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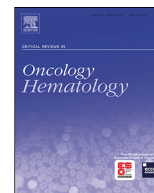

The influence of genetic variation on late toxicities in childhood cancer survivors: A review

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ABSTRACT

Introduction: The variability in late toxicities among childhood cancer survivors (CCS) is only partially explained by treatment and baseline patient characteristics. Inter-individual variability in the association between treatment exposure and risk of late toxicity suggests that genetic variation possibly modifies this association. We reviewed the available literature on genetic susceptibility of late toxicity after childhood cancer treatment related to components of metabolic syndrome, bone mineral density, gonadal impairment and hearing impairment.
Methods: A systematic literature search was performed, using Embase, Cochrane Library, Google Scholar, MEDLINE, and Web of Science databases. Eligible publications included all English language reports of candidate gene studies and genome wide association studies (GWAS) that aimed to identify genetic risk factors associated with the four late toxicities, defined as toxicity present after end of treatment.
Results: Twenty-seven articles were identified, including 26 candidate gene studies: metabolic syndrome (n = 6); BMD (n = 6); gonadal impairment (n = 2); hearing impairment (n = 12) and one GWAS (metabolic syndrome). Eighty percent of the genetic studies on late toxicity after childhood cancer had relatively small sample sizes (n < 200), leading to insufficient power, and lacked adjustment for multiple comparisons. Only four (4/26 = 15%) candidate gene studies had their findings validated in independent replication cohorts as part of their own report.
Conclusion: Genetic susceptibility associations are not consistent or not replicated and therefore, currently no evidence-based recommendations can be made for hearing impairment, gonadal impairment, bone mineral

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density impairment and metabolic syndrome in CCS. To advance knowledge related to genetic variation influencing late toxicities among CCS, future studies need adequate power, independent cohorts for replication, harmonization of disease outcomes and sample collections, and (international) collaboration.

1. Introduction

Survival rates after childhood cancer now approach 80% in developed countries as a result of enhanced stratification, more effective treatment and optimized supportive care (Gatta et al., 2014). The increasing number of childhood cancer survivors (CCS) has led to the growing awareness of chronic health effects resulting from treatment for childhood cancer (Geenen et al., 2007; Oeffinger et al., 2006). Examples of long-term consequences include hearing impairment, gonadal impairment and cardiotoxicity. The inter-individual variability in the number and magnitude of health problems in similarly treated CCS suggests that genetic variation modifies the association between treatment and risk of late toxicity.

To identify such genetic variants two common approaches have been applied: a candidate gene approach, and more recently, the genome wide association study (GWAS) approach. Candidate gene studies focus on associations between genetic variation within prespecified genes of interest and specific outcomes, while GWASs are hypothesis-free searches that can identify novel single-nucleotide polymorphisms (SNPs) that potentially modify the risk of a late toxicity.

After completion of the Human Genome Project (HGP) (HumanGenomeProject, 2015) in 2003 and the International HapMap project, GWASs have discovered many thousands of genetic variants associated with a variety of diseases (EMBL-EBI, 2017), which catalyzed research on genetic variation underlying late toxicity among cancer survivors (MacArthur et al., 2017). Except for cardiotoxicity (Aminkeng et al., 2016a), the resulting number of genetic variation studies in CCS have not produced unambiguous evidence in this field. The lack of strong evidence has impeded translation into clinical practice, such as patient counseling or dose-reduction trials. In contrast, genotyping of childhood cancer patients in order to risk-adapt treatment based on risk models predicting susceptibility to specific toxicities is expected to become standard of care. A comprehensive review of genetic aspects of acute toxicity was recently published (Mapes et al., 2017). However, a recent overview of genetic susceptibility studies concerning late toxicities in CCS is not yet available.

An international collaboration is currently working on the identification of genetic determinants associated with hearing impairment and female gonadal impairment, in a large cohort of CCS (European Union's Seventh Framework programme project PanCareLIFE). In the current study, we summarize the results of a systematic literature search and evaluate the results and quality of available literature on genetic susceptibility of these two late toxicities (hearing impairment and female gonadal impairment) and three hormone-related late toxicities (male

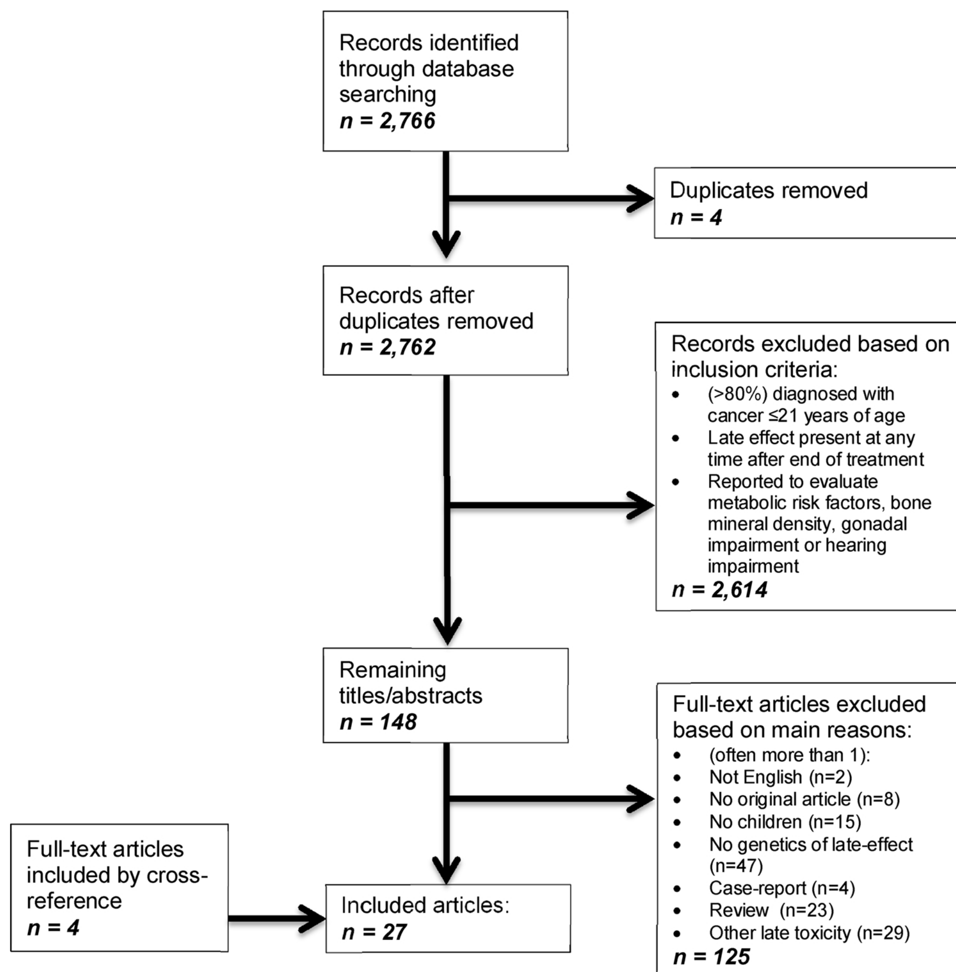

Fig. 1. Flowchart study selection process Review Genetics of Late Effects.

Table 1
Overview of studies on the influence of genetic variation on components of metabolic syndrome in CCS.

		Study population					Analyses								
Study	Method	Cohort size (cases/ control)*	Country of origin; ethnicity	Gender (% males)	Tumor type	Treatment	Replication	Definition endpoint	Studied no of SNPs (adj for multiple testing)	Gene /region	Variant	Effect allele/ genotype	Multivariate analysis adjust for:	OR	P-value
Wilson et al. (2015)	GWAS	1996 (723/ 1273)	USA; 86.5% white, 12.5% black	51	Solid and hematological	CRT	Yes	Obesity BMI ≥ 30 kg/m^2	N/A	SOX11	rs4971486	G	race; age at follow-up, age at diagnosis, chest/ abdominal/pelvic radiation, glucocorticoid, alkylating agents, obesity at diagnosis	2.01 (1.50-2.71)	**3.5E-6**
						CRT				GLA3	rs4530610	C		0.55 (0.40-0.76)	**0.0004**
						CRT				CDH18/ BASP1	rs2923762	G		1.78 (1.40-2.26)	**2.6E-6**
						CRT				FAM155A	rs3566997	G		0.57 (0.44-0.74	**2.8E-6**
						No CRT				VPS45	rs12073359	C		1.56 (1.24-1.96)	**0.0008**
Sawicka-Zkowska et al. (2013)	Cand. gene	74	Poland; 100% Caucasian	61	ALL and lymphoma	22% CRT	No (no replication in another CCS cohort)	leptin levels (linear)	1	LEPR	rs1137101	GG	total BMD SDS, spinal BMD SDS, lean mass SDS, cranial radiotherapy	NA	0.0952
Van Waas et al. (2013)	Cand. gene	532	Netherlands; 100% Caucasian	55	Solid and hematological	16% CRT	No	Hypertension: blood pressure ≥ 140/90 mmHg. MetS: two of the following: blood pressure ≥ 140/ 90 mmHg; BMI ≥ 30 kg/ m2; self-reported prevalence of diabetes or medication; serum total cholesterol ≥ 5.2 mmol/l or medication	7 (no multiple testing)	ATP2B1	rs2681472	CT vs TT	Age, gender, educational level, follow-up time, abdominal and cranial irradiation	None significant	n.s.
								Hypertension: blood pressure ≥ 140/90 mmHg. MetS		ATP2B1	rs2681492	GA vs AA			
								Waist circ: female above/ below 88 cm, males above/ below 102 cm. MetS		TFAP2B	rs987237	AG vs AA			
								Waist circ, Mets		MSRA	rs7826222	CG vs GG			
								Diabetes: using medication for diabetes, MetS		JAZF1	rs864745	AG vs AA			
								Diabetes, MetS		THADA	rs758597	TC vs TT			
										IRSI	rs2943641	CT vs CC			
Surapolchai et al. (2010)	Cand. gene	131 (IR 40/91 and IGT 10/121)	Thailand; (ethnicity not specified)	59	127 (97%) ALL and 4 (3%) Lymphoblastic lymphoma	low/ standard/ high ALL risk stratification	No	Impaired glucose tolerance: fasting plasma	6 (no multiple testing)	PAX4	rs2233580	AG vs GG	age at follow-up	5.28 (1.06-26.40)	**0.043**
								glucose level of 101 to 126 mg/dL and a 2-h plasma		TCF7L2	rs12255372	GT vs GG		n.s.	n.s.

(*continued on next page*)

Table 1 (*continued*)

		Study population					Analyses								
Study	Method	Cohort size (cases/ control)*	Country of origin; ethnicity	Gender (% males)	Tumor type	Treatment	Replication	Definition endpoint	Studied no of SNPs (adj for multiple testing)	Gene /region	Variant	Effect allele/ genotype	Multivariate analysis adjust for:	OR	P-value
								glucose level of 140 to 200 mg/dL. Insulin resistance: whole body insulin sensitivity index < 5ˆ27							
Skoczen et al. (2011)	Cand. gene	77 (24/ 53)	Poland; (ethnicity not specified)	55	ALL	BFM/New York treatment regimens	No	BMI (≥85 th percentile)	3 (no multiple testing)	LEPR LEPR Leptin gene	–	Gln/Gln Arg/Arg vs ARg/ Gln and Gln/Gln G > A	None	NA	n.s.
Skoczen et al. (2011)	Cand. gene	191 Polish ALL CCS (40/151)	Poland; (ethnicity not specified)	48	ALL	BFM/New York treatment regimens	No	BMI (≥ 85 t h percentile)	1 (no multiple testing)	FTO	rs9939609	AA	Stratification for treated with CRT (12-24 Gy) yes/ no	0.24 (0.08-0.7)	**0.016**
Ross et al. (2004)	Cand. gene	600 (278/ 322)	USA; non-hispanics	51	ALL	≥20 Gy CRT (females)	No	BMI ≥ 25 kg/m^2	1 (no multiple testing)	LEPR	GlnQ223Arg	Arg/Arg vs Arg/ Gln and Gln/Gln	Stratification for treated with CRT ≥ 20 Gy in females, adjusted for age at diagnosis	6.1 (2.1–22) (effect only in females)	**0.002**

*indicated is the cohort size (cases and controls), as defined by the authors of the original article.

Abbreviations: CRT = cranial radiotherapy, HT = hypertension, IGT = impaired glucose tolerance, MS = metabolic syndrome (defined by blood pressure ≥ 140/90 mmHg, BMI ≥ 30 kg/m2, self-reported prevalence of diabetes or serum total cholesterol ≥ 5.2 mmol/*l*, N/A = not applicable; NA = not available.

P-values in bold are considered statistically significant by the authors of the original article. Ethnic race is stated if reported in original article.

Where applicable, the multivariable analysis of the combined results of the discovery and replication cohort are reported. If no replication cohort was included, multivariable analysis of the discovery cohort is reported, or univariate analysis of the discovery if multivariable analysis was missing.

Where applicable, the adjusted p-value corrected for multiple testing was reported.

Table 2
Overview of studies on the influence of genetic variation on gonadal impairment in CCS.

		Study population					Analyses								
Study	Method	Cohort size (cases/ controls)*	Country of origin; ethnicity	Gender (% males)	Tumor type	Treatment	Replication	Definition endpoint	Studied no of SNPs (adj for multiple testing)	Gene/ region	Variant	Effect allele/ genotype	Multivariate analysis adjust for:	OR	P-value
Van Dorp et al. (2013)	Cand. gen	176 (61/ 115)	Dutch; 100% Caucasian	0	Solid and hematological	Miscellaneous, with and without alkylating agents and abdominal radiation	No	AMH level below/ above 1 μg/L	7 (multiple testing)	IGF2R	rs9457827	CT	Age at measurement, AAD score and abdominal radiotherapy	0.75 (0.24-2.40)	0.633
										MCM8	rs236114	CT		0.96 (0.44-2.11)	0.919
										ARHGEF7	rs7333181	GA		1.14 (0.46-2.83)	0.777
										PCSK1	rs271924	TT		1.40 (0.40-4.91)	0.602
										TNF	rs909253	GG		1.46 (0.47-4.49)	0.510
										BRSK1	rs1172822	CT		3.15 (1.35-7.32)	**0.008**
Romerius et al. (2011)	Cand. gene	127 (23/ 104)	Sweden; 100% Caucasian	100	Not specified	Miscellaneous, with and without alkylating agents and radiation	No	azoospermia: no sperms found in 40 microscopic fields of semen sediment at 400x magnification	51 (no multiple testing)	ER Alpha	rs2207396	AG vs GG	only univariate analyses, but stratified on high risk group (high doses alkylating agents or radiotherapy)	8.8 (2.1-36)	**0.004**
										ER Alpha	rs9340958	CT vs CC		16 (2.1-100)	**0.008**
										ER alpha	rs9340978	AG vs GG		8.1 (1.1-56)	0.091

*indicated is the cohort size (cases and controls), as defined by the authors of the original article.
Abbreviations: RT = radiotherapy, TBI = total body irradiation.
P-values in bold are considered statistically significant by the authors of the original article. Ethnic race is stated if reported in original article.
Where applicable, the multivariable analysis of the combined results of the discovery and replication cohort are reported. If no replication cohort was included, multivariable analysis of the discovery cohort is reported, or univariate analysis of the discovery if multivariable analysis was missing. Where applicable, the adjusted p-value corrected for multiple testing was reported.

Table 3
Overview of studies on the influence of genetic variation on bone mineral density in CCS.

		Study population					Analyses								
Study	Method	Cohort size	Country of origin; ethnicity	Gender (% males)	Tumor type	Treatment	Replication	Definition endpoint	Studied no of SNPs (adj for multiple testing)	Gene/region	Variant	Effect allele/ genotype	Multivariate analysis adjust for:	OR	P-value
Den Hoed et al. (2016)	Cand. gene	334	Netherlands; caucasian	59	ALL, AML, lymphoma, brain tumor, renal tumor, sarcoma, neuroblastoma	45% glucocorticoid; 17% CRT	No	lumbar spine bone mineral density (standard deviation score)	12 (no multiple testing)	VDR	rs4516035	Haplotype 3	Height	NA	–
										VDR	rs11568820	Haplotype 1-2			**0.02**
										ESR1	rs2504063	GG vs AG or AA			**0.03**
										LRP5	rs599083	TT vs TG or GG			**0.02**
										MTHFR	rs1801133	CC vs. CT or TT			0.21
										MTRR	rs1801394	GG vs Ga or AA			0.26
Park et al. (2016)	Cand. gene	59	USA (73% white; 27% other)	52	ALL	Glucocorticoid	No	lumbar spine bone mineral density (z-scores)	100 (multiple testing)	RAPGEF5	rs6461639	Ref. allele homozygote	age, gender, height, BMD, Z-score, height, Tanner stage and vitamin D level measured at baseline	NA (lower BMD)	**0.015**
Sawicka-Zkowska et al. (2013)	Cand. gene	74	Poland; caucasian	61	ALL, lymphoma	22% CRT	No	total bone mineral density (standard deviation score)	1 (no multiple testing)	LEPR (Q223R)	rs1137101	GG	No	NA	0.423
Te Winkel et al. (2011)	Cand. gene	83	Netherlands	57	ALL	Glucocorticoid	No	bone mineral density total body (standard deviation score)	2 (no multiple testing)	MTHFR	rs1801133	T	No	NA(lower BMD)	**0.01**
										MTRR	rs1801394	G		–	–
Te Winkel et al. (2010)	Cand. gene	69	Netherlands	57	ALL	Glucocorticoid	No	bone mineral density lumbar spine (standard deviation score)	7 (no multiple testing)	VDR 5'-end (haplotype 3, bAT)	rs4616035	G	No	NA (lower BMD)	**0.01**
Jones et al. (2008)	Cand. gene	309	USA (87% white, 12% black, 1% other)	51	ALL	Glucocorticoid	No	bone mineral density (z-scores)	9 (no multiple testing)	CRHR1	rs1876828	G	Ethnicity, weight, treatment	NA (lower BMD)	Males: **0.02**; female: 0.09

Abbreviations: CRT = cranial radiotherapy, N/A = not applicable, NA = not available.
P-values in bold are considered statistically significant by the authors of the original article. Ethnic race is stated if reported in original article.
Where applicable, the multivariable analysis of the combined results of the discovery and replication cohort are reported. If no replication cohort was included, multivariable analysis of the discovery cohort is reported, or univariate analysis of the discovery if multivariable analysis was missing.
Where applicable, the adjusted p-value corrected for multiple testing was reported.

Table 4
Overview of studies on the influence of genetic variation on hearing impairment in CCS.

		Study population					Analyses								
Study	Method	Cohort size (cases/ controls)*	Country of origin; ethnicity	Gender (% males)	Tumor type	Treatment	Repli-cation	Definition endpoint	Studied no of SNPs (adj for multiple testing)	Gene/ region	Variant	Effect allele/ genotype	Multivariate analysis adjust for:	OR	P-value
Thiesen et al. (2017)	Cand. gene	116	UK; 88% white, 5% Asian, 3% African	64	Medulloblastoma, hepatoblastoma, osteosarcoma, neuroblastoma, and other solid tumours	Cisplatin alone, combined cisplatin and carboplatin, or carboplatin after cisplatin; CRT (34%); vincristine (54%)	No	CTCAE and Chang	6 (multiple testing)	ACYP2	rs1872328	GG	Age at diagnosis, gender, CRT, cumulative dose cisplatin, exposure to carboplatin and vincristine	NA	**0.027**
										TPMT	rs12201199	AA		NA	0.34
										TPMT	rs1142345	TT		NA	1.00
										TPMT	rs1800460	CC		NA	1.00
										COMT	rs9332377	CC		NA	1.00
										COMT	rs4646316	CC		NA	1.00
Vos et al. (2016)	Cand. gene	156 (77/ 79)	Netherlands; 99% European descent	51	Osteosarcoma	Cisplatin (with or without coadministered carboplatin); no CRT; no amifostine	No	Chang	1 (no multiple testing)	ACYP2	rs1872328	A	No	12.06 (0.66-221.98)	**0.027**
Brown et al. 2015	Cand. gene	71 (26/ 45)	USA; 42% non-Hispanic white, 35% Hispanic, 24% other	73	Medulloblastoma or supratentorial primitive neuroectodermal	Cisplatin and CRT; amifostine (39%)	No	Use of hearing aid	5 (multiple testing)	SOD2	rs1880	C	Age at diagnosis, gender, ethnic group, cumulative cisplatin dose and CRT doses ≥ 34 Gy	3.06 (1.30-7.20)	**0.040** (FDR)
Hagleitner et al. (2014)	Cand. gene	110 (42/ 68)	Netherlands	50	Osteosarcoma	Cisplatin; no CRT; vincristine (4.5%); no otoprotectants	38 Osteosarcoma CCS; Spain; Cisplatin, no CRT	CTCAE, SIOP Boston	5 (no multiple testing)	TPMT	rs12201199	A	Vincristine exposure	0.65 (0.22-1.91)	0.44
										TPMT	rs1142345	G		0.96 (0.30-3.08)	0.95
										TPMT	rs1800460	A		0.49 (0.12-1.97)	0.31
										COMT	rs4646316	G		0.49 (0.22-1.14)	0.10
Yang et al. (2013)	Cand. gene	213 (64/ 149)	USA; 79% white, 21% non-white	66	Medulloblastoma	Cisplatin and CRT; amifostine (91%)	41 USA CCS; Cisplatin, no CRT	CTCAE, Chang	7 (no multiple testing)	TPMT	rs12201199	TT vs TA vs AA	No	NA	0.50
										TPMT	rs1142345	AA vs AG vs GG		NA	0.14
										TPMT	rs1800460	GG vs GA vs AA		NA	0.11
										COMT	rs4646316	GG vs GA vs AA		NA	0.15
										COMT	rs9332377	GG vs GA vs AA		NA	0.78
Rednam et al. (2013)	Cand. gene	86	USA; 44% non-Hispanic white, 33% Hispanic, 23% other	70	Medulloblastoma, supratentorial primitive neuroectodermal tumor	Cisplatin and CRT; no otoprotectants	No	Use of hearing aid	1 (no multiple testing)	GSTP1	RS1695	AG/GG vs AA	No	4.0 (1.2-13.5)	**0.03**

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Table 4 (*continued*)

		Study population					Analyses								
Study	Method	Cohort size (cases/ controls)*	Country of origin; ethnicity	Gender (% males)	Tumor type	Treatment	Repli-cation	Definition endpoint	Studied no of SNPs (adj for multiple testing)	Gene/ region	Variant	Effect allele/ genotype	Multivariate analysis adjust for:	OR	P-value
Pussegoda et al. (2013)	Cand. gene	162 (106/ 56)	Canada; 80% Caucasian	50	Brain tumor, germ-cell tumor, hepatoma, and other solid tumors	Cisplatin; CRT (19%); tobramycin (29%); vancomycin (22%); vincristine (40%); gentamicin (17%); no otoprotectants	155 Canadian CCS; cisplatin with and without CRT	CTCAE	6 (no multiple testing)	TPMT	rs12201199	A	Age, vincristine treatment, germ cell tumor and CRT	8.9 (3.2-24.9)	**4.0E-5**
										TPMT	rs1142345	G		6.1 (2.1-17.3)	**0.0039**
										TPMT	rs1800460	A		6.6 (2.0-21.8)	**0.00073**
										ABCC3	rs1051640	G		2.0 (1.3-2.9)	**0.0033**
										COMT	rs4646316	G		1.8 (1.2-2.6)	**0.0068**
										COMT	rs9332377	A		1.9 (1.2-3.1)	**0.043**
Choeyprasert et al. (2013)	Cand. gene	68 (54/ 14)	Thailand	59	Fibrosarcoma, germ cell tumor, hepatoblastoma, medulloblastoma, nasopharyngeal carcinoma, neuroblastoma, osteosarcoma, rhabdomyosarcoma	Cisplatin; CRT (29%); aminoglycosides (52%); no otoprotectants	No	Brock	4 (multiple testing)	LRP2	rs2228171	C	No	4.33 (1.01-18.57)	**0.034**
										LRP2	rs2075252	C		NA	0.763
										GSTM1	null	Non-null		NA	0.734
										GSTT1	null	Non-null		10.05 (1.80-56.00)	**0.023**
Ross et al. (2009)	Cand. gene	53 (33/ 20)	Canada	68	Brain tumor, germ cell tumor, hepatoblastoma, neuroblastoma, osteosarcoma, sarcoma	Cisplatin; CRT (17%); vancomycin (4%); vincristine (4%); no otoprotectants	109 CCS; Cisplatin with or without CRT	CTCAE	1,949 (multiple testing)	TPMT	rs12201199	A	Gender and age	16.89 (2.27-125.88)	**0.0318**
										TPMT	rs1142345	G		10.93 (1.44-82.74)	0.221
										TPMPT	rs1800460	A		17.96 (1.07-302.66)	0.413
										COMT	rs4646316	G		2.51 (1.48-4.27)	0.076
										COMT	rs9332377	A		5.52 (1.91-15.95)	**0.0261**
										GSTP1	rs1695	GG		0.71	0.61
										LRP2	rs2075252	A		1.2	0.55
										GSTM1	Null	Non-null		0.78	0.51

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Table 4 (*continued*)

		Study population					Analyses								
Study	Method	Cohort size (cases/ controls)*	Country of origin; ethnicity	Gender (% males)	Tumor type	Treatment	Repli-cation	Definition endpoint	Studied no of SNPs (adj for multiple testing)	Gene/ region	Variant	Effect allele/ genotype	Multivariate analysis adjust for:	OR	P-value
Riedemann et al. (2008)	Cand. gene	50 (25/ 25)	Germany	54	Ostesarcoma, neuroblastoma, medulloblastoma, germ cell tumor, teratoma, testicle cancer	Cisplatin; no CRT; no ototoxic comedication or otoprotectants	No	Muenster	2 (no multiple testing)	LRP2	rs2075252	A	No	3.45 (1.22-9.76)	**0.016**
Knoll et al. (2006)	Cand. gene	11	USA	NA	Osteosarcoma, soft tissue sarcoma, CNS tumor	Cisplatin; CRT (64%); no otoprotectants	No	Clinically apparent hearing loss	5 (no multiple testing)	GJB2	rs80338939	G	No	NA	**0.016**
Peters et al. (2000)	Cand. gene	39 (20/ 19)	Germany	56	Osteosarcoma, germ cell tumor, neuroblastoma, brain tumor	Cisplatin; no CRT; no otoprotectants	No	Muenster	5 (no multiple testing)	GSTM1 GSTM3 GSTT1 GSTP1 GSTZ1	*B, * *B *0 *B, * *B,*	*A *A *A *A *A	No	– 0.11 – – –	– **0.02** – – –

*indicated is the cohort size (cases and controls), as defined by the authors of the original article.
Abbreviations: CRT = cranial radiotherapy, N/A = not applicable, NA = not available.
P-values in bold are considered statistically significant by the authors of the original article. Ethnic race is stated if reported in original article.
Where applicable, the multivariable analysis of the combined results of the discovery and replication cohort are reported. If no replication cohort was included, multivariable analysis of the discovery cohort is reported, or univariate analysis of the discovery if multivariable analysis was missing.
Where applicable, the adjusted p-value corrected for multiple testing was reported.

gonadal impairment, metabolic risk factors and bone mineral density impairment).

2. Methods

2.1. Search strategy

To provide an overview of the established genetic susceptibility factors associated with late toxicities in childhood cancer survivors, we identified relevant articles, published up until September 2017, by systematically searching Embase, Cochrane, Google Scholar, MEDLINE and Web of science. Details of the full search strategy for each database are included in Appendix I. The computer-based searches were conducted by a medical information specialist at the university medical library in the Erasmus Medical Center.

2.2. Definitions

The majority (> 80%) of the cohort in every article had to be diagnosed with cancer ≤21 years of age. As we were specifically interested in 'late' toxicity, defined as toxicity still apparent at follow-up after end of treatment, we only included studies that evaluated metabolic risk factors, bone mineral density, gonadal impairment or hearing impairment in CCS present after end of treatment regardless of follow-up time. Definition of endpoints used by the authors were extracted from the corresponding papers and assembled in tables.

2.3. Study selection

Two independent investigators (EC and ALFvdK) reviewed all titles and abstracts, and independently selected potentially eligible studies. Case series, case reports, abstracts or reviews were excluded. Only studies published in English were selected for the analysis. Disagreements were resolved through consensus. Full text papers were retrieved to assess fulfillment of the selection criteria (Fig. 1). Cross reference check was performed to identify additional studies that were potentially overlooked during the initial search. Authors were contacted to clarify or supplement their results where necessary.

3. Results & discussion

The search strategy yielded 2762 unique records (Fig. 1). After screening titles and abstracts 148 articles were selected for detailed evaluation of full texts. For the purpose of the current review we focused on gene-association studies of metabolic syndrome, low bone mineral density, and gonadal impairment and hearing impairment. As a result, 27 articles were considered in this review, including seven studies on metabolic syndrome (six candidate gene studies and one GWAS), six candidate gene studies of low bone mineral density, two candidate gene studies of gonadal impairment, and 12 candidate gene studies of hearing impairment (Tables 1–4).

Of the candidate gene studies, 50% (13/26) had less than 100 participants while 80% (21/26) had less than 200 participants. Only two included a cohort of more than 500 CCS (n = 532 and n = 600) (Van Waas et al., 2013; Ross et al., 2004). Only six of the candidate studies (23%) adjusted for multiple testing to reduce the chance of type I error (false positive results), which would take into account the multiple models tested (Van Dorp et al., 2013; Park et al., 2016; Thiesen et al., 2017; Brown et al., 2015; Choeyprasert et al., 2013; Ross et al., 2009). One candidate study investigated both metabolic syndrome and bone mineral density (Van Waas et al., 2013). Where possible, the multivariable analysis of the combined results of the discovery and replication cohort are reported (Tables 1–4). Where applicable, the adjusted p-value corrected for multiple testing was reported.

3.1. Metabolic syndrome components

The prevalence of components of the metabolic syndrome, including obesity, hypertension, dyslipidemia and type 2 diabetes (or specifically hyperglycemia or hyperinsulinemia), has been reported to be higher in CCS compared to the general population (Dalton et al., 2003; Rogers et al., 2005; van Waas et al., 2010; Taskinen et al., 2000). Six candidate gene studies and one GWAS investigated polymorphisms associated with different aspects of metabolic syndrome. The polymorphisms in the candidate gene studies had been identified previously in GWASs performed in the general population or were based on the genes coding for hormones (or its receptor) associated with obesity. No studies addressed the genetic susceptibility of dyslipidemia. The only variants that had been investigated in multiple independent cohorts (Table 1) were variants within the gene coding for the leptin receptor (*LEPR)* which were evaluated because of their hypothesized functional contribution to obesity.

Leptin, a hormone secreted in adipocytes, has a key role in increasing satiety and energy homeostasis (Allison and Myers, 2014). Leptin insensitivity has been reported to be associated with obesity, leading to the hypothesis that obesity in CCS may be influenced by a carrier status of polymorphisms in the leptin receptor (*LEPR*) (Ross et al., 2004). Only one (Ross et al., 2004) of the three independent candidate gene studies in CCS that investigated the leptin pathway found a statistically significant correlation between a polymorphism in *LEPR* (GlnQ223Arg) and higher odds of being obese (Ross et al., 2004; Sawicka-Zkowska et al., 2013; Skoczen et al., 2011). The effect was sex-dependent and after stratification on sex, it was only significant in females (n = 294, OR 2.5 95% CI 1.3–4.8) and not in males (n = 306). In addition, in the female subgroup, a significant interaction with cranial radiation (> 20 Gy) (Ross et al., 2004) was observed, suggesting that the impact of the polymorphism is especially prominent in female survivors who were treated with cranial irradiation. The impact of cranial irradiation can for a large part be attributed to the subsequent increased risk for growth hormone deficiency. The association between the GlnQ223Arg *LEPR* polymorphism and obesity has not been validated in the other two candidate gene studies (Sawicka-Zkowska et al., 2013; Skoczen et al., 2011), although cranial radiotherapy did amplify the association with leptin levels (Sawicka-Zkowska et al., 2013; Skoczen et al., 2011). These two studies were small (77 and 74 survivors, respectively) as compared to the study by Ross (600 survivors) (Ross et al., 2004), which suggests that this inconsistency may be due to lack of power, especially considering the possible need for stratification for sex, which both studies did not carry out (Sawicka-Zkowska et al., 2013; Skoczen et al., 2011). Alternatively, this discrepancy in results could be due to a false positive result in the initial study by Ross et al, which did not include an independent replication cohort.

Using a candidate gene approach based on polymorphisms identified in GWASs in the general population, the association of seven polymorphisms (rs2681472, rs2681492, rs987237, rs7826222, rs864745, rs758597, and rs2943641) with respect to hypertension, waist circumference, diabetes and metabolic syndrome (defined as blood pressure ≥ 140/90 mmHg; BMI ≥30 kg/m^2; self-reported prevalence of diabetes, or serum total cholesterol ≥5.2 mmol/l) was investigated (Van Waas et al., 2013). None of these SNPs were associated with the development of any single parameter of metabolic syndrome among CCS (Van Waas et al., 2013), including the presence of diabetes, and adjustment for cranial and abdominal radiotherapy did not change these results. In contrast, cranial and abdominal radiotherapy were strongly associated with the presence of, or components of, metabolic syndrome. This may suggest that the impact of treatment, mainly radiotherapy, is more dominant than the influence of the tested variants on the components of metabolic syndrome (Van Waas et al., 2013).

The most recent genetic study was a GWAS in CCS of the St. Jude Lifetime Cohort, performed to identify genetic variants associated with obesity (Wilson et al., 2015). In this GWAS, the cohort was stratified on

cranial radiation exposure. Next, 70% of the strata was used as discovery cohort and 30% as replication cohort. Neither strata showed polymorphisms in the *LEPR* gene to be associated with obesity (Wilson et al., 2015). Polymorphisms in regions near or within the *SOX11* and *CDH18* genes, regulators of neuronal growth, repair, and connectivity (Haslinger et al., 2009; Hirano and Takeichi, 2012) increased the risk of obesity among cranial radiated CCS (Wilson et al., 2015). On the other hand, a polymorphism in *FAM155A*, thought to disrupt the hypothalamic-pituitary axis (Wilson et al., 2015; Ge et al., 2005), decreased the likelihood of obesity in cranial radiated CCS. These findings have not yet been investigated in independent cohorts. Nevertheless, it is important to stress that the observed genetic variation will only partly explain the total variation in obesity, as other environmental factors such as cancer treatment and lifestyle are of major importance. In this GWAS, the pseudo R^2 (a measure for the amount of variability explained) in the cranial radiated strata was 0.174 for the clinical risk factors model, and 0.303 for the clinical risk factors combined with the SNPs model (Wilson et al., 2015). Despite a significant increase, it also shows that this complex human trait deserves further research to understand its pathophysiological mechanism and its genetic components. Although a polymorphism in the *LEPR* gene would be a logical genetic determinant of metabolic risk factors, the evidence to date for the association is limited.

3.2. Gonadal impairment

Two candidate gene approach studies examined gonadal impairment; one in female and one in male CCS, and neither included a replication cohort.

The candidate gene study in female CCS explored the association between genetic variation and gonadal impairment based on high or low AMH levels (Van Dorp et al., 2013) (Table 2). Seven polymorphisms, each in a different gene, were evaluated. The polymorphisms had previously been identified in GWASs as associated with age at natural menopause in the general population (Stolk et al., 2009; He et al., 2010). In this study in CCS, females with a heterozygous genotype for rs1172822 in the *BRSK1* gene had higher odds of having a low AMH value (OR = 3.15, 95% CI 1.35–7.32, p = 0.008). A modifying effect of the SNPs on the impact of treatment was not specifically evaluated, but the OR was adjusted for alkylating agents score and abdominal radiotherapy. *BRSK1* is expressed in the human forebrain and to a lesser extent in mammalian ovaries. Overexpression of the *BRSK1* gene has been hypothesized to disturb hypothalamic-pituitary-ovary axis regulation by affecting the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus (He et al., 2009) or to influence cell-cycle progression since it is essential for centriole duplication.

In male non-CCS, estrogen receptor deficiencies and polymorphisms are associated with infertility, although the exact mechanism remains to be elucidated (Galan et al., 2005; Ferlin et al., 2007; Guarducci et al., 2006). The only genetic study addressing estrogen receptor polymorphisms in 127 CCS examined 51 SNPs. This study did not adjust for multiple comparison and had no replication cohort, increasing the risk of type 1 errors. Only SNPs in the estrogen receptor α gene were associated with increased risk of developing azoospermia, and this effect was stronger in the subgroup treated with high cumulative doses of alkylating agents/cisplatin or lower doses with additional radiotherapy (Romerius et al., 2011). Other polymorphisms, coding for androgen receptors and estrogen receptor β, were not found to be associated with infertility in these CCS.

In both male and female CCS only one candidate gene study has been performed to evaluate the genetic component of variation in long-term gonadal impairment. This variation needs further investigation, preferably in large GWASs with a replication cohort.

3.3. Bone mineral density impairment

Genetic variation in low bone mineral density (BMD) in CCS has been studied in six candidate gene studies (Table 3), of which one candidate gene study included up to 100 SNPs and adjusted for multiple comparisons (Park et al., 2016). The most recently published study (den Hoed et al., 2016) included a replication cohort, which failed to corroborate any of the earlier associations from the discovery cohort.

The *CRHR1* gene has previously been found to be associated with impaired lung function in asthma patients (Tantisira et al., 2004) and it has been suggested that *CRHR1* gene variants may also explain differences in susceptibility to exogenous corticosteroid therapy, thereby influencing lung function, but also BMD. The G allele of a polymorphism (rs1876828) in the *CRHR1* gene was associated with lower BMD in male survivors of acute lymphoblastic leukemia (ALL) (p = 0.02), while, in contrast, a non-significant higher BMD was observed in female ALL survivors (p = 0.09) (Jones et al., 2008). As previously indicated for obesity, stratification by gender can be valuable, which again stresses the need for adequately sized cohorts.

Te Winkel and colleagues investigated 69 and 83 ALL survivors for respectively two and seven polymorphisms of six candidate genes and published this in two articles that in previous studies had shown an association between BMD impairment in the general population (Alvarez-Hernandez et al., 2003; Fang et al., 2003; van Rossum et al., 2003; Lorentzon et al., 2001). ALL survivors who were carriers of the vitamin D receptor (*VDR*) 5′-end haplotype 3 ha d an increased risk for lower lumbar spine BMD (te Winkel et al., 2010). Similarly, the *MTHFR* gene T-allele (rs1801133) was also identified as a risk factor for lower total body BMD (te Winkel et al., 2011). These studies also showed that carrier status of both *VDR* and *MRHFR* polymorphisms were associated with low BMD at diagnosis, before any treatment had been administered. However, the subsequent rate of BMD decline during treatment did not differ between carriers and non-carriers. Also, parameters of body composition were not different between carriers and non-carriers of the *MTHFR* and *MTRR* polymorphisms at diagnosis, nor during treatment or after treatment. This suggests that while genetic variation may play a role in BMD variation, it does not modify the effect of treatment on BMD in ALL patients (Gjesdal et al., 2006; van Meurs et al., 2004; Steer et al., 2009).

3.4. Hearing impairment

Hearing impairment is commonly observed after treatment of CCS with the platinum agents cisplatin and carboplatin, or after cranial radiation (Langer et al., 2013). The effect of these treatments could be modified by genetic polymorphisms.

Twelve candidate gene studies have been performed, none of which included a discovery cohort larger than 250 subjects (Table 4). Only three of the studies included an independent replication cohort and to date, no GWAS has been published on CCS after completion of treatment.

In a study by Ross et al, in 53 CCS subjects almost 2000 SNPs in 220 key pharmacogenetic genes involved in the absorption, distribution, metabolism and elimination of drugs were genotyped. This study included an independent replication cohort of 109 CCS. They identified *COMT* and *TPMT* as genetic determinants of variation in hearing impairment between CCS (Ross et al., 2009). Catechol O-methyltransferase (*COMT*) is involved in the metabolism of catechol drugs and is highly expressed on hair cells of the mouse (Du et al., 2008). However, its role in auditory function remains unclear. Thiopurine S-methyltransferase (*TPMT*), involved in the metabolism of thiopurine drugs, has not yet been linked to cisplatin metabolism in the general population, although it has been demonstrated in murine inner ear cells to play a role in cisplatin metabolism and detoxification (Bhavsar et al., 2017; Lee et al., 2016). Four additional studies aimed to replicate the previously identified associations of hearing impairment with *COMT*

and *TPMT*. While one study confirmed these associations (Pussegoda et al., 2013), albeit with smaller effect sizes, the other three did not (Thiesen et al., 2017; Hagleitner et al., 2014; Yang et al., 2013). One small study in a population of 63 children with hearing function measured during cisplatin treatment, did not detect a significant association of *TMPT* and *COMT* polymorphisms in children with hearing impairment (Lanvers-Kaminsky et al., 2014). Despite the functional validation of the *TMPT* marker in murine inner ear cells (Bhavsar et al., 2017), uncertainty remains regarding whether *COMT* or *TPMT* polymorphisms are genetic risk factors for hearing impairment (Lanvers-Kaminsky et al., 2014). Lack of replication may be due to different methods for defining hearing impairment (e.g., Brock classification, Münster grading system, SIOP Boston criteria, CTCAE classification, Chang grading), heterogeneity of the study cohorts in regards to treatment exposure and age at diagnosis, or small sample sizes. In the study by Yang et al, nearly all patients (91%) received the otoprotectant amifostine and all had cranial radiotherapy, both of which might mask genetic susceptibility (Yang et al., 2013). However, in their small underpowered cohort of 41 survivors who did not receive amifostine or cranial radiation, the association between *TMPT* and hearing impairment are in line with the other studies (Ross et al., 2009; Pussegoda et al., 2013). This highlights the importance of a homogenous population with a large sample size, in order to avoid type 2 errors.

Polymorphisms in the low density lipoprotein-related protein 2, or megalin (*LRP2*) gene, which is expressed in the marginal cells of the stria vascularis in the inner ear, have been postulated to predispose to cisplatin-induced hearing impairment. Three studies investigated the association between the *LRP2* gene polymorphism (rs2075252) and hearing impairment, of which one study showed that the prevalence of hearing impairment was higher in CCS who carried the A allele of this polymorphism (Choeyprasert et al., 2013; Ross et al., 2009; Riedemann et al., 2008). However, this study did not include a replication cohort.

Another variant in this gene (rs2228171) was investigated in 68 CCS and was found to be significant, but has not been replicated in subsequent studies (Choeyprasert et al., 2013).

The association between hearing impairment and *GSTT1* and *GSTP1* loci, members of the glutathione S-transferases (*GSTs*) superfamily, was first described in survivors of adult cancer (Oldenburg et al., 2007). *GSTs* are known to play an important role in cell protection by scavenging free radicals caused by cisplatin by conjugating it with glutathione (Peters et al., 2000; McIlwain et al., 2006). In CCS, the association between cisplatin-induced hearing impairment and polymorphisms in the GST gene family (*GSTP1, GSTT1, GSTM1, GSTM3, GSTZ1*) was investigated in four studies (Choeyprasert et al., 2013; Ross et al., 2009; Peters et al., 2000; Rednam et al., 2013). One study of 39 survivors identified the *GSTM*B* allele to be associated with a lower risk of hearing impairment (OR: 0.11, 95% CI not given, p-value: 0.02) (Peters et al., 2000) and a larger study of 86 medulloblastoma survivors found that survivors with the *GSTP1* AG or the GG genotype had a greater risk of hearing impairment (OR 4.0, 95% CI: 1.2–13.6, $p = 0.03$) than survivors with the AA genotype (Rednam et al., 2013). However, the latter finding may be false positive since the study by Ross et al (Ross et al., 2009), in 162 subjects had 99.9% power to detect a similar effect at $p \le 0.05$, but did not find a significant association between the *GSTP1* genotype and hearing impairment.

While no GWAS examining hearing impairment has been performed in CCS after completion of therapy, one GWAS in 238 subjects reported on susceptibility to cisplatin-induced hearing impairment measured during childhood cancer treatment (Xu et al., 2015). Although this study did not meet the inclusion criterion of evaluation of the late effect after end treatment –the cisplatin-related hearing loss assessment was based on audiology data obtained between 9 and 24 months after the initiation of therapy- it yielded valuable results for this study field. This study identified one significant SNP in the *ACYP2* gene (Xu et al., 2015), which codes for an acylphosphatase that can influence Ca^{2+} homeostasis in the cochlea and is involved in hair cell development (Fuchs, 2014). This finding was replicated in an independent cohort of 156 CCS after treatment, although pooling of the results from both studies was needed to reach statistical significance (Vos et al., 2016). This stresses the need not only for replication in independent studies, but also for adequately sized studies. The replication indicates there is no difference in genetic susceptibility in the cohorts with hearing impairment measured during or after treatment, which is in line with current knowledge concerning the irreversibility of hearing impairment. However, recent data suggests that in some survivors, cisplatin-induced hearing impairment manifests later in life, suggesting that some cases of cisplatin-induced hearing impairment might be missed if hearing function is only measured during treatment (Clemens et al., 2017). Up until now, no GWAS has been published to study the effect of genetic variation on hearing impairment in long-term CCS. In summary, the following genes were associated with hearing impairment in at least two independent sets of CCS subjects: *COMT* (rs4646316 and rs9332377, five reports, two significant (Ross et al., 2009; Pussegoda et al., 2013)), *TPMT* (rs12201199, rs1142345, rs1800460, five reports, two significant (Ross et al., 2009; Pussegoda et al., 2013)) and *ACYP2* (rs1872328, two reports, two significant (Thiesen et al., 2017; Vos et al., 2016)). Although large cohorts and replication cohorts are requirements for solid genetic research, many studies on hearing impairment do not meet these criteria. The functional significance is not fully understood for all SNPs and the clinical implication of polymorphisms in *TPMT* in hearing impairment has only been recently demonstrated in murine inner ear cells (Bhavsar et al., 2017). The functional significance of polymorphisms in *COMT* in hearing impairment is still unclear.

3.5. Future directions

Among childhood cancer survivors the heterogeneity of late toxicities is broad, even in survivors who have been treated with the same protocols. This suggests a role for genetic variation. However, the evidence for an association between genetic variation and late toxicities after childhood cancer is largely insufficient or inconclusive to date, with few exceptions such as the reported associations between *ACYP2* and hearing impairment. The inconclusive evidence is mainly due to a lack of well-designed, adequately powered studies. To date, in the reported late effects, only one GWAS has been performed. Especially in candidate gene studies, a) cohorts are small, b) replication cohorts are often lacking, c) the definitions used for biological endpoints are inconsistent across studies, and d) there are differences in study design across studies which hinders comparability. The lack of consistent associations across studies can be largely explained by methodological factors. In addition, variations in biological factors play an important role, since most of the outcomes studied are known to have multi-factorial etiologies, which include differences in genetic background, environment, behavioral factor, as well as co-morbidity. Moreover, clinical feasibility to collect data in a sufficiently powered and homogeneous cohort may play a role. Future research studies in this field could therefore benefit from considering the following principles.

Firstly, future studies need to include adequately sized cohorts in order to have sufficient power to identify low risk variants, which are the expected risk variants in common traits such as the evaluated late toxicities (i.e., common disease, common variant hypothesis). Several studies highlight the need for stratification or sub-analyses (Ross et al., 2004; Jones et al., 2008), which again require larger study populations. Power calculations and adjustment for multiple testing are essential tools to minimize type 1 and 2 errors. GWASs are becoming more popular and are evaluating hundreds of thousands to millions of SNP markers at the same time and require a multiple testing adjustment to $p < 5*10^{-8}$. Therefore large sample sizes are required to achieve sufficient statistical power (Hong and Park, 2012). The number of SNPs to be included can increase exponentially when the sample size increases and studies with larger sample sizes are able to detect smaller

associations as a result of higher power (Liu and Fu, 2015). This highlights the need for international collaboration to assure sufficient sample sizes to identify genetic associations. Moreover, a large sample size is important as the focus of genetic studies in late toxicities after cancer often is on an interaction between treatment and a polymorphism, and interaction studies require even larger power than regular association studies.

Secondly, future genetic studies will benefit from inclusion of independent replication cohorts, as is common practice in the GWAS field, to strengthen the study design and avoid type I errors. Yet again this needs international collaboration to replicate findings in independent studies.

Thirdly, to ensure that the genetic difference observed between cohorts is related to the disease or condition under study and to rule-out spurious associations, inclusion of cohorts with similar genetic backgrounds (similar ethnicity) is preferred. For study situations, where this is not feasible by design, several methods have been developed to correct for ancestrally distinct populations, such as principal components analysis, based on the variance of the studied genotypes (Price et al., 2010). To date, most genetic studies have been performed in Caucasians. Genetic analyses in all ethnicities are required to avoid disparities in addressing knowledge gaps related to genetic susceptibility to late treatment effects.

In addition, to increase the chance of replication of results, harmonization by consistent definitions of outcomes and evaluation of possible confounders are necessary. Also, sufficient understanding of the molecular mechanisms underlying the disease or condition is important to adequately define cases and controls. In this regard, the proper selection of cases and controls has been extensively discussed within genetic epidemiology (Hattersley and McCarthy, 2005).

Next, it is essential that collection, processing, storage and retrieval of bio-specimens is conducted under quality control programs using standard operating procedures to guarantee low inter-sample variance and high quality of the samples. Within international collaborations, the establishment of an international biobank could be of value. Biobanks require high ethical practice standards, but offer research and researchers the possibility of cross-collaboration and synergy between different fields which is needed to further advance genetic research.

Finally, genetic technology is continuously improving, resulting in even bigger datasets with higher genetic resolution (MacArthur et al., 2017). Yet, the same principles as described above apply and with even more necessity given the even larger number of genetic variants tested. With the increasing availability of commercially available arrays and increasing affordability of large-scale GWAS, performance, coverage and imputation quality should be considered when choosing an array. While whole genome sequencing and whole exome sequencing have gained considerable attention in genetic epidemiology, and are gaining ground in the diagnostic phase of childhood cancer, none of these approaches have yet been taken in the evaluation of genetic susceptibility to late effects in CCS.

Up until now, evidence-based guidelines for CCS concerning genetic susceptibility testing have only been developed for cardiotoxicity (Aminkeng et al., 2016b). However, these guidelines are not implemented in clinical practice yet. For other late toxicities after childhood cancer the currently available literature is not robust enough, as yet, to inform reliable prediction models. However, genotyping childhood cancer patients in order to risk-adapt treatment based on risk models predicting susceptibility to specific late toxicities is likely to become standard of care. International collaboration is critical to advance knowledge of specific genetic risk factors in order to guide the development of scientifically rigorous prediction models. Currently, we are investigating the genetic susceptibility of hearing impairment and female gonadal impairment in an international consortium (European Union's Seventh Framework programme project PanCareLIFE) with replication planned in independent cohorts from North America (PanCareLIFE, 2017).

4. Conclusions

With growing knowledge of genetic determinants of late-effects and the continuation in decreasing genotyping costs, more personalized treatment protocols may become possible in the future. The criteria of 1) adequately sized cohorts and 2) the inclusion of independent replication cohorts are mandatory for well-founded research in genetic variability. International collaboration can ensure adherence to these criteria and thus be beneficial for the quality of research.

Competing interests

None to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.critrevonc.2018.04.001.

References

Allison, M.B., Myers, M.G., 2014. 20 YEARS OF LEPTIN: connecting leptin signaling to biological function. J. Endocrinol. 223, T25–T35.
Alvarez-Hernandez, D., Naves, M., Diaz-Lopez, J.B., Gomez, C., Santamaria, I., Cannata-Andia, J.B., 2003. Influence of polymorphisms in VDR and COLIA1 genes on the risk of osteoporotic fractures in aged men. Kidney Int. (Suppl), S14–S18.
Aminkeng, F., Ross, C.J., Rassekh, S.R., Hwang, S., Rieder, M.J., Bhavsar, A.P., et al., 2016a. Recommendations for Genetic Testing to Reduce the Incidence of Anthracycline-induced Cardiotoxicity.
Aminkeng, F., Ross, C.J., Rassekh, S.R., Hwang, S., Rieder, M.J., Bhavsar, A.P., et al., 2016b. Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. Br. J. Clin. Pharmacol. 82, 683–695.
Bhavsar, A.P., Gunaretnam, E.P., Li, Y., Hasbullah, J.S., Carleton, B.C., Ross, C.J., 2017. Pharmacogenetic variants in TPMT alter cellular responses to cisplatin in inner ear cell lines. PLoS One 12, e0175711.
Brown, A.L., Lupo, P.J., Okcu, M.F., Lau, C.C., Rednam, S., Scheurer, M., 2015. SOD2 genetic variant associated with treatment-related ototoxicity in cisplatin-treated pediatric medulloblastoma. Cancer Med. 4, 1679–1686.
Choeyprasert, W., Sawangpanich, R., Lertsukprasert, K., Udomsubpayakul, U., Songdej, D., Unurathapan, U., et al., 2013. Cisplatin-induced ototoxicity in pediatric solid tumors: the role of glutathione S-transferases and megalin genetic polymorphisms. J. Pediatr. Hematol. Oncol. 35, e138–e143.
Clemens, E., De Vries, A.C., Am Zehnhoff-Dinnesen, A., Tissing, W., Loonen, J., Pluijm, S.M., et al., 2017. Hearing Loss after Platinum-Treatment Is Irreversible at Long-Term Follow-Up in Non-Cranial Irradiated CCS, a DCOG Study. Submitted.
Dalton, V.K., Rue, M., Silverman, L.B., Gelber, R.D., Asselin, B.L., Barr, R.D., et al., 2003. Height and weight in children treated for acute lymphoblastic leukemia: relationship to CNS treatment. J. Clin. Oncol. 21, 2953–2960.
den Hoed, M.A.H., Pluijm, S.M.F., Stolk, L., Uitterlinden, A.G., Pieters, R., van den Heuvel-Eibrink, M.M., 2016. Genetic variation and bone mineral density in long-term adult survivors of childhood cancer. Pediatr. Blood Cancer 63, 2212–2220.
Du, X., Schwander, M., Moresco, E.M., Viviani, P., Haller, C., Hildebrand, M.S., et al., 2008. A catechol-O-methyltransferase that is essential for auditory function in mice and humans. Proc. Natl. Acad. Sci. U. S. A. 105, 14609–14614.
EMBL-EBI, 2017. The NHGRI-EBI Catalog of Published Genome-Wide Association Studies.
Fang, Y., van Meurs, J.B., Bergink, A.P., Hofman, A., van Duijn, C.M., van Leeuwen, J.P., et al., 2003. Cdx-2 polymorphism in the promoter region of the human vitamin d receptor gene determines susceptibility to fracture in the elderly. J. Bone Min. Res. 18, 1632–1641.
Ferlin, A., Raicu, F., Gatta, V., Zuccarello, D., Palka, G., Foresta, C., 2007. Male infertility: role of genetic background. Reprod. Biomed. Online 14, 734–745.
Fuchs, P.A., 2014. A' calcium capacitor' shapes cholinergic inhibition of cochlear hair cells. J. Physiol. 592, 3393–3401.
Galan, J.J., Buch, B., Cruz, N., Segura, A., Moron, F.J., Bassas, L., et al., 2005. Multilocus analyses of estrogen-related genes reveal involvement of the ESR1 gene in male infertility and the polygenic nature of the pathology. Fertil. Steril. 84, 910–918.

Gatta, G., Botta, L., Rossi, S., Aareleid, T., Bielska-Lasota, M., Clavel, J., et al., 2014. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5–a population-based study. Lancet Oncol. 15, 35–47.
Ge, X., Yamamoto, S., Tsutsumi, S., Midorikawa, Y., Ihara, S., Wang, S.M., et al., 2005. Interpreting expression profiles of cancers by genome-wide survey of breadth of expression in normal tissues. Genomics 86, 127–141.
Geenen, M.M., Cardous-Ubbink, M.C., Kremer, L.C., van den Bos, C., van der Pal, H.J., Heinen, R.C., et al., 2007. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. Jama 297, 2705–2715.
Gjesdal, C.G., Vollset, S.E., Ueland, P.M., Refsum, H., Drevon, C.A., Gjessing, H.K., et al., 2006. Plasma total homocysteine level and bone mineral density: the hordaland homocysteine study. Arch. Intern. Med. 166, 88–94.
Guarducci, E., Nuti, F., Becherini, L., Rotondi, M., Balercia, G., Forti, G., et al., 2006. Estrogen receptor α promoter polymorphism: stronger estrogen action is coupled with lower sperm count. Hum. Reprod. 21, 994–1001.
Hagleitner, M.M., Coenen, M.J.H., Patino-Garcia, A., de Bont, E., Gonzalez-Neira, A., Vos, H.I., et al., 2014. Influence of genetic variants in TPMT and COMT associated with cisplatin induced hearing loss in patients with cancer: two New cohorts and a meta-analysis reveal significant heterogeneity between cohorts. PLoS One 9.
Haslinger, A., Schwarz, T.J., Covic, M., Chichung Lie, D., 2009. Expression of Sox11 in adult neurogenic niches suggests a stage-specific role in adult neurogenesis. Eur. J. Neurosci. 29, 2103–2114.
Hattersley, A.T., McCarthy, M.I., 2005. What makes a good genetic association study? Lancet 366, 1315–1323.
He, C., Kraft, P., Chen, C., Buring, J.E., Pare, G., Hankinson, S.E., et al., 2009. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. Nat. Genet. 41, 724–728.
He, C., Kraft, P., Chasman, D.I., Buring, J.E., Chen, C., Hankinson, S.E., et al., 2010. A large-scale candidate gene association study of age at menarche and age at natural menopause. Hum. Genet. 128, 515–527.
Hirano, S., Takeichi, M., 2012. Cadherins in brain morphogenesis and wiring. Physiol. Rev. 92, 597–634.
Hong, E.P., Park, J.W., 2012. Sample size and statistical power calculation in genetic association studies. Genomics Inf. 10, 117–122.
HumanGenomeProject, 2015. All About the Human Genome Project (HGP). https://www.genome.gov/10001772/.
Jones, T.S., Kaste, S.C., Liu, W., Cheng, C., Yang, W., Tantisira, K.G., et al., 2008. CRHR1 polymorphisms predict bone density in survivors of acute lymphoblastic leukemia. J. Clin. Oncol. 26, 3031–3037.
Knoll, C., Smith, R.J.H., Shores, C., Blatt, J., 2006. Hearing genes and cisplatin deafness: a pilot study. Laryngoscope 116, 72–74.
Langer, T., Am Zehnhoff-Dinnesen, A., Radtke, S., Meitert, J., Zolk, O., 2013. Understanding platinum-induced ototoxicity. Trends Pharmacol. Sci. 34, 458–469.
Lanvers-Kaminsky, C., Malath, I., Deuster, D., Ciarimboli, G., Boos, J., Am Zehnhoff-Dinnesen, A.G., 2014. Evaluation of pharmacogenetic markers to predict the risk of cisplatin-induced ototoxicity. Clin. Pharmacol. Ther. 96, 156–157.
Lee, J.W., Pussegoda, K., Rassekh, S.R., Monzon, J.G., Liu, G., Hwang, S., et al., 2016. Clinical practice recommendations for the management and prevention of cisplatin-induced hearing loss using pharmacogenetic markers. Ther. Drug Monit. 38, 423–431.
Liu, X., Fu, Y.X., 2015. Exploring population size changes using SNP frequency spectra. Nat. Genet. 47, 555–559.
Lorentzon, M., Lorentzon, R., Nordstrom, P., 2001. Vitamin d receptor gene polymorphism is related to bone density, circulating osteocalcin, and parathyroid hormone in healthy adolescent girls. J. Bone Min. Metab. 19, 302–307.
MacArthur, J., Bowler, E., Cerezo, M., Gil, L., Hall, P., Hastings, E., et al., 2017. The new NHGRI-EBI catalog of published genome-wide association studies (GWAS catalog). Nucleic Acids Res. 45, D896–D901.
Mapes, B., El Charif, O., Al-Sawwaf, S., Dolan, M.E., 2017. Genome-wide association studies of chemotherapeutic toxicities: genomics of inequality. Clin. Cancer Res. 23, 4010–4019.
McIlwain, C.C., Townsend, D.M., Tew, K.D., 2006. Glutathione S-transferase polymorphisms: cancer incidence and therapy. Oncogene 25, 1639–1648.
Oeffinger, K.C., Mertens, A.C., Sklar, C.A., Kawashima, T., Hudson, M.M., Meadows, A.T., et al., 2006. Chronic health conditions in adult survivors of childhood cancer. N. Engl. J. Med. 355, 1572–1582.
Oldenburg, J., Kraggerud, S.M., Cvancarova, M., Lothe, R.A., Fossa, S.D., 2007. Cisplatin-induced long-term hearing impairment is associated with specific glutathione S-transferase genotypes in testicular cancer survivors. J. Clin. Oncol. 25, 708–714.
PanCareLIFE, 2017. The Project. PanCareLIFE.
Park, H.W., Tse, S., Yang, W., Kelly, H.W., Kaste, S.C., Pui, C.H., et al., 2016. A genetic factor associated with low final bone mineral density in children after a long-term glucocorticoids treatment. Pharmacogenomics J.
Peters, U., Preisler-Adams, S., Hebeisen, A., Hahn, M., Seifert, E., Lanvers, C., et al., 2000. Glutathione S-transferase genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. Anticancer Drugs 11, 639–643.
Price, A.L., Zaitlen, N.A., Reich, D., Patterson, N., 2010. New approaches to population stratification in genome-wide association studies. Nat. Rev. Genet. 11, 459–463.
Pussegoda, K., Ross, C.J., Visscher, H., Yazdanpanah, M., Brooks, B., Rassekh, S.R., et al., 2013. Replication of TPMT and ABCC3 genetic variants highly associated with cisplatin-induced hearing loss in children. Clin. Pharmacol. Ther. 94, 243–251.
Rednam, S., Scheurer, M.E., Adesina, A., Lau, C.C., Okcu, M.F., 2013. Glutathione S-transferase P1 single nucleotide polymorphism predicts permanent ototoxicity in children with medulloblastoma. Pediatr. Blood Cancer 60, 593–598.
Riedemann, L., Lanvers, C., Deuster, D., Peters, U., Boos, J., Jurgens, H., et al., 2008. Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. Pharmacogenomics J. 8, 23–28.
Rogers, P.C., Meacham, L.R., Oeffinger, K.C., Henry, D.W., Lange, B.J., 2005. Obesity in pediatric oncology. Pediatric Blood Cancer 45, 881–891.
Romerius, P., Giwercman, A., Moëll, C., Relander, T., Cavallin-Ståhl, E., Wiebe, T., et al., 2011. Estrogen receptor α single nucleotide polymorphism modifies the risk of azoospermia in childhood cancer survivors. Pharmacogenet. Genomics 21, 263–269.
Ross, J.A., Oeffinger, K.C., Davies, S.M., Mertens, A.C., Langer, E.K., Kiffmeyer, W.R., et al., 2004. Genetic variation in the leptin receptor gene and obesity in survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. J. Clin. Oncol. 22, 3558–3562.
Ross, C.J.D., Katzov-Eckert, H., Dubé, M.P., Brooks, B., Rassekh, S.R., Barhdadi, A., et al., 2009. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat. Genet. 41, 1345–1349.
Sawicka-Zkowska, M., Krawczuk-Rybak, M., Muszynska-Roslan, K., Panasiuk, A., Latoch, E., Konstantynowicz, J., 2013. Does Q223R polymorphism of leptin receptor influence on anthropometric parameters and bone density in childhood cancer survivors? Intl. J. Endocrinol. 2013.
Skoczen, S., Tomasik, P.J., Bik-Multanowski, M., Surmiak, M., Balwierz, W., Pietrzyk, J.J., et al., 2011. Plasma levels of leptin and soluble leptin receptor and polymorphisms of leptin gene -18G & a and leptin receptor genes K109R and Q223R, in survivors of childhood acute lymphoblastic leukemia. J. Exp. Clin. Cancer Res. 30.
Steer, C.D., Emmett, P.M., Lewis, S.J., Smith, G.D., Tobias, J.H., 2009. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with spinal BMD in 9-year-old children. J. Bone Min. Res. 24, 117–124.
Stolk, L., Zhai, G., van Meurs, J.B., Verbiest, M.M., Visser, J.A., Estrada, K., et al., 2009. Loci at chromosomes 13, 19 and 20 influence age at natural menopause. Nat. Genet. 41, 645–647.
Surapolchai, P., Hongeng, S., Mahachoklertwattana, P., Pakakasama, S., Winaichatsak, A., Wisanuyothin, N., et al., 2010. Impaired glucose tolerance and insulin resistance in survivors of childhood acute lymphoblastic leukemia: prevalence and risk factors. J. Pediatr. Hematol. Oncol. 32, 383–389.
Tantisira, K.G., Lake, S., Silverman, E.S., Palmer, L.J., Lazarus, R., Silverman, E.K., et al., 2004. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Hum. Mol. Genet. 13, 1353–1359.
Taskinen, M., Saarinen-Pihkala, U.M., Hovi, L., Lipsanen-Nyman, M., 2000. Impaired glucose tolerance and dyslipidaemia as late effects after bone-marrow transplantation in childhood. Lancet 356, 993–997.
te Winkel, M.L., van Beek, R.D., Keizer-Schrama, S.M.P.F.M., Uitterlinden, A.G., Hop, W.C.J., Pieters, R., et al., 2010. Pharmacogenetic risk factors for altered bone mineral density and body composition in pediatric acute lymphoblastic leukemia. Haematologica 95, 752–759.
te Winkel, M.L., de Muinck Keizer-Schrama, S.M.P.F., de Jonge, R., van Beek, R.D., van der Sluis, I.M., Hop, W.C.J., et al., 2011. Germline variation in the MTHFR and MTRR genes determines the nadir of bone density in pediatric acute lymphoblastic leukemia: a prospective study. Bone 48, 571–577.
Thiesen, S., Yin, P., Jorgensen, A.L., Zhang, J.E., Manzo, V., McEvoy, L., et al., 2017. TPMT, COMT and ACYP2 genetic variants in paediatric cancer patients with cisplatin-induced ototoxicity. Pharmacogenet Genomics 27, 213–222.
Van Dorp, W., Van Den Heuvel-Eibrink, M.M., Stolk, L., Pieters, R., Uitterlinden, A.G., Visser, J.A., et al., 2013. Genetic variation may modify ovarian reserve in female childhood cancer survivors. Hum. Reprod. 28, 1069–1076.
van Meurs, J.B., Dhonukshe-Rutten, R.A., Pluijm, S.M., van der Klift, M., de Jonge, R., Lindemans, J., et al., 2004. Homocysteine levels and the risk of osteoporotic fracture. N. Engl. J. Med. 350, 2033–2041.
van Rossum, E.F., Koper, J.W., van den Beld, A.W., Uitterlinden, A.G., Arp, P., Ester, W., et al., 2003. Identification of the BclI polymorphism in the glucocorticoid receptor gene: association with sensitivity to glucocorticoids in vivo and body mass index. Clin. Endocrinol. (Oxf.) 59, 585–592.
van Waas, M., Neggers, S.J.C.M.M., Pieters, R., van den Heuvel-Eibrink, M.M., 2010. Components of the metabolic syndrome in 500 adult long-term survivors of childhood cancer. Ann. Oncol. 21, 1121–1126.
Van Waas, M., Neggers, S.J.C.M.M., Uitterlinden, A.G., Blijdorp, K., Van Der Geest, I.M.M., Pieters, R., et al., 2013. Treatment factors rather than genetic variation determine metabolic syndrome in childhood cancer survivors. Eur. J. Cancer 49, 668–675.
Vos, H.I., Guchelaar, H.J., Gelderblom, H., De Bont, E.S.J.M., Kremer, L.C.M., Naber, A.M., et al., 2016. Replication of a genetic variant in ACYP2 associated with cisplatin-induced hearing loss in patients with osteosarcoma. Pharmacogenet. Genomics. 26, 243–247.
Wilson, C.L., Liu, W., Yang, J.J., Kang, G., Ojha, R.P., Neale, G.A., et al., 2015. Genetic and clinical factors associated with obesity among adult survivors of childhood cancer: a report from the St. Jude lifetime Cohort. Cancer 121, 2262–2270.
Xu, H., Robinson, G.W., Huang, J., Lim, J.Y., Zhang, H., Bass, J.K., et al., 2015. Common variants in ACYP2 influence susceptibility to cisplatin-induced hearing loss. Nat. Genet. 47, 263–266.
Yang, J.J., Lim, J.Y.S., Huang, J., Bass, J., Wu, J., Wang, C., et al., 2013. The role of inherited TPMT and COMT genetic variation in cisplatin-induced ototoxicity in children with cancer. Clin. Pharmacol. Ther. 94, 252–259.