

The three APOE isoforms ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) are encoded by the genotypic combination of two SNPs (rs429358, rs7412) [35] and studies assessing associations between these and CRCI categorized patients into non-carriers or carriers of at least one $\epsilon 4$ allele. Four studies [19,20,25,26] showed that carrying at least one $\epsilon 4$ allele was associated with some degree of CRCI, while six studies [21–24,27,28] found no association. Of the studies finding $\epsilon 4$ to be a risk factor for cognitive impairment, three were longitudinal and administered neuropsychological tests before, during and/or after further treatment. In the most recent study [26], testicular cancer patients carrying $\epsilon 4$ (33%) showed statistically significant decline in overall cognitive performance compared to non-carriers following CT. In an earlier longitudinal study [20] with BC patients treated with aromatase inhibitors (AIs) alone or in combination with CT, $\epsilon 4$ carriers (28%) in both

Table 1. Study characteristics

Study	Cancer type	Groups	Gender	N ^a	Age ^b	Design	Genes	Assessment times ^c	Cognitive domains ^d	Findings ^e
Ahles et al. [25]	Breast/lymphoma	CT ⁺	Women	80 (80)	55.9 (8.8)	Cross-sectional	APOE	8.8 (4.3) yrs since last treatment	Motor functioning: Psychomotor function; Attention (Accuracy and reaction time); Verbal ability; Verbal learning: Verbal memory; Spatial ability; Visual memory	Carrying at least one ε4 allele was associated with impairments in visual memory (OR = 2.48 (1.08–5.72)) and spatial ability (OR = 2.25 (0.98–5.15))
Ahles et al. [19]	Breast	CT ⁺ Matched CT (mostly endocrine) Matched HC	Women	60 (55) 72 (68) 45 (43)	51.9 (7.1) 56.8 (8.3) 53.0 (10.1)	Prospective	APOE	Prior to CT, after S, FU 1, 6 and 18 mo. after CT	Reaction time; Processing speed; Distractibility; Working memory; Verbal ability; Verbal memory; Visual memory; Sorting; Block design	Moderating effect of smoking on APOE so that ε4 was a risk factor for decline in processing speed (OR = 9.61 (3.01–30.71)) and working memory (OR = 1.42 (0.81–2.49)) only in patients who did not have a smoking history
Amidi et al. [26]	Testicular	CT ⁺ CT Matched HC	Men	22 (22) 44 (39) 25 (0)	31.9 (9.4) 39.6 (10.1) 32.8 (11.1)	Prospective	APOE	Prior to CT >30 days after S FU 6 mo. after CT	Reaction time; Processing speed; Attention and working memory; Executive function; Verbal Fluency; Auditory learning and memory; Premorbid intellectual functioning	Statistical interaction effect between ε4 and CT on overall cognitive performance with ε4 carriers performing more poorly (OR = 3.11 (1.05–9.24))
Bender et al. [23] Same sample as Koleck et al. [30,31]	Breast	CT + AI AI HC	Women	261 (both patient groups) (190) 106 (0)	60.2 (6.15) (whole sample)	Prospective	APOE DNA repair genes: ERCC2, ERCC3, ERCC5, PARP1 Oxidative stress: genes: CAT, GPX1, SEPP1, SOD1, SOD2	Prior to CT, after S FU 6, 12, and 18 mo. after AI start	Concentration; Visual working memory; Executive function	The minor allele of SNPs in PARP1 (rs2271347), ERCC3 (rs4150402), and ERCC5 (rs751492) increased the odds of belonging to the low executive functioning trajectory subgroup (i.e., low performance at pretherapy that remained low) (ORs = 3.87 (1.49–10.03), 2.75 (1.14–6.64), and 0.29 (0.10–0.82), respectively). Carriers of at least one minor allele of rs1050450 in GPX1 and rs4150407 ERCC3 were at increased odds of belonging to the high and low concentration trajectory subgroup, respectively (i.e., high and stable vs. low and stable) (ORs = 5.83 (1.43–23.71), and 8.26 (1.34–50.98)). Finally, G homozygous for the minor allele of rs873601 in ERCC5 had increased odds of belonging to the low visual working memory trajectory subgroup (i.e., low and improving) (OR = 3.84 (1.16–12.69))
Chae et al. [32]	Breast	CT	Women	125 (125)	50.3 (8.8)	Prospective	IL6-174, TNF-308	Before CT FU 6 and 12 wks after CT start	Response speed; Processing speed; Attention; Memory	No association reported between APOE and trajectories (OR: data unavailable) No statistically significant association between IL6-174 and attention (OR = 1.004, (0.51–1.91)), memory (OR = 1.002 (0.51–1.97)), processing speed (OR = 1.010 (0.52–1.98)), or response speed (OR = 1.002 (0.52–1.98)) No statistically significant association between TNF-308 and any cognitive measures (OR: data unavailable)
Cheng et al. [24]	Breast	3 × negative Non-3 × negative	Females	80 (80) 165 (165)	48.8 (10.6) 49.4 (10.6)	Prospective	APOE, COMT, BDNF	Prior to CT, after S FU after CT (not specified)	Short-term memory; Verbal fluency; Global cognitive functioning (MMSE)	Association between cognitive functioning and COMT SNP (rs165599), with homozygous G individuals being at increased risk for short-term memory decline compared with heterozygous and homozygous A individuals. No impact of APOE and BDNF on cognitive functioning (OR: data unavailable)
	Prostate		Men			Prospective				(continued)

Table 1. Continued.

Study	Cancer type	Groups	Gender	N ^a	Age ^b	Design	Genes	Assessment times ^c	Cognitive domains ^d	Findings ^e
Gonzalez et al. [33]		ADT Matched patients (5) Matched HC		58 (58) 84 (84) 88 (88)	67.1 (8.9) 67.7 (7.4) 69.1 (8.0)		<i>GNBR3</i> (384 SNPs measured, 31 excluded)	Within 21 days of ADT start FU after 6 and 12 mo	Attention; Executive function; Verbal memory; Visual memory; Cognitive reserve	<i>GNBR3</i> rs104776 G homozygotes treated with ADT was at increased risk for cognitive impairment from diagnosis to follow-up compared with G heterozygotes and A homozygotes in both the ADT and non-ADT patient group (OR = 14 (2.97–66.09))
Koleck et al. [20]	Breast	CT + AI AI Matched HC	Females	37 (37) 41 (41) 50 (50)	59.31 (5.7) (whole sample)	Prospective	<i>APOE</i>	For CT + AI: Prior to CT (T0), prior to AI (T1), 6 mo. after AI (T3) For AI: Prior to AI (T0), 6 mo. after AI (T1), 12 mo. after AI (T3) FU 6 mo. after start of AI	Psychomotor speed; Attention; Executive function; Visuospatial ability; Learning and memory	<i>Cross-sectional:</i> ε4 carriers were at increased risk for poorer verbal learning and memory compared to non-carriers in both groups at T0 (OR = 4.23 (2.17–8.53)) and T1 (OR = 4.26 (2.13–8.52)). ε4 carriers prescribed AI were at increased risk for poorer executive functioning compared to non-carriers at T0 (OR = 7.05 (3.42–14.51)) and T1 (OR = 12.39 (5.66–27.11)) <i>Longitudinal:</i> ε4 carriers were at increased risk for decline in visual learning and memory from T1 to T2 regardless of treatment (OR = 3.34 (1.58–6.64)). ε4 carriers prescribed AI were at increased risk for decline in visual learning and memory from T0 to T2 (OR = 11.84 (5.19–26.98)) and in attention from T1 to T2 (OR = 12.07 (5.26–27.67))
Koleck et al. [30] Same sample as Bender et al. [23] and Koleck et al. [31]	Breast	CT + AI AI Matched HC	Females	55 (55) 83 (83) 81 (81)	58.8 (5.5) 62.5 (6.0) 60.1 (6.1)	Cross-sectional	<i>CAT, GPX1, SEPP1, SOD1, SOD2, ERCC2, ERCC3, ERCC5, PARP1</i> (39 SNPs)	Prior to CT, after S	Psychomotor function; Concentration; Attention; Mental flexibility; Executive function; Verbal memory; Visual working memory; Visual memory	All cognitive domains except from mental flexibility were associated with one or more genes by either SNP main effects and/or SNP × group interaction. <i>ERCC5</i> influenced cognition most globally (see [30] for data)
Koleck et al. [31] Same sample as Bender et al. [23] and Koleck et al. [30]	Breast	CT + AI AI Matched HC	Females	55 (55) 83 (83) 82 (82)	58.8 (5.5) 62.5 (6.0) 60.1 (6.1)	Cross-sectional	<i>AURKA, BAG1, BCL2, CCNB1, CD68, CENPA, CMC2, CTSL2, DIAPH3, ERBB2, GRB7, GSTM1, MELK, MK167, MYBL2, NDC80, ORC6, PGR, RACGAP1, RFC4, RRM2, SCUBE2</i> (131 SNPs)	Prior to CT and/or AI, after S	Psychomotor speed; Attention; Concentration; Executive function; Mental flexibility; Verbal memory; Visual working memory; Visual memory	With the exception of <i>CMC2</i> , <i>MMP11</i> , and <i>RACGAP1</i> , all genes were associated with at least one cognitive factor by either a main effect and/or an interaction effect between genotype and prescribed treatment (see [31] for data)
Mandelblatt et al. [21]	Breast	Stages 0–I Stages II–III Matched HC	Females	106 (106) 58 (58) 182 (182)	68.0 (6.7) 68.4 (6.8) 67.3 (6.5)	Cross-sectional	<i>APOE</i> (131 SNPs)	Prior to CT and/or RT after S	Attention, working memory and processing speed domain; Executive function; Language; Learning and memory domain; Visual-spatial domain	No statistical significant difference in patients and controls in neuropsychological performance scores when stratified by <i>APOE</i> genotype (OR: data unavailable)
Ng et al. [14]	Breast	Scheduled to CT	Females	145 (145)	50.8 (8.8)	Prospective	<i>BDNF</i>	Prior to CT, after S FU: 6 and 12 wks. after CT start	Processing speed; Response speed; Memory and attention	No statistical significant association between genotype and neuropsychological test scores (ORs: 0.59–1.65)
Peila et al. [34]	Hematological (71%) / solid tumors (29%)	CT ⁺ CT [−]	24 M/25 F 22 M/14 F	49 (49) 36 (36)	49.0 (14) 58.0 (13)	Cross-sectional	<i>IL1β-511</i>	15 (23) mo. after start of CT	Attentional-executive functions; Language; Phonemic fluency; Orientation; Verbal memory; Visual-spatial skills; Global Cognition	No statistical significant association between genotype and neuropsychological deficits (OR: data unavailable)
Small et al. [29]	Breast		Females			Cross-sectional	<i>COMT</i>	6.16 (1.24) mo. after start of CT		Compared with Met homozygotes, <i>COMT</i> SNP rs4680 Val carriers were at increased risk of

(continued)

Table 1. Continued.

S: surgerv; RT: radiation therapy; CT: chemotherapy; AI: aromatase inhibitors; HC: healthy controls; M: male; F: female; EU: follow-up; wks: weeks; mo: months; yrs: years; ADT: androgen deprivation therapy; MMSE: mini

^aNumber of included patients and controls. Number of genotyped in parenthesis.

^bGroup mean age and standard deviation in parenthesis unless otherwise stated. Range in parenthesis when median age is reported.

‘Timing for assessments of patients and controls relative to patients’ treatment.

^dTested cognitive domains as reported by the authors.

^eMost important findings related to the research question of the present review with accompanying odds ratios (OR) and 95% confidence intervals in parentheses, when sufficient data were available.

treatment groups showed statistically significant impaired verbal learning and memory before treatment and after treatment in addition to statistically significant decline in visual learning and memory during treatment. Results from this study also showed impaired executive functioning before treatment in $\epsilon 4$ carriers scheduled for AI without CT. In addition, this study revealed statistically significant interaction effects between $\epsilon 4$ and treatment in the form of more decline in executive functioning and attention in BC $\epsilon 4$ carriers vs. non-carriers 12 months following treatment with AI alone without CT. No difference between carriers and non-carriers was seen in those who were treated with AI combined with CT [20]. Finally, a third longitudinal study [19] revealed a moderating effect of smoking on the effect of $\epsilon 4$, with $\epsilon 4$ being a risk factor for decline in processing speed and working memory only in BC patients without a smoking history ($\epsilon 4$ carriers = 23%). The number of genotyped study participants in these three longitudinal studies ranged from 61 to 166. The remaining cross-sectional study [25] revealed that carrying at least one $\epsilon 4$ allele (21%) was associated with impairments in visual memory and spatial ability several years after CT in BC and lymphoma patients ($N = 80$). As seen in Table 1, effect sizes (ORs) varied considerably between studies ranging from OR = 1.42 (95% CI: 0.81–2.49) to 12.7 (95% CI: 5.26–27.67). In general, the largest effects were seen for the interaction effects between $\epsilon 4$ carrier ship and treatment with AI and smoking history, respectively.

Of the six studies finding no association between *APOE* genotypes and CRCI, two were longitudinal, investigating BC [23] and colorectal cancer patients [27], respectively ($N = 190$ and 243, respectively) and only the latter of these reported percentage of $\epsilon 4$ allele carriers (23%). Four cross-sectional studies failed to find an association between $\epsilon 4$ and cognitive impairment (carriers: 18–23%; average $N = 246$). Two studies included BC patients treated with CT [22,24], one study included older (>60 years) BC patients assessed prior to adjuvant treatment [21], and one study included colorectal cancer patients assessed prior to adjuvant treatment [28]. Unfortunately, none of the six studies reporting null-findings provided sufficient data for calculating effect sizes.

COMT and BDNF

Two cross-sectional studies found *COMT* variants to be significantly associated with CRCI in BC patients following CT [24,29]. In one study, *COMT* Val carriers (rs4680) had poorer performance on tests of motor speed, attention, and verbal fluency compared with *COMT* Met carriers, with effect sizes ranging from OR = 1.73 (95% CI: 1.17–2.57) to 1.87 (95% CI: 1.26–2.78) (Table 1). In addition, *COMT* Val was shown to interact with CT to induce poorer performance in attention tests in CT-treated *COMT* Val carriers compared with non-treated *COMT* Val carriers (OR = 5.63, 95% CI: 1.95–16.28) [29]. In contrast, no association between the rs4680 and cognitive functioning was found in the second study. This study, however, reported statistically significant associations between cognitive functioning and another *COMT* SNP (rs165599), with homozygous G individuals being at

increased risk for cognitive decline compared with heterozygous and homozygous A individuals [24]. Importantly though, these latter results did not appear to have been corrected for multiple testing. One cross-sectional [25] and one longitudinal [14] study investigated a variant (rs6265) in *BDNF*, but found no statistically significant associations of rs6265 with post-CT cognitive impairments in BC patients.

Genes associated with DNA damage and oxidative stress

One cross-sectional [30] and one longitudinal follow-up study [23] investigated associations of four DNA repair genes and five oxidative stress genes, with CRCI in BC patients recruited from the same parent study and scheduled for treatment with AI and/or CT. Neuropsychological test scores were combined into eight cognitive factors. Prior to adjuvant treatment, each cognitive factor was significantly associated with one or more DNA repair or oxidative stress gene SNPs. A multi-polymorphism genetic risk score (GRS) was calculated for each cognitive factor to evaluate the collective effect of possessing multiple identified risk SNPs. A lower GRS was taken to indicate greater risk and a higher GRS indicated lower risk of cognitive impairment. Results revealed that each GRS was significantly associated with its respective cognitive factor, indicating that the higher the genetic protection, the better the cognitive performance [30]. In the follow-up study [23], group-based trajectory modeling was used to investigate trajectories of three cognitive factors, i.e., executive functioning, concentration and visual working memory. Three distinct executive functioning trajectory subgroups were identified: low pretreatment performance that remained low (low), pretreatment performance slightly below the norm that improved linearly (moderate), and high performance that improved and then declined (high). Results showed that the minor allele of SNPs in three DNA repair genes (*PARP1* (rs2271347), *ERCC3* (rs4150402) and *ERCC5* (rs751492)) increased the odds of belonging to the executive functioning low trajectory subgroup. Similar findings of increased odds of belonging to various trajectory subgroups were found for various DNA repair and oxidative stress genes in the domains of concentration and visual working memory (Table 1). Effect sizes varied considerably with the lowest risk seen for an executive functioning trajectory subgroup (OR = 0.29, 95% CI: 0.10–0.82) and the largest risk seen for a concentration trajectory subgroup (OR = 8.26, 95% CI: 1.34–50.98). Taken together, these results provide preliminary evidence that genetic variation in DNA repair and oxidative stress genes may impart differential risks for trajectories of cognitive functioning during treatment.

Genes associated with inflammation

Two studies investigated associations of CRCI with variants located in genes coding for pro-inflammatory cytokines often found increased in cancer patients [36], i.e., interleukin-6 (*IL6*), tumor necrosis factor alpha (*TNF*) and interleukin 1 beta (*IL1B*). One study investigated SNPs in *TNF* and *IL6* in BC

patients treated with CT and revealed no statistically significant associations with prospectively assessed CRCI [32]. Likewise, in the second study, no associations were shown between cross-sectionally assessed CRCI and two variants *IL1B* (rs16944, rs1800587), in a mixed sample of non-CNS cancers [34].

Other genes

Two studies investigated other genes. A cross-sectional study of newly diagnosed BC patients revealed that all but three out of 25 genes related to BC phenotypes were significantly associated with at least one of eight cognitive factors by either a main effect and/or an interaction effect between genotype and prescribed treatment [31]. Another study investigated 353 SNPs previously found to be associated with cognitive impairment, depression, fatigue or circadian rhythm as possible moderators of prospectively assessed CRCI in prostate cancer patients [33]. The results revealed that only one of these SNPs, rs104776, located in *GNB3*, was significantly associated with impaired cognitive performance over time in patients receiving androgen deprivation therapy (ADT), but not in the matched non-ADT prostate patients group. While the homozygous G genotype for rs104776 was associated with increased cognitive impairment in ADT patients, heterozygosity and A-allele homozygosity was associated with decreased cognitive impairment from diagnosis to follow-up in both the group of ADT patients and in the whole non-ADT prostate cancer control group (OR = 14, 95% CI: 2.97–66.09).

Discussion

To our knowledge, the present review represents the first systematic review of genetic risk factors for CRCI. The most extensively studied risk gene was *APOE* with 10 identified studies, and while there was some longitudinal evidence to support the association between the risk allele ($\epsilon 4$) and changes in cognitive functioning, the evidence was characterized by inconsistent findings. For the remaining identified genes with hypothesized relevance for CRCI, evidence exists to suggest that the *COMT* gene, four DNA repair genes, five oxidative stress genes and 22 genes related to BC phenotype either increase the risk for or protect against CRCI. No associations were found for variants in *BDNF*, *TNF*, *IL6* and *IL1B*. Importantly though, each of these remaining identified genes was only investigated in one or two studies. Overall, the available evidence thus appears inconsistent and sparse.

Regarding *APOE*, the results of three longitudinal studies [19,20,26] together with a cross-sectional study [25] support the hypothesis that the $\epsilon 4$ allele may act as a risk factor for CRCI during both CT and endocrine treatment, and that this effect may last several years after treatment termination. Common to the longitudinal studies were findings of statistical interactions of *APOE* genotype with treatment type [20,26] or smoking history [19], suggesting that the effect of $\epsilon 4$ may be moderated by the biological effects of the treatment, the biologic characteristics of the cancer that

determine treatment regimen, and by life-style factors such as smoking. When comparing the four studies that revealed an association between *APOE* and CRCI with the six studies that did not, the only clear-cut methodological between-study differences were related to sample sizes and percentage of $\epsilon 4$ carriers. While the sample sizes were substantially smaller in the four studies that revealed an association (mean $N = 109$ vs. 248 in the studies that revealed no association), the percentage of individuals with at least one $\epsilon 4$ allele was larger in these studies (mean = 26% vs. 20% in the studies that revealed no association). The larger sample sizes in the studies with null-findings could be taken to suggest that the results from these were more robust than the results of the studies with positive findings. On the other hand, the higher percentage of carriers in the studies that found an association could suggest that these were more sufficiently statistically powered to detect a difference between carriers and non-carriers. Unfortunately, studies reporting no statistical significant association between $\epsilon 4$ carrier ship and CRCI did not provide sufficient data to determine effect sizes and statistical power. When examining longitudinal studies separately, one study that failed to find an association [23] differed from the three studies that did by investigating associations between *APOE* genotypes and *trajectories* of three cognitive factors rather than composite scores on several cognitive domains. Regarding the four cross-sectional studies that found no associations between the *APOE* and CRCI, these mainly differed from the cross-sectional study that did [25] by investigating cognitive functioning either shortly after diagnosis [21,28] or within two years from surgery [22,24], while the study that found an association had investigated this on average nine years after CT. This could suggest that the detrimental effect of the *APOE* $\epsilon 4$ allele may be more pronounced over longer periods of time following treatment, perhaps due to that the $\epsilon 4$ allele is associated with less effective neuronal repair and neuronal growth after injury [9]. Globally, the frequency of *APOE* $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ alleles is estimated to be 0.07, 0.79 and 0.14, respectively [37], and in individuals with European ancestry $\sim 28\%$ is estimated to carry one $\epsilon 4$ allele, and $\sim 2\%$ are $\epsilon 4$ homozygotes [38]. It should be noted that the studies investigating $\epsilon 4$ as a risk factor for CRCI all dichotomized groups into non-carriers vs. carriers of at least one $\epsilon 4$ allele. While the dichotomization is probably due to the low frequency of $\epsilon 4$ homozygotes in the included studies, for example in the study by Vardy et al. [27] only two of 243 patients and three of 70 healthy controls were $\epsilon 4$ homozygotes, studies with healthy elderly have reported a gene dose-response relationship showing that $\epsilon 4$ homozygotes have faster age-related cognitive decline compared with $\epsilon 4$ heterozygotes [39]. It would thus be of interest to investigate whether a similar gene dose-response relationship exists in cancer patients. Taken together, the evidence on the role of genetic variation in *APOE* is limited and inconsistent, and findings of detrimental effects of the $\epsilon 4$ allele on cognition clearly need to be replicated in large-scale prospective studies.

The available evidence concerning other potential genetic risk factors for CRCI is even sparser. Two studies [24,29]

Table 2. Direction of results in assessed cancer populations with proportion of risk allele carriers.

Gene (risk allele(s))	Breast	Lymphoma	Testicular	Colorectal	Prostate	Hematological and solid tumor
APOE (APOE ε4)	↓ Ahles et al. [19] (23%) ↓ Ahles et al. [25] (21%) 0 Bender et al. [23] (NR) ↓ Cheng et al. [24] (18%) ↓ Koleck et al. [20] (28%) 0 Mandelblatt et al. [21] (21%) 0 Vardy et al. [22] (17%)	↓ Ahles et al. [25] (21%)	↓ Amidi et al. [26] (33%)	0 Vardy et al. [27]/[28] (23%)		
COMT						
(rs165599: G)	↓ Cheng et al. [24] (80%)					
(rs4680: Val)	0 Cheng et al. [24] (42%) ↓ Small et al. [29] (75%) 0 Cheng et al. [24] (75%) 0 Ng et al. 2017 (74%) 0 Chae et al. [32] (100%) 0 Chae et al. [32] (17%)					0 Peila et al. [34] (55%)
BDNF (rs6265: Met)						
IL6-174 (rs: 1800795: G)						
IL1B-511 (rs16944: T)						
TNF-308 (rs1800629: G)						
DNA repair (minor alleles)						
ERCC2	0 Bender et al. [23] (NR)					
ERCC3	↓ Bender et al. [23] (NR)					
ERCC5	↓ Bender et al. [23] (NR)					
PARP1	↓ Bender et al. [23] (NR)					
Oxidative stress (minor alleles)						
CAT	0 Bender et al. [23] (NR)					
GPX1	↑ Bender et al. [23] (NR)					
SEPP1	0 Bender et al. [23] (NR)					
SOD1	0 Bender et al. [23] (NR)					
SOD2	0 Bender et al. [23] (NR)					
25 selected genes^a	↑ Koleck et al. [31] (NR)					
GNBR3 (rs104776: GG)^b					↓ Gonzalez et al. [33] (44%)	

↑ indicates a statistically significant positive association between assessed SNP(s) and cognitive functioning (i.e., protective gene(s)). ↓ indicates a statistically significant negative association between assessed SNP(s) and cognitive functioning (i.e., risk gene(s)). 0 indicates no statistically significant association between assessed SNP(s) and cognitive functioning.

% of risk allele carriers in parenthesis. NR: not reported.

^aTwenty-five selected genes related to breast cancer phenotype (131 SNPs): *AURKA*, *BAG1*, *BCL2*, *BIRC5*, *CCNB1*, *CD68*, *CENPA*, *CMC2*, *CTSL2*, *DIAPH3*, *ERBB2*, *ESR1*, *GRB7*, *GSTM1*, *MELK*, *MK167*, *MMP11*, *MYBL2*, *NDC80*, *ORC6*, *PGR*, *RACGAP1*, *RFC4*, *RRM2*, *SCUBE2*. With the exception of *CMC2*, *MMP11* and *RACGAP1*, all genes were statistically significantly associated with cognitive functioning by a SNP main effect and/or by SNP by treatment group interactions. All associations were positive, i.e., the investigated alleles acted as protective genetic factors.

^bThree hundred and eighty-four selected SNPs associated with cognitive impairment, depression, fatigue, or circadian rhythm were investigated: Only rs104776, located in *GNBR3*, was statistically significantly associated with cognitive functioning.

examined the role of *COMT*, with one showing that *COMT* SNP rs4680 Val carriers were at increased risk for CRCI [29] (estimated frequency of individuals of European ancestry having at least one allele =0.75 [38]) and the other [24] failing to replicate this. Instead, this study reported an association between CRCI and another *COMT* SNP, rs165599, with G homozygotes being at increased risk for CRCI (frequency of G allele homozygotes in individuals with European ancestry =0.21 [38]). Two studies showing associations between DNA repair genes, oxidative stress genes and cognitive factors included patients from the same parent study and were thus not independent [23,30]. With the exception of the *BDNF* rs6265 polymorphism, where two studies found no association [14,24], the remaining genes were each investigated in one study only.

Strengths and limitations

Strengths of the present review include a comprehensive and systematic literature search conducted in four different databases as well as the inclusion of multiple possible genetic risk factors for CRCI. A limitation could be that a meta-analysis of the identified results was not undertaken. However, the identified studies were too heterogenic regarding the assessed genotypes, cancer and treatment types, and assessment time points to allow for quantitative analysis.

The study quality assessment highlighted several methodological strengths of the reviewed studies, including clearly stated research questions and hypotheses and the adjustment for important covariates. Furthermore, with few exceptions [14,24,32,34], studies generally adhered to recommendations from the International Cancer and Cognition Task Force (ICCTF), which has worked to harmonize selection of tests used to operationalize CRCI [40]. The quality assessment, however, also revealed shortcomings. First, studies generally failed to justify sample sizes with statistical power analyses. This may be reasonable given that analyses of genetic risk factors for CRCI are often exploratory in nature. However, as many sample sizes were small, this could indicate that the sample sizes were insufficient to detect a true association, especially because CRCI most likely is polygenic and under influence of many variants with low effect sizes in line with what has been demonstrated for large studies of cognition-related traits in general (e.g., [41]). Second, several studies failed to provide information about the participation rates of eligible participants, raising the possibility that the study population may not adequately represent the target cancer population. A third issue relates to follow-up rates. Only little more than half of the prospective studies provided information on follow-up, and less than half of these met the 80% criterion [18] raising the possibility that the observed estimate may be biased (e.g., by patients with poorer clinical outcomes being more prone to drop out). A fourth issue relates to the operationalization of CRCI. While studies generally followed recommendations for neuropsychological testing, between-study differences were observed regarding how neuropsychological scores were calculated (e.g., raw scores, standardized z scores or composite domain scores) and the

cognitive domains the tests were claimed to measure. For example, one study [23] classified 'Rey's Complex Figure: Immediate and delayed recall test' [42] as part of a visual working memory factor, although this test is commonly classified as measuring visuospatial ability and/or visuospatial learning and memory and/or executive functioning [43]. Fifth, most studies included Caucasian participants only, limiting the generalizability of the results to more diverse populations. Sixth, the majority of the available studies, i.e., 12 out of 17, investigated BC patients, and there is a need for studies investigating genetic risk factors for CRCI in other cancer populations. Finally, nine studies reporting no statistically significant associations between genes and CRCI failed to report effect sizes or sufficient data to allow estimation, thus limiting the interpretability of results.

Summary and recommendations for future research

In summary, the available literature on the association of genetic variants in candidate genes with CRCI is sparse and inconsistent and does not allow for clear-cut conclusions regarding the role of genetic factors in the development of CRCI. While there is some evidence to tentatively suggest that individuals having at least one *APOE* ε4 allele may be at an increased risk for CRCI, more research is clearly needed to corroborate these findings. Regarding other potential risk variants, the available results do not allow for tentative conclusions due to lack of studies. Future studies should investigate this further while also exploring other potential genetic risk factors associated with CRCI, e.g., genes associated with telomere length and cell senescence [7]. Despite the limitations of the available evidence, the identification of potential genetic risk factors for CRCI should be of high priority as it would make the detection of patients at an increased risk for CRCI possible in order to provide necessary psycho-social support and to further develop effective preventive interventions.

Disclosure statement

The authors have no conflicts of interest to report.

References

- [1] Cancer statistics [Internet]. NIH National Cancer Institute website; [cited 2018 Sep 4]. Available from: <https://www.cancer.gov/about-cancer/understanding/statistics>
- [2] Ahles TA, Root JC. Cognitive effects of cancer and cancer treatments. *Annu Rev Clin Psychol*. 2018;14:425–451.
- [3] Joly F, Giffard B, Rigal O, et al. Impact of cancer and its treatments on cognitive function: advances in research from the Paris International Cognition and Cancer Task Force Symposium and Update Since 2012. *J Pain Symptom Manage*. 2015;50:830–841.
- [4] Janelsins MC, Kesler SR, Ahles TA, et al. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry*. 2014;26:102–113.
- [5] Wefel JS, Kesler SR, Noll KR, et al. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin*. 2015;65:123–138.

- [6] Wefel JS, Lenzi R, Theriault RL, et al. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer*. 2004;100:2292–2299.
- [7] Mandelblatt JS, Hurria A, McDonald BC, et al. Cognitive effects of cancer and its treatments at the intersection of aging: what do we know; what do we need to know? *Semin Oncol*. 2013;40:709–725.
- [8] Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. *JCO*. 2012;30:3675–3686.
- [9] Morley KL, Montgomery GW. The genetics of cognitive processes: candidate genes in humans and animals. *Behav Genet*. 2001;31:511–531.
- [10] Liu C-C, Kanekiyo T, Xu H, et al. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013;9:106–118.
- [11] Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: dopamine, COMT and BDNF. *Genes Brain Behav*. 2006;5:311–328.
- [12] Weinberger DR, Egan MF, Bertolino A, et al. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry*. 2001;50:825–844.
- [13] Malhotra AK, Kestler LJ, Mazzanti C, et al. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry*. 2002;159:652–654.
- [14] Ng T, Teo SM, Yeo HL, et al. Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer. *Neuro Oncol*. 2016;18:244–251.
- [15] Booth A, Clarke M, Dooley G, et al. The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Syst Rev*. 2012;1.
- [16] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339.
- [17] Sackett DL, Richardson WS, Rosenberg W, et al. Evidence-based medicine: how to practice and teach. New York (NY): Churchill Livingstone; 1997.
- [18] NIH: Study Quality Assessment Tools [Internet]. NIH National Heart Lung and Blood; [cited 2018 Sep 4]. Available from: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>
- [19] Ahles TA, Li Y, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: the impact of APOE and smoking. *Psychooncology*. 2014;23:1382–1390.
- [20] Koleck TA, Bender CM, Sereika SM, et al. Apolipoprotein E genotype and cognitive function in postmenopausal women with early-stage breast cancer. *Oncol Nurs Forum*. 2014;41:313–325.
- [21] Mandelblatt JS, Stern RA, Luta G, et al. Cognitive impairment in older patients with breast cancer before systemic therapy: is there an interaction between cancer and comorbidity? *J Clin Oncol*. 2014;32:1909–1918.
- [22] Vardy JL, Stouten-Kemperman MM, Pond G, et al. A mechanistic cohort study evaluating cognitive impairment in women treated for breast cancer. *Brain Imaging Behav*. 2017.
- [23] Bender CM, Merriman JD, Sereika SM, et al. Trajectories of cognitive function and associated phenotypic and genotypic factors in breast cancer. *Oncol Nurs Forum*. 2018;45:308–326.
- [24] Cheng HD, Li W, Gan C, et al. The COMT (rs165599) gene polymorphism contributes to chemotherapy-induced cognitive impairment in breast cancer patients. *Am J Transl Res*. 2016;8:5087–5097.
- [25] Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology*. 2003;12:612–619.
- [26] Amidi A, Agerbaek M, Wu LM, et al. Changes in cognitive functions and cerebral grey matter and their associations with inflammatory markers, endocrine markers, and APOE genotypes in testicular cancer patients undergoing treatment. *Brain Imaging Behav*. 2017;11:769–783.
- [27] Vardy JL, Dhillon HM, Pond GR, et al. Cognitive function in patients with colorectal cancer who do and do not receive chemotherapy: a prospective, longitudinal, controlled study. *JCO*. 2015;33:4085–4092.
- [28] Vardy J, Dhillon HM, Pond GR, et al. Cognitive function and fatigue after diagnosis of colorectal cancer. *Ann Oncol*. 2014;25:2404–2412.
- [29] Small BJ, Rawson KS, Walsh E, et al. Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. *Cancer*. 2011;117:1369–1376.
- [30] Koleck TA, Bender CM, Sereika SM, et al. Polymorphisms in DNA repair and oxidative stress genes associated with pre-treatment cognitive function in breast cancer survivors: an exploratory study. *Springerplus*. 2016;5:422.
- [31] Koleck TA, Bender CM, Clark BZ, et al. An exploratory study of host polymorphisms in genes that clinically characterize breast cancer tumors and pretreatment cognitive performance in breast cancer survivors. *BCTT*. 2017;9:95–110.
- [32] Chae JW, Ng T, Yeo HL, et al. Impact of TNF- α (rs1800629) and IL-6 (rs1800795) polymorphisms on cognitive impairment in Asian breast cancer patients. *PLoS One*. 2016;11:e0164204.
- [33] Gonzalez BD, Jim HSL, Booth-Jones M, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: a controlled comparison. *JCO*. 2015;33:2021U54.
- [34] Peila E, D'Agata F, Caroppo P, et al. Chemotherapy-induced neurotoxicity: evidence of a protective role of CC homozygosity in the interleukin-1 beta gene-511 C > T polymorphism. *Neurotox Res*. 2016;30:521–529.
- [35] Urfer-Buchwalder A, Urfer R. Identification of a nuclear respiratory factor 1 recognition motif in the apolipoprotein E variant APOE4 linked to Alzheimer's disease. *Sci Rep*. 2017;7.
- [36] Miller AH, Ancoli-Israel S, Bower JE, et al. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *JCO*. 2008;26:971–982.
- [37] ALZGENE [Internet]. Meta-analysis of all published AD association studies (case-control only) APOE_E2/3/4; date accessed: 9 March 2016; [cited 2018 Sep 23]; 2010. Available from: <http://www.alz-gene.org/meta.asp?genelD=83>
- [38] Auton A, Brooks LD, Durbin RM, et al. A global reference for human genetic variation. *Nature*. 2015;526:68.
- [39] Rawle MJ, Davis D, Bendayan R, et al. Apolipoprotein-E (ApoE) ϵ 4 and cognitive decline over the adult life course. *Transl Psychiatry*. 2018;8:18.
- [40] Wefel JS, Vardy J, Ahles T, et al. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12:703–708.
- [41] Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nat Genet*. 2018;50:912–919.
- [42] Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique [The psychological examination in cases of traumatic encephalopathy]. *Arch Psychol*. 1941;28:286–340.
- [43] Lezak MD. Neuropsychological assessment. 5th ed. Oxford: Oxford University Press; 2012. 1161 p.