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Mini-review

Identification of novel hereditary cancer genes by whole exome sequencing

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ABSTRACT

Whole exome sequencing (WES) provides a powerful tool for medical genetic research. Several dozens of WES studies involving patients with hereditary cancer syndromes have already been reported. WES led to breakthrough in understanding of the genetic basis of some exceptionally rare syndromes; for example, identification of germ-line SMARCA4 mutations in patients with hypercalcemic small cell carcinomas indeed explains a noticeable share of familial aggregation of this disease. However, studies on common cancer types turned out to be more difficult. In particular, there is almost a dozen of reports describing WES analysis of breast cancer patients, but none of them yet succeeded to reveal a gene responsible for the significant share of missing heritability. Virtually all components of WES studies require substantial improvement, e.g. technical performance of WES, interpretation of WES results, mode of patient selection, etc. Most of contemporary investigations focus on genes with autosomal dominant mechanism of inheritance; however, recessive and oligogenic models of transmission of cancer susceptibility also need to be considered. It is expected that the list of medically relevant tumor-predisposing genes will be rapidly expanding in the next few years.

1Introduction

Inherited genetic defects contribute to a significant share of familial cancer clustering and overall cancer morbidity. Earlier hereditary cancer studies were based mainly on the linkage analysis of large pedigrees, and led to the identification of a number of well-known highly-penetrant genes, e.g. BRCA1, BRCA2, MSH2, MLH1 [1–5]. Another strategy relies on the candidate gene analysis; it involves selection of genes with presumable cancer-related function, genetic screening of series of patients with clinical features of hereditary cancer (i.e., family history, early onset, multiple malignancies, specific disease appearance etc.) and subsequent case–control study for newly identified variants. This approach allows to reveal even those genes, which are not easily transmitted through generations due to severity of disease manifestation (e.g., TP53 [6]) or characterized by incomplete penetrance (e.g., CHEK2, NBS1 (NBN), ATM, BLM [7–9]).

All gene-seeking studies critically depend on the accessibility of DNA sequencing technologies. First discoveries of germ-line mutations were achieved by the manual DNA sequencing. Introduction of the automated DNA analysis in the mid-1990s and invention of high-resolution melting (HRM) prescreening technique in 2000s significantly improved the throughput of single-gene testing [10,11]. The development of the next-generation sequencing, with potential applications for whole genome sequencing, apparently represents the most remarkable methodological breakthrough in the entire biomedical science since the discovery of PCR [12]. Whole exome sequencing (WES), being capable to cover almost the entire protein-coding region of the human genome, is considered to be an outstandingly powerful tool for medical genetic studies [13]. Indeed, WES already has led to the identification of causative mutations for a number of rare familial syndromes [14–17]. Furthermore, WES revealed previously unknown roles for some cancer related genes. For example, PALB was initially discovered as a breast cancer gene; however, a whole exome study demonstrated its involvement in

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familial aggregation of pancreatic cancer [18]. As expected, the list of novel cancer-predisposing genes is also rapidly expanding (Table 1). Nevertheless, the impact of WES studies in resolving the issue of missing heritability for cancer patients remains somewhat lower than initially anticipated [110].

2Breast cancer

Breast cancer (BC) is the most comprehensively investigated tumor type, and it is therefore appropriate to refer to BC as the most informative example. Pedigree-based studies led to the discovery of BRCA1 and BRCA2 two decades ago [1,2]. These data were quickly replicated by other groups using additional sets of families [111–114]. Furthermore, systematic screening for BRCA1 and BRCA2 mutations revealed that approximately 5% of total breast cancer morbidity, and about 15–25% of familial BC clustering, is attributed to BRCA1/2 mutations [115–120]. Although the frequencies of BRCA1 and BRCA2 defects vary between different ethnic groups, with increased prevalence of BRCA1 in some and BRCA2 in others, these genes appear to have a worldwide medical significance [121]. Similarly, many reported findings on candidate breast-cancer predisposing genes were subsequently validated in independent studies and turned out to be relevant to significant share of breast cancer patients. For example, CHEK2 mutations contribute to 2–3% of BC incidence at least in some European countries and are associated with moderate but nevertheless clinically meaningful elevation of risk of the disease [7,122,123]. The role of PALB2 was also revealed via candidate gene approach, and convincingly replicated in other patient series [124–126]. Data on ATM, NBS1 (NBN), BRIP1, BLM, etc. are less comprehensive, but nevertheless these genes may also be regarded as substantial contributors to breast cancer risk [8,9,26,127–131].

Based on the highly successful experience with identification of breast cancer genes via linkage studies or candidate gene testing, it was suggested that a presumably unbiased approach, such as exome sequencing, will immediately fill some gaps in the missing breast cancer heritability. However, most of the breast cancer exome studies reported so far failed to discover genes, whose significance is similar to BRCA1, BRCA2, CHEK2, PALB2, etc. [19–22,25,28,132–136]. For example, Snape et al. [133] subjected to WES 50 patients with familial breast cancer; they composed the list of promising candidates, but did not communicate yet the results of subsequent case–control study or segregation analysis. Importantly, the same group of researchers achieved remarkable success in identifying new breast cancer genes by a candidate gene approach [124,130]. Thompson et al. [25] analyzed 33 BC patients from 15 families, but their findings were limited to the genes, whose breast cancer predisposing role had already been demonstrated in prior studies [9,27,137]. Park et al. [28] suggested a role of very rare mutations in XRCC2 gene; however, subsequent reports failed to replicate these findings [138,139]. Hilbers et al. [134] and Gracia-Aznarez et al. [22] analyzed several well-selected families, but no major new gene was identified. Gracia-Aznarez et al. [22] and Kiiski et al. [21] revealed rare mutations in the FANCM gene, which turned out to be overrepresented in breast cancer cases vs. controls. Arguably, the study of Sokolenko et al. [135] is the most successful for the time being: they reported identification of recurrent mutations in the RECQL gene, which occurred approximately 5 times more frequently in patients vs. healthy donors, and were present in 0.69% patients from Poland and in 0.23% BC cases in Canada. Still, the frequency of RECQL germ-line mutations in affected women is manifold lower as compared to “classical” BC genes.

The success rate of the candidate gene approach is extremely difficult to estimate, because negative studies are rarely reported in a systematic way. Nevertheless, some rough assumptions can be drawn. For example, the studies from our laboratory considered 95 genetically enriched BC cases, which were negative for known breast cancer predisposing mutations. We subjected to full-length sequencing 22 DNA repair genes and revealed a role of truncating mutations of BLM gene in breast cancer predisposition [9,140]; importantly, these findings were later replicated in independent studies [25,26]. There are somewhat more robust investigations involving several hundreds of high-risk BC patients; they reported the identification of several new BC genes; however, they did not communicate the overall number of genes tested [124,130]. In any event, if we consider successful gene discovery studies, the number of the genes analyzed by the candidate approach is unlikely to exceed a few dozens, and the number of tested patients would at best be in the range of several hundreds. In contrast to targeted investigations of a few dozen of candidate genes whole exome sequencing is capable of analyzing essentially the entire protein-coding gene complement of the human genome, whose estimated count currently stands at around 19,000 [141]. At least a few thousands of genes within exome appear to be attractive for consideration due to their role in tumor development, cell division, apoptosis, genomic maintenance, etc., or similarity to known cancer-related genes. One would thus expect that the whole exome sequencing of just a few well-selected patients or families has very good chances to reveal new important genes. However, pedigree and candidate gene studies still remain a main contributor in the discovery of new BC genes, while the whole exome sequencing has not met the expectations yet [110].

3Other cancer types

Studies of familial cancer cases may be more efficient for those tumor types, which are characterized by moderate or rare incidence. Indeed, while the presence of multiple cases of common cancers within family, e.g. breast cancer, may occur by chance, this probability is significantly lower for many other malignancies. For example, strong familial clustering of multiple colorectal adenomas and carcinomas is relatively rare. Palles et al. [35] analyzed families with this disease, and revealed the role of mutations in POLE and POLD1 genes. Strikingly, these findings received a high number of confirmatory reports [36–43]. Whole exome sequencing and subsequent validation studies on familial melanoma revealed a role of MITF and POT1 mutations; however, their actual impact on the disease incidence remains to be determined [52–56]. BAP1 germline mutations were initially identified upon the study of uveal melanoma [57] and later turned out to be involved in the development of several other tumor types [58–72]. Instances of lung cancer clustering due to high-penetrance mutations are very infrequent; however, the analysis of individual large families revealed potentially relevant genes [50,51].

High level of efficiency and reproducibility is characteristic for the WES studies of exceptionally rare syndromes presenting with unique clinical manifestation. For example, identification of SMARCA4 mutations in hypercalcemic small cell carcinomas of the ovary led to a breakthrough in understanding of genetic basis of this disease [73–76]. Similarly, SMARCE1 mutations were revealed upon the study of multiple spinal meningiomas [82–85]. It is important to understand that most of WES studies were reported very recently, therefore their validation is yet expected to come.

4Challenges and possible solutions

Technical limitations of whole exome sequencing are widely acknowledged. Some protein-coding regions of genome cannot be efficiently read by existing WES tools [14,16,17]. Furthermore, while the frequency of false-positive findings of WES can be easily analyzed by Sanger sequencing, systematic analysis of the rate of false-negatives is highly expensive and rarely performed in routine. Indeed, most of the current reasoning regarding the reliability of WES is

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Table 1
Examples of novel tumor-predisposing genes identified by whole exome sequencing.

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Breast cancer								
Cybulski et al. [19]	Breast cancer	Poland, Canada	144 Polish and 51 French-Canadian patients with strong family history and/or young onset, negative for founder mutation in BRCA1, BRCA2, CHEK2, NBN and PALB2	Search for rare truncating mutations occurring in 2 or more of the analyzed patients; only one gene, RECQL, was present in both Polish and French-Canadian patients, and had cancer-related biological function	RECQL (truncating mutations)	Selected founder mutations were identified in 7/1013 (0.69%) cases vs. 1/7136 (0.14%) controls in Canada, and in 30/13136 (0.23%) cases vs. 2/4702 (0.04%) controls in Poland	Segregation with the disease in families, however no LOH in the tumor tissue	The same gene was simultaneously identified in a Chinese WES study [20]
Sun et al. [20]	Breast cancer	China	9 very early-onset (<35 years) breast cancer patients with family history, negative for BRCA1 and BRCA2 mutations	Search for novel rare truncating mutation occurring in 2 or more of the analyzed patients; 3 genes meeting these criteria identified, one of those, RECQL, had clear cancer-related biological function	RECQL (truncating mutations)	9/448 (2.01%) cases vs. 1/1588 (0.06%) controls carried either truncating mutations or missense substitutions with proven functional impact (*in vitro* helicase assay)	No LOH in the tumor tissue	The same gene was simultaneously identified in a Polish-Canadian WES study [19]
Kiiski et al. [21]	Breast cancer	Finland	24 breast cancer patients from 11 families, negative for BRCA1 and BRCA2 mutations	Search for rare protein-truncating variants, with the emphasis on DNA repair genes	FANCM (p.Gln1701*)	69/2405 (2.87%) cases vs. 18/1271 (1.42%) controls in Helsinki; 27/674 (4.00%) cases vs. 20/809 (2.47%) controls in Tampere	Incomplete segregation with the disease within families	Gracia-Aznarez et al., 2013 [22] identified FANCM nonsense mutation (p.Arg1931*) upon the analysis of breast cancer patient with family history of the disease, and revealed a trend to its increased prevalence in breast cancer cases vs. controls; Peterlongo et al. [23] also demonstrated increased frequency of this mutation in breast cancer cases vs. controls
Park et al. [24]	Breast cancer	Multiple countries	89 early-onset breast cancer patients from 47 families	RINT1 gene was selected based on the occurrence of its rare pathogenic or presumably pathogenic variants in 3 out of 47 analyzed families	RINT1	Role of RINT1 mutations was confirmed by the analysis of additional families and by a case-control study	Evidence for association with other cancer types	

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Table 1 (*continued*)

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Thompson et al. [25]	Breast cancer	Australia	33 breast cancer patients from 15 families, negative for BRCA1 and BRCA2 mutations	Search for overtly deleterious mutations, occurring in multiple affected relatives within a family or in multiple families, followed by prioritization according to breast cancer-related function	FANCC (p.Arg179* and p.Arg185*) BLM (p.Gln645*)	1 FANCC and 1 BLM mutation in 438 additional BRCA1/2-negative families	Segregation with the disease in families	This report confirms earlier observation of Sokolenko et al. [9], who revealed breast cancer predisposing role of BLM truncating mutations using candidate gene approach; increased prevalence of BLM heterozygotes in breast cancer cases vs. controls was demonstrated in 2 independent data sets [9,26]; evidence for breast cancer predisposing role of FANCC were obtained in the study of relatives of Fanconi anemia patients [27]
Park et al. [28]	Breast cancer	Multiple countries	13 families	Truncating and presumably pathogenic mutations in genes prioritized according to potential cancer-predisposing role	XRCC2 (p.Cys217* and p.Arg91Trp)	Presumably pathogenic XRCC2 mutations in 6/1308 (0.46%) cases vs. 0/1120 (0.00%) controls, and in 10/689 (1.45%) additional breast cancer families		
Gastrointestinal tumors								
Zhang et al. [29]	Colorectal cancer	China	23 early onset colorectal cancer patients from 21 families	Search for novel truncating variants in those families, who turned out to be negative for mutations in known colorectal cancer genes; EIF2AK4 mutation present in 7 families	EIF2AK4 (p.Glu738_Asp739insArgArg)	This mutation occurred at significantly lower frequency in controls (7/100)		
Seguí et al. [30]	Colorectal cancer	Spain	Large family	Search for rare variants shared by all 3 analyzed patients, then prioritization of genes according to their cancer-related biological function	FAN1, p.Cys47*	1 truncating and 3 pathogenic or presumably pathogenic missense variants in additional 176 colorectal cancer families	No LOH in the tumor tissue; evidence for haploinsufficiency in mutation carriers; distinct somatic mutation pattern in FAN1-associated tumors	
Esteban-Jurado et al. [31]	Colorectal cancer	Spain	Patients from 29 families, negative for mutations in known colorectal cancer genes	Selection of rare truncating mutations or rare presumably pathogenic (*in silico*) missense mutations in genes with cancer-related biological function, then segregation analysis	CDKN1B, XRCC4, EPHX1, NFKBIZ, SMARCA4, BARD1		Somatic LOH of the wild-type allele was demonstrated for CDKN1B, XRCC4, EPHX1, but not for NFKBIZ, SMARCA4 and BARD1	

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Table 1 (*continued*)

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Nieminen et al. [32]	Colorectal cancer	Finland	4 patients from a large family, negative for mutations in known colorectal cancer genes	Search for truncating mutation shared by all tested patients	RPS20 (p.Val50SerfsX23)	No RPS20 mutations in other 25 Finnish pedigrees	Complete segregation within the family, but no LOH in the tumor tissue	
Gylfe et al. [33]	Colorectal cancer	Finland	96 patients with family history of colorectal cancer, negative for mutations in known colorectal cancer genes	Search for rare truncating mutations occurring in several patients identified 18 candidate genes; 7 of these genes were subsequently excluded due to high occurrence in ethnicity-matched controls	UACA, SFXN4, TWSG1, PSPH, NUDT7, ZNF490, PRSS37, CCDC18, PRADC1, MRPL3, AKR1C4	Rare occurrence of UACA and ZNF490, but not TWSG1, in colorectal cancer patients	Somatic LOH of the wild-type allele was demonstrated for UACA, TWSG1, PSPH and ZNF490, but not for the remaining genes	
Weren et al. [34]	Adenomatous polyposis and colorectal carcinomas	the Netherlands, USA	51 patient form 48 families, negative for APC and MUTYH mutations	Search for novel recurrent truncating heterozygous mutations and for novel recurrent homozygous variants; 3 families with homozygous NTHL1 mutations identified	NTHL1 (p.Gln90*), biallelic	Absent in additional 149 patients with polyposis; minor allele frequency in population: 0.0036	Pattern of somatic mutations in NTHL1-driven tumors is consistent with biological function of NTHL1 gene	
Palles et al. [35]	Colorectal adenomas and carcinomas	UK	Probands from 15 colorectal adenoma families, negative for mutations in APC and MUTYH	Search for potentially pathogenic mutations occurring in several families (none detected); then consideration of individual families	POLE (p.Leu424Val) POLD1 (p.Ser478Asn)	POLE p.Leu424Val: 12/3805 (2.94%) colorectal cancer patients vs. 0/6721 controls; POLD1 p.Ser478Asn: same mutation was identified in another family and in one of the patients included in case-control study	Somatic LOH of the wild-type allele of the involved gene was detected in some of the analyzed tumors. POLD1 mutation was also associated with endometrial cancer.	Confirmed by multiple studies [36–43]
Sei et al. [44]	Small intestinal carcinoids	USA	Large family	Linkage analysis followed by WES, with selection of segregating variants located within the linkage region	IPMK (p.Ser331Argfs*4)	No IPMK mutations in additional 32 families	No LOH in the tumor tissue	
Donner et al. [45]	Gastric cancer	Finland	Large family with the diffuse type of gastric cancer, negative for mutations in CDH1	Segregation analysis for rare variants, which were predicted to be non-neutral by the CONsensus DELeteriousness score	3 candidates identified: INSR (p.Glu1313Lys), FBXO24 (p.Arg81Pro), DOT1L (p.Pro1146Leu)	None of these variants was detected in 26 additional patients with the diffuse gastric cancer, although one patient carried another rare missense polymorphism in FBXO24	No LOH in the tumor tissue	

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Table 1 (*continued*)

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Majewski et al. [46]	Gastric cancer	the Netherlands	Large family with the diffuse type of gastric cancer, negative for mutations in CDH1	Analysis of known cancer-predisposing genes (none detected); then consideration of variants located within genomic regions linked to the disease inheritance; segregation analysis of selected variants in additional family members	CTNNA1 (p.Arg27Thrfs*17)	No truncating CTNNA1 mutations in other pedigrees (10 Dutch and 15 Canadian)	Evidence for somatic inactivation of CTNNA1 in tumor tissues (loss of protein expression)	A multicenter study revealed heterozygous inactivating CTNNA1 mutation in 2/144 CDH1-negative families [47]
Calvete et al. [48]	Atypical gastric neuroendocrine tumor, type 1	Spain	Large family, with consanguineous parents and 5/10 affected children	Search for biallelic mutations segregating with the disease	ATP4A (p.Arg703Cys), biallelic			
Ngeow et al. [49]	Juvenile hamartomatous polyposis syndrome, associated with ganglioneuromas	USA	Single patient, with extensive family history, negative for known disease-causing mutations	Emphasis in genetic variations affecting PTEN and TGF-beta/BMP signaling pathways	SMAD9 (p.Val90Met)	Lack of this variant in 80 patients with related syndromes, who tested negative for known disease-causing mutations	Additional experimental evidence for a functional significance of this mutation	
Lung cancer								
Xiong et al. [50]	Lung cancer	USA	Large family	Search for rare protein-coding segregating variants located within the linkage interval, defined to be presumably pathogenic by *in silico* tools	PARK (p.Arg275Trp)	Present in 3 additional families; 4/167 (2.40%) unrelated patients with familial cancer vs. 30/13008 (0.23%) controls		
Chen et al. [51]	Lung cancer	Taiwan	Large family	Search for rare segregating protein-coding variants, then exclusion of Taiwanese recurrent polymorphisms by genotyping of control subjects, then validation of remaining variants in a case-control study	YAP1 (p.Arg331Trp)	14/1312 (1.07%) cases vs. 2/1135 controls (0.18%)	High level of segregation with the disease in the studied family and among relatives of the carriers identified upon the case-control study; additional experimental evidence for a functional significance of this mutation	
Melanoma								
Shi et al. [52]	Melanoma	Italy and other countries	101 patient from 56 melanoma families, negative for CDKN2A and CDK4 mutations	Search for rare segregating variants	POT1 (p.Ser270Asn); founder mutation for Romagna, Italy	This or other rare POT1 variants were identified in additional melanoma families and sporadic cases at frequencies higher than in controls	Additional experimental evidence for a functional significance of this mutation	The same gene was simultaneously identified in another WES study [53]

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Table 1 (*continued*)

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Robles-Espinoza et al. [53]	Melanoma	UK, Australia and other countries	184 patients from 105 melanoma families, negative for CDKN2A and CDK4 mutations	Search for rare segregating variants in 28 families with 3 or more affected members, then emphasis on genes detected in more than one pedigree; 4 families with presumably pathogenic POT1 mutation identified	POT1 (various mutations)	None of these mutations was present in 2402 controls	Additional experimental evidence for a functional significance of these mutations	The same gene was simultaneously identified in another WES study [52]
Yokoyama et al. [54]	Melanoma	USA, Australia, UK	Patient from large melanoma family	MITF is selected based on its involvement in melanoma pathogenesis	MITF (p.Glu318Lys)	34/2059 (1.65%) cases vs. 14/1953 (0.72%) controls; 6/270 (2.22%) melanoma families	Incomplete segregation with the disease within families; additional experimental evidence for a functional significance of this mutation	Confirmed in several studies [55,56]
Harbour et al. [57]	Uveal melanoma	USA	Uveal melanoma patients	Exome sequencing of metastasizing uveal melanomas identified high frequency of BAP1 mutation; the analysis of normal DNA revealed 1 germ-line mutation carrier	BAP1 (truncating mutation)			Confirmed in multiple studies [58–72]
Miscellaneous								
Witkowski et al. [73]	Small cell carcinoma of the ovary, hypercalcemic type	USA, Canada, UK	6 patients from 3 families	Search for a gene inactivated in all 3 families	SMARCA4 (truncating mutations)	Germ-line SMARCA4 inactivating mutation in the additional family and in 6/12 sporadic cases	Somatic inactivation of the wild-type allele	The same gene was simultaneously identified in another WES study [74]; confirmed in several studies [75,76]
Ramos et al. [74]	Small cell carcinoma of the ovary, hypercalcemic type	Several countries	7 patients	Search for recurrent inactivating somatic mutations in tumors, then analysis of germ-line DNA (2/7 mutation carriers identified)	SMARCA4 (truncating mutations)		Somatic inactivation of the wild-type allele	The same gene was simultaneously identified in another WES study [73]; confirmed in several studies [75,76]
FitzGerald et al. [77]	Prostate cancer	USA	91 patient from 19 families	Search for variants segregating with the disease; BTNL2 mutations were present in 2/19 analyzed families	BTNL2 (p.Asp336Asn and p.Gly454Cys)	Segregation with the disease was confirmed in additional 270 families; higher incidence in unselected prostate cancer patients vs. controls		

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Table 1 (*continued*)

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Gara et al. [78]	Non-medullary thyroid cancer	USA	Large family	Search for rare, segregating variants	HABP2 (Gly543Glu)	Analysis of TCGA data revealed this mutation in 20/423 (4.7%) of patients with papillary thyroid cancer, as compared with 0.7% in subjects with unknown disease status in multiethnic population databases	HABP2 overexpression in tumors from mutation carriers; additional experimental evidence for a functional significance of this mutation	
Bainbridge et al. [79]	Glioma	Multiple countries	90 patients from 55 families	Search for rare, segregating, presumably pathogenic variants in genes with known cancer-related role; 2 families with presumably pathogenic POT1 mutation identified	POT1 (various mutations)	Additional truncating mutation in POT1 was revealed in the validation set (264 patients from 246 families)		
Cascón et al. [80]	Paraganglioma	Spain	Patient with multiple paragangliomas and family history of the disease	MDH2 gene selected due to functional similarity to the known paraganglioma genes	MDH2 (mutation in the splice site, c.429 + 1G > T)		Evidence for somatic inactivation of MDH2 in tumor tissues obtained from this patient (LOH of the wild-type allele and decreased expression of the gene); incomplete penetrance within the studied family	
Zhang et al. [81]	Familial schwannomatosis	Chinese	Large family, negative for mutations in known disease-causing genes	Search for variants shared among affected family members and presumably pathogenic by in silico tools; prioritization according to the gene function	COQ6 (p.Asp208His)		Additional experimental evidence for a functional significance of this mutation	
Smith et al. [82]	Multiple spinal meningiomas	UK	3 unrelated individuals with familial multiple spinal meningiomas, negative for mutations in NF2 and SMARCB1	Search for protein-inactivating variants in subunits of the SWI/SNF complex	SMARCE1 (truncating mutations)	Truncating mutations in 2/6 additional patients	Loss of SMARCE1 protein in tumor tissue	Confirmed in several studies [83–85]
Comino-Méndez et al. [86]	Pheochromocytoma	Spain	3 patients with familial pheochromocytoma, negative for mutations in known disease-causing genes	Search for rare heterozygous variants affecting the same gene in all 3 analyzed patients; then segregation analysis in family members	MAX (truncating mutations)	2 truncating mutations in 59 cases with clinical features of hereditary disease vs. 0/750 controls	Somatic LOH of the wild-type allele in all analyzed cases	Confirmed in several studies [87,88]

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Table 1 (*continued*)

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Tomsic et al. [89]	Papillary thyroid carcinoma	USA, Canada	Large family	Linkage analysis followed by WES; selection of candidates based on haplotype analysis	SRRM2 (p.Ser346Phe)	7/1170 (0.60%) sporadic cases vs. 0/1404 (0.00%) controls	Evidence for involvement of this variant in regulation of alternative splicing of various genes	
Aavikko et al. [90]	Kaposi sarcoma	Finland	Large family	Search for rare protein-coding variants segregating with the disease	STAT4 (p.Thr446Ile)	This variant was absent in 18 additional Kaposi sarcoma families, 56 sporadic cases and 422 controls	Reduced IFN-gamma production in T-helper cells obtained from mutation carriers vs. controls	
Linhares et al. [91]	Infantile myofibromatosis	Brazil	2 affected brothers and their healthy consanguineous parents	Search for rare variants with presumably moderate or high impact (determined by SnpEff tool), homozygous in the patients and heterozygous in the parents	NDRG4 (p.Val171Leu), biallelic			
Cheung et al [92]	Infantile myofibromatosis	Multiple countries	11 patients form 4 families, and 5 simplex cases	Search for rare heterozygous protein-coding variants segregating with the disease	PDGFRB (p.Arg561Cys)		Evidence for somatic mutations in the remaining PDGFRB allele	The same gene was simultaneously identified in another WES study [93]
Martignetti et al [93]	Infantile myofibromatosis	USA	11 patients from 9 families	Search for rare heterozygous protein-coding variants segregating with the disease	PDGFRB (p.Arg561Cys and p.Pro660Thr)			The same gene was simultaneously identified in another WES study [92]
Martignetti et al. [93]	Infantile myofibromatosis	USA	Large family, negative for PDGFRB mutations	Search for rare heterozygous protein-coding variants segregating with the disease	NOTCH3 (p.Leu1519Pro)			
Vilarinho et al. [94]	Paediatric hepatocellular carcinoma	USA	Analysis of single patients with a rare disease	Consideration of protein-damaging mutations in genes involved liver/abdomen diseases	ABCB11, biallelic missense mutation (compound heterozygote)			
Hanks et al. [95]	Wilms tumor	UK	35 families	Search for rare truncating mutations segregating with the disease; CTR9 mutations detected in 3 families	CTR9 (truncating mutations)	Lack of CTR9 mutations in healthy controls	Somatic inactivation of the wild-type allele in the tumor tissue	
Ristolainen et al. [96]	Hodgkin lymphoma	Middle East	Family with 3 out of 5 affected children and healthy parents	Search for rare segregating variants; selection of mutation, which is heterozygous in both parents, absent or heterozygous in healthy children, but homozygous in all affected children	ACAN (57-bp biallelic in-frame deletion with several linked missense variants)			

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Table 1 (*continued*)

Study	Tumor type	Country or ethnicity	Patients	Principles of selection of causative genetic determinant	Genes and mutations	Analysis of additional patients	Additional information	Relevant data from independent studies
Saarinen et al. [97]	Hodgkin lymphoma	Finland	Large family with nodular lymphocyte predominant Hodgkin lymphoma	Linkage analysis followed by whole exome sequencing of a single patient; search for segregating variants	NPAT (p.Leu814Phefs*6)		Decreased NPAT expression in lymphoma samples obtained from mutation carriers	
Noetzli et al. [98]	Lymphoblastic leukemia, being part of syndrome manifested by thrombocytopenia and high erythrocyte mean corpuscular volume	USA and other countries	Large family	Knowledge on ETV6 involvement in pathogenesis of leukemia	ETV6 (p.Pro214Leu)	ETV6 protein-damaging mutations were identified in 2/23 additional families with this syndrome	Additional experimental evidence for a functional significance of this mutation; no LOH in the leukemic cells	The same gene was simultaneously identified in a candidate gene study [99]
Shah et al. [100]	Pre-B cell acute lymphoblastic leukemia	Families of Puerto-Rican African-American ancestry	2 families	PAX2 is selected based on its known role B cell function, and presence of identical segregating mutation in both affected families	PAX2 (p.Gly183Ser)		Somatic deletion of the remaining PAX2 allele in the leukemic cells; additional experimental evidence for a functional significance of this mutation; somatic PAX2 mutations in codon 183 in sporadic cases of the disease	
Ostergaard et al. [101]	Primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome)	Patients of European and Chinese descent	2 unrelated patients with family history and 1 sporadic case	Search for rare heterozygous protein-coding variants shared by all analyzed patients	GATA2 (truncating mutations)	GATA2 truncating or missense mutations were detected in 5 additional subjects with the same syndrome, but not in 300 controls		Confirmed in multiple studies [102–108]

PubMed search was performed using a string (exome OR exom* OR NGS OR "whole genome" OR "next-generation" OR "next generation" OR WES) AND (familial OR hereditary OR susceptib* OR risk OR germline OR "germ-line") AND (sequencing OR analysis) AND (cancer OR malignancy OR tumor* OR tumour*) AND English [lang]. We considered only those studies, which reported identification of novel genes by exome sequencing. Data on the new role of already known cancer predisposing genes, e.g. evidence for involvement of PALB2 in pancreatic cancer [18], were not included. We also did not include NGS studies, which did not cover the entire exome but used multigene targeted panels instead [109]. Search for confirmatory studies was accomplished using a string "Gene name" AND (familial OR hereditary OR susceptib* OR risk OR germline OR "germ-line") AND (cancer OR malignancy OR tumor* OR tumour*) AND English [lang]".

based on the studies, which had *a priori* knowledge on the involvement of a particular group of genes in the predisposition to a given disease. For example, we recently reported the identification of a causative recurrent mutation in a family suffering from Bardet–Biedl syndrome (BBS), and concluded on suitability of WES for the diagnosis of this disease. However, the spectrum of analyzed genetic loci was *de facto* limited only to twenty known BBS genes, so this approach cannot be defined as unbiased [142]. The conclusions on acceptable sensitivity of WES are often based on the successful detection of a single disease-causing mutation in a single control DNA sample. It is evident that revealing a true incidence of false-negatives require, for example, blind WES testing of a relatively large panel of DNA samples with known mutation status in multiple genes. Furthermore, small intragenic deletions and insertions, which constitute the majority of cancer predisposing germ-line mutations, are somewhat more difficult to detect than missense variants [143–145]. The issue of false negatives may become particularly important upon the analysis of patient groups. For example, many WES studies focus on novel mutations which occur in more than one family within the analyzed group of patients [19,20,24] or are shared by all affected members within the kindred [30,32,73]. Given the rarity of considered variants, insufficient sensitivity of WES may substantially compromise study outcomes.

Even if we assume that WES provides perfect knowledge on the nucleotide sequence of individual genomes, the interpretation of newly identified variants presents a significant challenge. Many WES studies focus on protein-truncating mutations; this approach is justified by the fact that overtly deleterious alleles (stop-codons, frameshifts, splice site aberrations) represent the majority of known disease-causing germ-line mutations in cancer genes [19–21,25,29,32,33,82,95]. Current tools for characterization of missense variants remain limited. There are multiple software instruments, which provide *in silico* prediction of the influence of aminoacid substitutions on protein function [146,147]. Validation of these predictions requires cumbersome biological assays, which are limited in scope and address only some but not all aspects of protein behavior. Furthermore, even synonymous nucleotide substitutions may be pathogenic, e.g. due to altered interaction with microRNAs [148,149].

Proper selection of genes of interest represents another challenge. In theory, WES is usually positioned as an agnostic approach offering unbiased information on the genome sequence. For practical reasons, many researchers opt for consideration of genes, which have known cancer-related role and/or are functionally similar or related to already known disease-causing modules. This is essentially a candidate gene analysis, which is utilized via WES technology. Although intuitively attractive, this approach misses the opportunity to find a new function for those genes, which are seemingly unrelated to cancer pathogenesis. For example, genes implicated in cellular metabolism were not within the primary focus of cancer research in previous decades, yet identification of tumor-driving mutations in IDH1, IDH2, FH, etc. revived interest to cancer biochemistry [150,151].

Most of contemporary medical genetic research is carried out on patients of European descent residing in North America or Western Europe. By definition, each ethnic group has distinct ancestors, which are characterized by a distinct pool of pathogenic mutations. Consideration of yet unstudied ethnicities may facilitate the discovery of new medically relevant genes. For example, breast cancer predisposing role of NBS1 (NBN) was initially discovered in Polish patients, which are characterized by increased frequency of NBS1 mutations, and later validated in other studies [127,128,131,152].

Emphasis on founder populations is also potentially helpful. Some nations have elevated level of genetic homogeneity due to geographical, social or cultural biological isolation, and *de facto* represent extremely large pedigrees. If a gene defect is detected in a founder community, it is usually presented as a recurrent allele with an elevated population frequency. Ashkenazi Jews and Icelanders represent the most known founder populations [153]. Somewhat surprisingly, Eastern Slavs residing in Russia, Poland, Ukraine and Belarus are also characterized by pronounced founder effect, and apparently represent the largest known founder community in the world [123].

Consideration of clinical characteristics of the patients also deserves discussion. Overall, studies analyzing multiple members of large pedigrees appear to be somewhat more successful than the screening of multiple individual patients (Table 1). However, the collection of biological material from extensive families is very complicated in the countries which experienced significant turbulences in the past and/or practice strict birth control and/or do not have highly developed medical system. It is also not immediately clear whether findings obtained upon the analysis of unique large cancer families are always applicable to the cancer susceptibility burden on the population level. For example, studies of extensive breast cancer pedigrees suggest that all major highly-penetrant genes, i.e. BRCA1 and BRCA2, have already been discovered, and the finding of the third single contributor ("BRCA3") in a significant portion of BRCA1/2 mutation-negative families seems unlikely. It is proposed that a major share of familial breast cancer clustering is attributed to "private" family-specific mutations. If BRCA1/2 mutation-negative hereditary breast cancer is indeed an exceptionally heterogeneous disease entity, being composed from a multitude of rare phenocopies with unique genetic cause underlying each particular kindred, the translation of research findings into actionable diagnostic tests will turn out to be extremely difficult [134,137]. However, strong family aggregation of breast cancer is relatively rare; furthermore, pedigree-based approach may not be optimal for the identification of the genes, which do not have complete segregation with the disease. There are some reasons to expect that the screening of large groups of individual patients for the presence of moderately-penetrant recurrent gene defects has significant potential for explaining missing heritability.

Heterogeneity of clinical presentation of cancer disease is widely recognized and needs to be considered in genomic studies. For example, natural history of breast cancer may significantly differ between pre- and postmenopausal women due to huge difference in systemic concentration of estrogens. Furthermore, immunohistochemical and RNA expression studies revealed several distinct subtypes of BC, and at least some of these subtypes are strongly tailored to particular germ-line mutations. For example, up to 80% of breast tumors arising in BRCA1 heterozygous carriers have receptor triple-negative and/or basal-like phenotype, which is relatively uncommon in unselected BC patients [154,155]. Some researchers pay specific attention to the heterogeneity of common cancer types, and attempt to collect patients with similar disease characteristics. This approach appears to be successful. For example, Sun et al. [20] limited collection of breast cancer patients to a very young-onset cases (<35 years old), and succeeded to discover the role of RECQL gene.

Virtually all known cancer syndromes have the autosomal-dominant mechanism of inheritance, while most of the non-cancer medical genetic disorders are recessive. This difference is very unlikely to be attributed to biological factors, and probably reflects the methodology of discovering causative genes. Classical medical genetic syndromes are exceptionally rare and unique in their clinical features, therefore the occurrence of just two cases of the disease within the family is considered to be a non-random event. Contrary to cystic fibrosis or phenylketonuria, most of hereditary cancer types have sporadic phenocopies. Therefore, in order to decrease the impact of phenocopies, initial activities for identification of hereditary cancer genes relied on uniquely extensive pedigrees

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with multiple affected relatives [1,2]. There is growing evidence that the recessive model of inheritance also plays a role in cancer susceptibility. Biallelic mutations have already been discovered for a number of rare cancer syndromes [34,48,91,94,96,156]. Modeling of inheritance suggests that patients with rare homozygous germline defects are unlikely to report family history [157], therefore the continuing emphasis on members of cancer families (Table 1) may further compromise the discovery of recessive genes. Some studies indicate that patients with multiple primary tumors may be a promising resource for the discovery of recessive hereditary cancer syndromes.

Oligogenic inheritance is well-known in "classical" medical genetics, but less studied in cancer research. The Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) revealed a number of common single nucleotide polymorphisms (SNP) affecting the risk of the disease in BRCA1/2 mutation carriers [158]. However, genome-wide association studies (GWAS) are unable to discover rare disease-predisposing variants. Some data sets demonstrate that the frequency of double heterozygosity for known predisposing genes (BRCA1, CHEK2, NBS, BLM, ATM) is higher in breast cancer patients than expected by chance [123]. Therefore, rare germ-line defects may act in a cooperative manner for cancer development. In agreement with this notion, our exome sequencing study led to the identification of rare mutation in a GPRC5A gene, which appears to significantly influence the penetrance of BRCA1 gene [135]. Studies on oligogenic inheritance may require the development of novel bioinformatics tools, which allow for robust analysis of gene combinations.

5Conclusion

Whole exome sequencing is a powerful tool for medical genetic research. WES studies already resulted in identification of a number of genes causing rare cancer syndromes, and contributed to the understanding of genetics of common cancer types. Improvement of patients' selection and consideration of other than autosomal dominant modes of inheritance may further facilitate cancer genetic studies.

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Conflict of interest

There are no conflicts of interest in the studies reported in the paper.

References

[1] Y. Miki, J. Swensen, D. Shattuck-Eidens, P.A. Futreal, K. Harshman, S. Tavtigian, et al., A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1, Science 266 (1994) 66–71.
[2] R. Wooster, S.L. Neuhausen, J. Mangion, Y. Quirk, D. Ford, N. Collins, et al., Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13, Science 265 (1994) 2088–2090.
[3] R. Fishel, M.K. Lescoe, M.R. Rao, N.G. Copeland, N.A. Jenkins, J. Garber, et al., The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer, Cell 75 (1993) 1027–1038.
[4] F.S. Leach, N.C. Nicolaides, N. Papadopoulos, B. Liu, J. Jen, R. Parsons, et al., Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer, Cell 75 (1993) 1215–1225.
[5] N. Papadopoulos, N.C. Nicolaides, Y.F. Wei, S.M. Ruben, K.C. Carter, C.A. Rosen, et al., Mutation of a mutL homolog in hereditary colon cancer, Science 263 (1994) 1625–1629.
[6] D. Malkin, F.P. Li, L.C. Strong, J.F. Fraumeni Jr., C.E. Nelson, D.H. Kim, et al., Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms, Science 250 (1990) 1233–1238.
[7] P. Vahteristo, J. Bartkova, H. Eerola, K. Syrjäkoski, S. Ojala, O. Kilpivaara, et al., A CHEK2 genetic variant contributing to a substantial fraction of familial breast cancer, Am. J. Hum. Genet. 71 (2002) 432–438.
[8] N. Bogdanova, C. Cybulski, M. Bermisheva, I. Datsyuk, P. Yamini, P. Hillemanns, et al., A nonsense mutation (E1978X) in the ATM gene is associated with breast cancer, Breast Cancer Res. Treat. 118 (2009) 207–211.
[9] A.P. Sokolenko, A.G. Iyevleva, E.V. Preobrazhenskaya, N.V. Mitiushkina, S.N. Abysheva, E.N. Suspitsin, et al., High prevalence and breast cancer predisposing role of the BLM c.1642 C>T (Q548X) mutation in Russia, Int. J. Cancer 130 (2012) 2867–2873.
[10] D. Meldrum, Automation for genomics, part two: sequencers, microarrays, and future trends, Genome Res. 10 (2000) 1288–1303.
[11] C.T. Wittwer, High-resolution DNA melting analysis: advancements and limitations, Hum. Mutat. 30 (2009) 857–859.
[12] D.A. Wheeler, M. Srinivasan, M. Egholm, Y. Shen, L. Chen, A. McGuire, et al., The complete genome of an individual by massively parallel DNA sequencing, Nature 452 (2008) 872–876.
[13] S.B. Ng, E.H. Turner, P.D. Robertson, S.D. Flygare, A.W. Bigham, C. Lee, et al., Targeted capture and massively parallel sequencing of 12 human exomes, Nature 461 (2009) 272–276.
[14] K. Danielsson, L.J. Mun, A. Lordemann, J. Mao, C.H. Lin, Next-generation sequencing applied to rare diseases genomics, Expert Rev. Mol. Diagn. 14 (2014) 469–487.
[15] P. Lapunzina, R.O. López, L. Rodríguez-Laguna, P. García-Miguel, A.R. Martínez, V. Martínez-Glez, Impact of NGS in the medical sciences: genetic syndromes with an increased risk of developing cancer as an example of the use of new technologies, Genet. Mol. Biol. 37 (Suppl. 1) (2014) 241–249.
[16] B. Rabbani, M. Tekin, N. Mahdieh, The promise of whole-exome sequencing in medical genetics, J. Hum. Genet. 59 (2014) 5–15.
[17] X. Zhang, Exome sequencing greatly expedites the progressive research of Mendelian diseases, Front Med. 8 (2014) 42–57.
[18] S. Jones, R.H. Hruban, M. Kamiyama, M. Borges, X. Zhang, D.W. Parsons, et al., Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene, Science 324 (2009) 217.
[19] C. Cybulski, J. Carrot-Zhang, W. Kluźniak, B. Rivera, A. Kashyap, D. Wokołorczyk, et al., Germline RECQL mutations are associated with breast cancer susceptibility, Nat. Genet. 47 (2015) 643–646.
[20] J. Sun, Y. Wang, Y. Xia, Y. Xu, T. Ouyang, J. Li, et al., Mutations in RECQL gene are associated with predisposition to breast cancer, PLoS Genet. 11 (2015) e1005228.
[21] J.I. Kiiski, L.M. Pelttari, S. Khan, E.S. Freysteinsdottir, I. Reynisdottir, S.N. Hart, et al., Exome sequencing identifies FANCM as a susceptibility gene for triple-negative breast cancer, Proc. Natl. Acad. Sci. USA 111 (2014) 15172–15177.
[22] F.J. Gracia-Aznarez, V. Fernandez, G. Pita, P. Peterlongo, O. Dominguez, M. de la Hoya, et al., Whole exome sequencing suggests much of non-BRCA1/BRCA2 familial breast cancer is due to moderate and low penetrance susceptibility alleles, PLoS ONE 8 (2013) e55681.
[23] P. Peterlongo, I. Catucci, M. Colombo, L. Caleca, E. Mucaki, M. Bogliolo, et al., FANCM c.5791C>T nonsense mutation (rs144567652) induces exon skipping, affects DNA repair activity and is a familial breast cancer risk factor, Hum. Mol. Genet. (2015) pii: ddv251.
[24] D.J. Park, K. Tao, F. Le Calvez-Kelm, T. Nguyen-Dumont, N. Robinot, F. Hammet, et al., Rare mutations in RINT1 predispose carriers to breast and Lynch syndrome-spectrum cancers, Cancer Discov. 4 (2014) 804–815.
[25] E.R. Thompson, M.A. Doyle, G.L. Ryland, S.M. Rowley, D.Y. Choong, R.W. Tothill, et al., Exome sequencing identifies rare deleterious mutations in DNA repair genes FANCC and BLM as potential breast cancer susceptibility alleles, PLoS Genet. 8 (2012) e1002894.
[26] D. Prokofyeva, N. Bogdanova, N. Dubrowinskaja, M. Bermisheva, Z. Takhirova, N. Antonenkova, et al., Nonsense mutation p.Q548X in BLM, the gene mutated in Bloom's syndrome, is associated with breast cancer in Slavic populations, Breast Cancer Res. Treat. 137 (2013) 533–539.
[27] M. Berwick, J.M. Satagopan, L. Ben-Porat, A. Carlson, K. Mah, R. Henry, et al., Genetic heterogeneity among Fanconi anemia heterozygotes and risk of cancer, Cancer Res. 67 (2007) 9591–9596.
[28] D.J. Park, F. Lesueur, T. Nguyen-Dumont, M. Pertesi, F. Odefrey, F. Hammet, et al., Rare mutations in XRCC2 increase the risk of breast cancer, Am. J. Hum. Genet. 90 (2012) 734–739.
[29] J.X. Zhang, L. Fu, R.M. de Voer, M.M. Hahn, P. Jin, C.X. Lv, et al., Candidate colorectal cancer predisposing gene variants in Chinese early-onset and familial cases, World J. Gastroenterol. 21 (2015) 4136–4149.
[30] N. Seguí, L.B. Mina, C. Lázaro, R. Sanz-Pamplona, T. Pons, M. Navarro, et al., Germline mutations in FAN1 cause hereditary colorectal cancer by impairing DNA repair, Gastroenterology (2015) pii: S0016-5085(15)00783-0.
[31] C. Esteban-Jurado, M. Vila-Casadesús, P. Garre, J.J. Lozano, A. Pristoupilova, S. Beltran, et al., Whole-exome sequencing identifies rare pathogenic variants in new predisposition genes for familial colorectal cancer, Genet. Med. 17 (2015) 131–142.
[32] T.T. Nieminen, M.F. O'Donohue, Y. Wu, H. Lohi, S.W. Scherer, A.D. Paterson, et al., Germline mutation of RPS20, encoding a ribosomal protein, causes predisposition to hereditary nonpolyposis colorectal carcinoma without DNA mismatch repair deficiency, Gastroenterology 147 (2014) 595–598.
[33] A.E. Gylfe, R. Katainen, J. Kondelin, T. Tanskanen, T. Cajuso, U. Hänninen, et al., Eleven candidate susceptibility genes for common familial colorectal cancer, PLoS Genet. 9 (2013) e1003876.

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[34] R.D. Weren, M.J. Ligtenberg, C.M. Kets, R.M. de Voer, E.T. Verwiel, L. Spruijt, et al., A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer, Nat. Genet. 47 (2015) 668–671.
[35] C. Palles, J.B. Cazier, K.M. Howarth, E. Domingo, A.M. Jones, P. Broderick, et al., Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas, Nat. Genet. 45 (2013) 136–144.
[36] C.G. Smith, M. Naven, R. Harris, J. Colley, H. West, N. Li, et al., Exome resequencing identifies potential tumor-suppressor genes that predispose to colorectal cancer, Hum. Mutat. 34 (2013) 1026–1034.
[37] A. Rohlin, T. Zagoras, S. Nilsson, U. Lundstam, J. Wahlström, L. Hultén, et al., A mutation in POLE predisposing to a multi-tumour phenotype, Int. J. Oncol. 45 (2014) 77–81.
[38] L. Valle, E. Hernández-Illán, F. Bellido, G. Aiza, A. Castillejo, M.I. Castillejo, et al., New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis, Hum. Mol. Genet. 23 (2014) 3506–3512.
[39] F. Bellido, M. Pineda, G. Aiza, R. Valdés-Mas, M. Navarro, D.A. Puente, et al., POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance, Genet. Med. (2015) doi:10.1038/gim.2015.75.
[40] D. Chubb, P. Broderick, M. Frampton, B. Kinnersley, A. Sherborne, S. Penegar, et al., Genetic diagnosis of high-penetrance susceptibility for colorectal cancer (CRC) is achievable for a high proportion of familial CRC by exome sequencing, J. Clin. Oncol. 33 (2015) 426–432.
[41] F.A. Elsayed, C.M. Kets, D. Ruano, B. van den Akker, A.R. Mensenkamp, M. Schrumpf, et al., Germline variants in POLE are associated with early onset mismatch repair deficient colorectal cancer, Eur. J. Hum. Genet. 23 (2015) 1080–1084.
[42] M.F. Hansen, J. Johansen, I. Bjørnevoll, A.E. Sylvander, K.S. Steinsbekk, P. Sætrom, et al., A novel POLE mutation associated with cancers of colon, pancreas, ovaries and small intestine, Fam. Cancer 14 (2015) 437–448.
[43] I. Spier, S. Holzapfel, J. Altmüller, B. Zhao, S. Horpaopan, S. Vogt, et al., Frequency and phenotypic spectrum of germline mutations in POLE and seven other polymerase genes in 266 patients with colorectal adenomas and carcinomas, Int. J. Cancer 137 (2015) 320–331.
[44] Y. Sei, X. Zhao, J. Forbes, S. Szymczak, Q. Li, A. Trivedi, et al., A Hereditary form of small intestinal carcinoid associated with a germline mutation in inositol polyphosphate multikinase, Gastroenterology 149 (2015) 67–78.
[45] I. Donner, T. Kiviluoto, A. Ristimäki, L.A. Aaltonen, P. Vahteristo, Exome sequencing reveals three novel candidate predisposition genes for diffuse gastric cancer, Fam. Cancer 14 (2015) 241–246.
[46] I.J. Majewski, I. Kluijt, A. Cats, T.S. Scerri, D. de Jong, R.J. Kluin, et al., An α-E-catenin (CTNNA1) mutation in hereditary diffuse gastric cancer, J. Pathol. 229 (2013) 621–629.
[47] S. Hansford, P. Kaurah, H. Li-Chang, M. Woo, J. Senz, H. Pinheiro, et al., Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond, JAMA Oncol. 1 (2015) 23–32.
[48] O. Calvete, J. Reyes, S. Zuñiga, B. Paumard-Hernández, V. Fernández, L. Bujanda, et al., Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour, Hum. Mol. Genet. 24 (2015) 2914–2922.
[49] J. Ngeow, W. Yu, L. Yehia, F. Niazi, J. Chen, X. Tang, et al., Exome Sequencing reveals germline SMAD9 mutation that reduces PTEN expression and is associated with hamartomatous polyposis and gastrointestinal ganglioneuromas, Gastroenterology (2015) pii: S0016-5085(15)00886-0.
[50] D. Xiong, Y. Wang, E. Kupert, C. Simpson, S.M. Pinney, C.R. Gaba, et al., A recurrent mutation in PARK2 is associated with familial lung cancer, Am. J. Hum. Genet. 96 (2015) 301–308.
[51] H.Y. Chen, S.L. Yu, B.C. Ho, K.Y. Su, Y.C. Hsu, C.S. Chang, et al., R331W missense mutation of oncogene YAP1 is a germline risk allele for lung adenocarcinoma with medical actionability, J. Clin. Oncol. 33 (2015) 2303–2310.
[52] J. Shi, X.R. Yang, B. Ballew, M. Rotunno, D. Calista, M.C. Fargnoli, et al., Rare missense variants in POT1 predispose to familial cutaneous malignant melanoma, Nat. Genet. 46 (2014) 482–486.
[53] C.D. Robles-Espinoza, M. Harland, A.J. Ramsay, L.G. Aoude, V. Quesada, Z. Ding, et al., POT1 loss-of-function variants predispose to familial melanoma, Nat. Genet. 46 (2014) 478–481.
[54] S. Yokoyama, S.L. Woods, G.M. Boyle, L.G. Aoude, S. MacGregor, V. Zismann, et al., A novel recurrent mutation in MITF predisposes to familial and sporadic melanoma, Nature 480 (2011) 99–103.
[55] P. Ghiorzo, L. Pastorino, P. Queirolo, W. Bruno, M.G. Tibiletti, S. Nasti, et al., Prevalence of the E318K MITF germline mutation in Italian melanoma patients: associations with histological subtypes and family cancer history, Pigment Cell Melanoma Res. 26 (2013) 259–262.
[56] M. Berwick, J. MacArthur, I. Orlow, P. Kanetsky, C.B. Begg, L. Luo, et al., MITF E318K's effect on melanoma risk independent of, but modified by, other risk factors, Pigment Cell Melanoma Res. 27 (2014) 485–488.
[57] J.W. Harbour, M.D. Onken, E.D. Roberson, S. Duan, L. Cao, L.A. Worley, et al., Frequent mutation of BAP1 in metastasizing uveal melanomas, Science 330 (2010) 1410–1413.
[58] J.R. Testa, M. Cheung, J. Pei, J.E. Below, Y. Tan, E. Sementino, et al., Germline BAP1 mutations predispose to malignant mesothelioma, Nat. Genet. 43 (2011) 1022–1025.
[59] T. Wiesner, A.C. Obenauf, R. Murali, I. Fried, K.G. Griewank, P. Ulz, et al., Germline mutations in BAP1 predispose to melanocytic tumors, Nat. Genet. 43 (2011) 1018–1021.
[60] M.H. Abdel-Rahman, R. Pilarski, C.M. Cebulla, J.B. Massengill, B.N. Christopher, G. Boru, et al., Germline BAP1 mutation predisposes to uveal melanoma, lung adenocarcinoma, meningioma, and other cancers, J. Med. Genet. 48 (2011) 856–859.
[61] L.G. Aoude, K. Wadt, A. Bojesen, D. Crüger, A. Borg, J.M. Trent, et al., A BAP1 mutation in a Danish family predisposes to uveal melanoma and other cancers, PLoS ONE 8 (2013) e72144.
[62] M. Cheung, J. Talarchek, K. Schindeler, E. Saraiva, L.S. Penney, M. Ludman, et al., Further evidence for germline BAP1 mutations predisposing to melanoma and malignant mesothelioma, Cancer Genet. 206 (2013) 206–210.
[63] M.N. Farley, L.S. Schmidt, J.L. Mester, S. Peña-Llopis, A. Pavia-Jimenez, A. Christie, et al., A novel germline mutation in BAP1 predisposes to familial clear-cell renal cell carcinoma, Mol. Cancer Res. 11 (2013) 1061–1071.
[64] T. Popova, L. Hebert, V. Jacquemin, S. Gad, V. Caux-Moncoutier, C. Dubois-d'Enghien, et al., Germline BAP1 mutations predispose to renal cell carcinomas, Am. J. Hum. Genet. 92 (2013) 974–980.
[65] D.A. Maerker, M. Zeschnigk, J. Nelles, D.R. Lohmann, K. Worm, A.K. Bosserhoff, et al., BAP1 germline mutation in two first grade family members with uveal melanoma, Br. J. Ophthalmol. 98 (2014) 224–227.
[66] R. Pilarski, C.M. Cebulla, J.B. Massengill, K. Rai, T. Rich, L. Strong, et al., Expanding the clinical phenotype of hereditary BAP1 cancer predisposition syndrome, reporting three new cases, Genes Chromosomes Cancer 53 (2014) 177–182.
[67] C.M. Cebulla, E.M. Binkley, R. Pilarski, J.B. Massengill, K. Rai, D.A. Liebner, et al., Analysis of BAP1 germline gene mutation in young uveal melanoma patients, Ophthalmic Genet. 36 (2015) 126–131.
[68] A. de la Fouchardière, O. Cabaret, L. Savin, P. Combemale, H. Schvartz, C. Penet, et al., Germline BAP1 mutations predispose also to multiple basal cell carcinomas, Clin. Genet. 88 (2015) 273–277.
[69] S. Klebe, J. Driml, M. Nasu, S. Pastorino, A. Zangiabadi, D. Henderson, et al., BAP1 hereditary cancer predisposition syndrome: a case report and review of literature, Biomark Res. 3 (2015) 14.
[70] P. Gerami, O. Yélamos, C.Y. Lee, R. Obregon, P. Yazdan, L.M. Sholl, et al., Multiple cutaneous melanomas and clinically atypical moles in a patient with a novel germline BAP1 mutation, JAMA Dermatol. (2015) doi:10.1001/jamadermatol.2015.1701.
[71] K. Rai, R. Pilarski, C.M. Cebulla, M.H. Abdel-Rahman, Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases, Clin. Genet. (2015) doi:10.1111/cge.12630.
[72] K.A. Wadt, L.G. Aoude, P. Johansson, A. Solinas, A. Pritchard, O. Crainic, et al., A recurrent germline BAP1 mutation and extension of the BAP1 tumor predisposition spectrum to include basal cell carcinoma, Clin. Genet. 88 (2015) 267–272.
[73] L. Witkowski, J. Carrot-Zhang, S. Albrecht, S. Fahiminiya, N. Hamel, E. Tomiak, et al., Germline and somatic SMARCA4 mutations characterize small cell carcinoma of the ovary, hypercalcemic type, Nat. Genet. 46 (2014) 438–443.
[74] P. Ramos, A.N. Karnezis, D.W. Craig, A. Sekulic, M.L. Russell, W.P. Hendricks, et al., Small cell carcinoma of the ovary, hypercalcemic type, displays frequent inactivating germline and somatic mutations in SMARCA4, Nat. Genet. 46 (2014) 427–429.
[75] P.M. Lavrut, F. LE Loarer, C. Normand, C. Grosos, R. Dubois, A. Buenerd, et al., Small cell carcinoma of the ovary, hypercalcemic type/ovarian malignant rhabdoid tumor: report of a bilateral case in a teenager associated with SMARCA4 germline mutation, Pediatr. Dev. Pathol. (2015) [Epub ahead of print].
[76] J. Moes-Sosnowska, L. Szafron, D. Nowakowska, A. Dansonka-Mieszkowska, A. Budzilowska, B. Konopka, et al., Germline SMARCA4 mutations in patients with ovarian small cell carcinoma of hypercalcemic type, Orphanet J. Rare Dis. 10 (2015) 32.
[77] L.M. Fitzgerald, A. Kumar, E.A. Boyle, Y. Zhang, L.M. McIntosh, S. Kolb, et al., Germline missense variants in the BTNL2 gene are associated with prostate cancer susceptibility, Cancer Epidemiol. Biomarkers Prev. 22 (2013) 1520–1528.
[78] S.K. Gara, L. Jia, M.J. Merino, S.K. Agarwal, L. Zhang, M. Cam, et al., Germline HABP2 mutation causing familial nonmedullary thyroid cancer, N. Engl. J. Med. 373 (2015) 448–455.
[79] M.N. Bainbridge, G.N. Armstrong, M.M. Gramatges, A.A. Bertuch, S.N. Jhangiani, H. Doddapaneni, et al., Germline mutations in shelterin complex genes are associated with familial glioma, J. Natl Cancer Inst. 107 (2014) 384.
[80] A. Cascón, I. Comino-Méndez, M. Currás-Freixes, A.A. de Cubas, L. Contreras, S. Richter, et al., Whole-exome sequencing identifies MDH2 as a new familial paraganglioma gene, J. Natl Cancer Inst. 107 (2015) pii: djv053.
[81] K. Zhang, J.W. Lin, J. Wang, X. Wu, H. Gao, Y.C. Hsieh, et al., A germline missense mutation in COQ6 is associated with susceptibility to familial schwannomatosis, Genet. Med. 16 (2014) 787–792.
[82] M.J. Smith, J. O'Sullivan, S.S. Bhaskar, K.D. Hadfield, G. Poke, J. Caird, et al., Loss-of-function mutations in SMARCE1 cause an inherited disorder of multiple spinal meningiomas, Nat. Genet. 45 (2013) 295–298.
[83] M.J. Smith, A.J. Wallace, C. Bennett, M. Hasselblatt, E. Elert-Dobkowska, L.T. Evans, et al., Germline SMARCE1 mutations predispose to both spinal and cranial clear cell meningiomas, J. Pathol. 234 (2014) 436–440.
[84] H. Raffalli-Ebezant, S.A. Rutherford, S. Stivaros, A. Kelsey, M. Smith, D.G. Evans, et al., Pediatric intracranial clear cell meningioma associated with a germline mutation of SMARCE1: a novel case, Childs Nerv. Syst. 31 (2015) 441–447.

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[85] L.T. Evans, J. Van Hoff, W.F. Hickey, M.J. Smith, D.G. Evans, W.G. Newman, et al., SMARCE1 mutations in pediatric clear cell meningioma: case report, J. Neurosurg. Pediatr. (2015) 1–5.
[86] I. Comino-Méndez, F.J. Gracia-Aznárez, F. Schiavi, I. Landa, L.J. Leandro-García, R. Letón, et al., Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma, Nat. Genet. 43 (2011) 663–667.
[87] N. Burnichon, A. Cascón, F. Schiavi, N.P. Morales, I. Comino-Méndez, N. Abermil, et al., MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma, Clin. Cancer Res. 18 (2012) 2828–2837.
[88] M. Pęczkowska, A. Kowalska, J. Sygut, D. Waligórski, A. Malinoc, H. Janaszek-Sitkowska, et al., Testing new susceptibility genes in the cohort of apparently sporadic phaeochromocytoma/paraganglioma patients with clinical characteristics of hereditary syndromes, Clin. Endocrinol. (Oxf) 79 (2013) 817–823.
[89] J. Tomsic, H. He, K. Akagi, S. Liyanarachchi, Q. Pan, B. Bertani, et al., A germline mutation in SRRM2, a splicing factor gene, is implicated in papillary thyroid carcinoma predisposition, Sci. Rep. 5 (2015) 10566.
[90] M. Aavikko, E. Kaasinen, J.K. Nieminen, M. Byun, I. Donner, R. Mancuso, et al., Whole-genome sequencing identifies STAT4 as a putative susceptibility gene in classic kaposi sarcoma, J. Infect. Dis. 211 (2015) 1842–1851.
[91] N.D. Linhares, M.C. Freire, R.G. Cardenas, H.B. Pena, M. Bahia, S.D. Pena, Exome sequencing identifies a novel homozygous variant in NDRG4 in a family with infantile myofibromatosis, Eur. J. Med. Genet. 57 (2014) 643–648.
[92] Y.H. Cheung, T. Gayden, P.M. Campeau, C.A. LeDuc, D. Russo, V.H. Nguyen, et al., A recurrent PDGFRB mutation causes familial infantile myofibromatosis, Am. J. Hum. Genet. 92 (2013) 996–1000.
[93] J.A. Martignetti, L. Tian, D. Li, M.C. Ramirez, O. Camacho-Vanegas, S.C. Camacho, et al., Mutations in PDGFRB cause autosomal-dominant infantile myofibromatosis, Am. J. Hum. Genet. 92 (2013) 1001–1007.
[94] S. Vilarinho, E.Z. Erson-Omay, A.S. Harmanci, R. Morotti, G. Carrion-Grant, J. Baranoski, et al., Paediatric hepatocellular carcinoma due to somatic CTNNB1 and NFE2L2 mutations in the setting of inherited bi-allelic ABCB11 mutations, J. Hepatol. 61 (2014) 1178–1183.
[95] S. Hanks, E.R. Perdeaux, S. Seal, E. Ruark, S.S. Mahamdallie, A. Murray, et al., Germline mutations in the PAF1 complex gene CTR9 predispose to Wilms tumour, Nat. Commun. 5 (2014) 4398.
[96] H. Ristolainen, O. Kilpivaara, P. Kamper, M. Taskinen, S. Saarinen, S. Leppä, et al., Identification of homozygous deletion in ACAN and other candidate variants in familial classical Hodgkin lymphoma by exome sequencing, Br. J. Haematol. 170 (2015) 428–431.
[97] S. Saarinen, M. Aavikko, K. Aittomäki, V. Launonen, R. Lehtonen, K. Franssila, et al., Exome sequencing reveals germline NPAT mutation as a candidate risk factor for Hodgkin lymphoma, Blood 118 (2011) 493–498.
[98] L. Noetzli, R.W. Lo, A.B. Lee-Sherick, M. Callaghan, P. Noris, A. Savoia, et al., Germline mutations in ETV6 are associated with thrombocytopenia, red cell macrocytosis and predisposition to lymphoblastic leukemia, Nat. Genet. 47 (2015) 535–538.
[99] S. Topka, J. Vijai, M.F. Walsh, L. Jacobs, A. Maria, D. Villano, et al., Germline ETV6 mutations confer susceptibility to acute lymphoblastic leukemia and thrombocytopenia, PLoS Genet. 11 (2015) e1005262.
[100] S. Shah, K.A. Schrader, E. Waanders, A.E. Timms, J. Vijai, C. Miething, et al., A recurrent germline PAX5 mutation confers susceptibility to pre-B cell acute lymphoblastic leukemia, Nat. Genet. 45 (2013) 1226–1231.
[101] P. Ostergaard, M.A. Simpson, F.C. Connell, C.G. Steward, G. Brice, W.J. Woollard, et al., Mutations in GATA2 cause primary lymphedema associated with a predisposition to acute myeloid leukemia (Emberger syndrome), Nat. Genet. 43 (2011) 929–931.
[102] C.N. Hahn, C.E. Chong, C.L. Carmichael, E.J. Wilkins, P.J. Brautigan, X.C. Li, et al., Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia, Nat. Genet. 43 (2011) 1012–1017.
[103] H. Holme, U. Hossain, M. Kirwan, A. Walne, T. Vulliamy, I. Dokal, Marked genetic heterogeneity in familial myelodysplasia/acute myeloid leukaemia, Br. J. Haematol. 158 (2012) 242–248.
[104] J. Kazenwadel, G.A. Secker, Y.J. Liu, J.A. Rosenfeld, R.S. Wildin, J. Cuellar-Rodriguez, et al., Loss-of-function germline GATA2 mutations in patients with MDS/AML or MonoMAC syndrome and primary lymphedema reveal a key role for GATA2 in the lymphatic vasculature, Blood 119 (2012) 1283–1291.
[105] M. Pasquet, C. Bellanné-Chantelot, S. Tavitian, N. Prade, B. Beaupain, O. Larochelle, et al., High frequency of GATA2 mutations in patients with mild chronic neutropenia evolving to MonoMac syndrome, myelodysplasia, and acute myeloid leukemia, Blood 121 (2013) 822–829.
[106] J. Gao, R.D. Gentzler, A.E. Timms, M.S. Horwitz, O. Frankfurt, J.K. Altman, et al., Heritable GATA2 mutations associated with familial AML-MDS: a case report and review of literature, J. Hematol. Oncol. 7 (2014) 36.
[107] C.N. Hahn, P.J. Brautigan, C.E. Chong, A. Janssan, P. Venugopal, Y. Lee, et al., Characterisation of a compound in-cis GATA2 germline mutation in a pedigree presenting with myelodysplastic syndrome/acute myeloid leukemia with concurrent thrombocytopenia, Leukemia 29 (2015) 1795–1797.
[108] X. Wang, H. Muramatsu, Y. Okuno, H. Sakaguchi, K. Yoshida, N. Kawashima, et al., GATA2 and secondary mutations in familial myelodysplastic syndromes and pediatric myeloid malignancies, Haematologica (2015) pii: haematol.2015.127092.
[109] T. Walsh, S. Casadei, M.K. Lee, C.C. Pennil, A.S. Nord, A.M. Thornton, et al., Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing, Proc. Natl. Acad. Sci. USA 108 (2011) 18032–18037.
[110] Z.K. Stadler, K.A. Schrader, J. Vijai, M.E. Robson, K. Offit, Cancer genomics and inherited risk, J. Clin. Oncol. 32 (2014) 687–698.
[111] J.P. Struewing, L.C. Brody, M.R. Erdos, R.G. Kase, T.R. Giambarresi, S.A. Smith, et al., Detection of eight BRCA1 mutations in 10 breast/ovarian cancer families, including 1 family with male breast cancer, Am. J. Hum. Genet. 57 (1995) 1–7.
[112] S.A. Gayther, W. Warren, S. Mazoyer, P.A. Russell, P.A. Harrington, M. Chiano, et al., Germline mutations of the BRCA1 gene in breast and ovarian cancer families provide evidence for a genotype-phenotype correlation, Nat. Genet. 11 (1995) 428–433.
[113] T. Peelen, R.S. Cornelis, M. van Vliet, A. Petrij-Bosch, A.M. Cleton-Jansen, H. Meijers-Heijboer, et al., The majority of 22 Dutch high-risk breast cancer families are due to either BRCA1 or BRCA2, Eur. J. Hum. Genet. 4 (1996) 225–230.
[114] J. Gudmundsson, G. Johannesdottir, A. Arason, J.T. Bergthorsson, S. Ingvarsson, V. Egilsson, et al., Frequent occurrence of BRCA2 linkage in Icelandic breast cancer families and segregation of a common BRCA2 haplotype, Am. J. Hum. Genet. 58 (1996) 749–756.
[115] G. Johannesdottir, J. Gudmundsson, J.T. Bergthorsson, A. Arason, B.A. Agnarsson, G. Eiriksdottir, et al., High prevalence of the 999del5 mutation in icelandic breast and ovarian cancer patients, Cancer Res. 56 (1996) 3663–3665.
[116] A. Ganguly, K. Leahy, A.M. Marshall, R. Dhulipala, L. Godmilow, T. Ganguly, Genetic testing for breast cancer susceptibility: frequency of BRCA1 and BRCA2 mutations, Genet. Test. 1 (1997) 85–90.
[117] J.M. Satagopan, K. Offit, W. Foulkes, M.E. Robson, S. Wacholder, C.M. Eng, et al., The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations, Cancer Epidemiol. Biomarkers Prev. 10 (2001) 467–473.
[118] A.P. Sokolenko, N.V. Mitiushkina, K.G. Buslov, E.M. Bit-Sava, A.G. Iyevleva, E.V. Chekmariova, et al., High frequency of BRCA1 5382insC mutation in Russian breast cancer patients, Eur. J. Cancer 42 (2006) 1380–1384.
[119] T.A. Rich, A.H. Woodson, J. Litton, B. Arun, Hereditary breast cancer syndromes and genetic testing, J. Surg. Oncol. 111 (2015) 66–80.
[120] S. Shiovitz, L.A. Korde, Genetics of breast cancer: a topic in evolution, Ann. Oncol. 26 (2015) 1291–1299.
[121] A.W. Kurian, BRCA1 and BRCA2 mutations across race and ethnicity: distribution and clinical implications, Curr. Opin. Obstet. Gynecol. 22 (2010) 72–78.
[122] M. Weischer, B.G. Nordestgaard, P. Pharoah, M.K. Bolla, H. Nevanlinna, L.J. Van't Veer, et al., CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer, J. Clin. Oncol. 30 (2012) 4308–4316.
[123] A.P. Sokolenko, N. Bogdanova, W. Kluzniak, E.V. Preobrazhenskaya, E.S. Kuligina, A.G. Iyevleva, et al., Double heterozygotes among breast cancer patients analyzed for BRCA1, CHEK2, ATM, NBN/NBS1, and BLM germ-line mutations, Breast Cancer Res. Treat. 145 (2014) 553–562.
[124] N. Rahman, S. Seal, D. Thompson, P. Kelly, A. Renwick, A. Elliott, et al., PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene, Nat. Genet. 39 (2007) 165–167.
[125] N. Bogdanova, A.P. Sokolenko, A.G. Iyevleva, S.N. Abysheva, M. Blaut, M. Bremer, et al., PALB2 mutations in German and Russian patients with bilateral breast cancer, Breast Cancer Res. Treat. 126 (2011) 545–550.
[126] A.C. Antoniou, S. Casadei, T. Heikkinen, D. Barrowdale, K. Pylkäs, J. Roberts, et al., Breast-cancer risk in families with mutations in PALB2, N. Engl. J. Med. 371 (2014) 497–506.
[127] B. Górski, T. Debniak, B. Masojć, M. Mierzejewski, K. Medrek, C. Cybulski, et al., Germline 657del5 mutation in the NBS1 gene in breast cancer patients, Int. J. Cancer 106 (2003) 379–381.
[128] K.G. Buslov, A.G. Iyevleva, E.V. Chekmariova, E.N. Suspitsin, A.V. Togo, E. Kuligina, et al., NBS1 657del5 mutation may contribute only to a limited fraction of breast cancer cases in Russia, Int. J. Cancer 114 (2005) 585–589.
[129] A. Renwick, D. Thompson, S. Seal, P. Kelly, T. Chagtai, M. Ahmed, et al., ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles, Nat. Genet. 38 (2006) 873–875.
[130] S. Seal, D. Thompson, A. Renwick, A. Elliott, P. Kelly, R. Barfoot, et al., Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles, Nat. Genet. 38 (2006) 1239–1241.
[131] F. Aloraifi, D. McCartan, T. McDevitt, A.J. Green, A. Bracken, J. Geraghty, Protein-truncating variants in moderate-risk breast cancer susceptibility genes: a meta-analysis of high-risk case-control screening studies, Cancer Genet. (2015) pii: S2210-7762(15)00123-4.
[132] D.J. Park, F.A. Odefrey, F. Hammet, G.G. Giles, L. Baglietto, ABCFS, et al., FAN1 variants identified in multiple-case early-onset breast cancer families via exome sequencing: no evidence for association with risk for breast cancer, Breast Cancer Res. Treat. 130 (2011) 1043–1049.
[133] K. Snape, E. Ruark, P. Tarpey, A. Renwick, C. Turnbull, S. Seal, et al., Predisposition gene identification in common cancers by exome sequencing: insights from familial breast cancer, Breast Cancer Res. Treat. 134 (2012) 429–433.
[134] F.S. Hilbers, C.M. Meijers, J.F. Laros, M. van Galen, N. Hoogerbrugge, H.F. Vasen, et al., Exome sequencing of germline DNA from non-BRCA1/2 familial breast cancer cases selected on the basis of aCGH tumor profiling, PLoS ONE 8 (2013) e55734.
[135] A.P. Sokolenko, D.R. Bulanova, A.G. Iyevleva, S.N. Aleksakhina, E.V. Preobrazhenskaya, A.O. Ivantsov, et al., High prevalence of GPRC5A germline

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mutations in BRCA1-mutant breast cancer patients, Int. J. Cancer 134 (2014) 2352–2358.
[136] J.M. Noh, J. Kim, D.Y. Cho, D.H. Choi, W. Park, S.J. Huh, Exome sequencing in a breast cancer family without BRCA mutation, Radiat Oncol. J. ;33 (2015) 149–154.
[137] F.S. Hilbers, M.P. Vreeswijk, C.J. van Asperen, P. Devilee, The impact of next generation sequencing on the analysis of breast cancer susceptibility: a role for extremely rare genetic variation?, Clin. Genet. 84 (2013) 407–414.
[138] F.S. Hilbers, J.T. Wijnen, N. Hoogerbrugge, J.C. Oosterwijk, M.J. Collee, P. Peterlongo, et al., Rare variants in XRCC2 as breast cancer susceptibility alleles, J. Med. Genet. 49 (2012) 618–620.
[139] L.M. Pelttari, J.I. Kiiski, S. Ranta, S. Vilske, C. Blomqvist, K. Aittomäki, et al., RAD51, XRCC3, and XRCC2 mutation screening in Finnish breast cancer families, Springerplus 4 (2015) 92.
[140] A.P. Sokolenko, E.V. Preobrazhenskaya, S.N. Aleksakhina, A.G. Iyevleva, N.V. Mitiushkina, O.A. Zaitseva, et al., Candidate gene analysis of BRCA1/2 mutation-negative high-risk Russian breast cancer patients, Cancer Lett. 359 (2015) 259–261.
[141] I. Ezkurdia, D. Juan, J.M. Rodriguez, A. Frankish, M. Diekhans, J. Harrow, et al., Multiple evidence strands suggest that there may be as few as 19,000 human protein-coding genes, Hum. Mol. Genet. 23 (2014) 5866–5878.
[142] E.N. Suspitsin, A.P. Sokolenko, L.V. Lyazina, E.V. Preobrazhenskaya, A.Y. Lepenchuk, E.N. Imyanitov, Exome sequencing of a family with Bardet-Biedl syndrome identifies Russian recurrent mutation BBS7 c.1967_1968delTAinsC, Mol. Syndromol. 6 (2015) 96–98.
[143] J.F. Boland, C.C. Chung, D. Roberson, J. Mitchell, X. Zhang, K.M. Im, et al., The new sequencer on the block: comparison of Life Technology's Proton sequencer to an Illumina HiSeq for whole-exome sequencing, Hum. Genet. 132 (2013) 1153–1163.
[144] J. O'Rawe, T. Jiang, G. Sun, Y. Wu, W. Wang, J. Hu, et al., Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing, Genome Med. 5 (2013) 28.
[145] D.H. Ghoneim, J.R. Myers, E. Tuttle, A.R. Paciorkowski, Comparison of insertion/deletion calling algorithms on human next-generation sequencing data, BMC Res Notes 7 (2014) 864.
[146] R. Bao, L. Huang, J. Andrade, W. Tan, W.A. Kibbe, H. Jiang, et al., Review of current methods, applications, and data management for the bioinformatics analysis of whole exome sequencing, Cancer Inform. 13 (2014) 67–82.
[147] L. Wu, D.J. Schaid, H. Sicotte, E.D. Wieben, H. Li, G.M. Petersen, Case-only exome sequencing and complex disease susceptibility gene discovery: study design considerations, J. Med. Genet. 52 (2015) 10–16.
[148] P. Brest, P. Lapaquette, M. Souidi, K. Lebrigand, A. Cesaro, V. Vouret-Craviari, et al., A synonymous variant in IRGM alters a binding site for miR-196 and causes deregulation of IRGM-dependent xenophagy in Crohn's disease, Nat. Genet. 43 (2011) 242–245.
[149] J.J. Gartner, S.C. Parker, T.D. Prickett, K. Dutton-Regester, M.L. Stitzel, J.C. Lin, et al., Whole-genome sequencing identifies a recurrent functional synonymous mutation in melanoma, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 13481–13486.
[150] I.P. Tomlinson, N.A. Alam, A.J. Rowan, E. Barclay, E.E. Jaeger, D. Kelsell, et al., Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer, Nat. Genet. 30 (2002) 406–410.
[151] H. Yan, D.W. Parsons, G. Jin, R. McLendon, B.A. Rasheed, W. Yuan, et al., IDH1 and IDH2 mutations in gliomas, N. Engl. J. Med. 360 (2009) 765–773.
[152] H. Ebi, K. Matsuo, N. Sugito, M. Suzuki, H. Osada, K. Tajima, et al., Novel NBS1 heterozygous germ line mutation causing MRE11-binding domain loss predisposes to common types of cancer, Cancer Res. 67 (2007) 11158–11165.
[153] A. Abbott, Manhattan versus Reykjavik, Nature 406 (2000) 340–342.
[154] D.P. Atchley, C.T. Albarracin, A. Lopez, V. Valero, C.I. Amos, A.M. Gonzalez-Angulo, et al., Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer, J. Clin. Oncol. 26 (2008) 4282–4288.
[155] W. Pfeifer, A.P. Sokolenko, O.N. Potapova, A.A. Bessonov, A.O. Ivantsov, S.A. Laptiev, et al., Breast cancer sensitivity to neoadjuvant therapy in BRCA1 and CHEK2 mutation carriers and non-carriers, Breast Cancer Res. Treat. 148 (2014) 675–683.
[156] M.L. Poulsen, M.L. Bisgaard, MUTYH associated polyposis (MAP), Curr. Genomics 9 (2008) 420–435.
[157] E. Kuligina, A.P. Sokolenko, N.V. Mitiushkina, S.N. Abysheva, E.V. Preobrazhenskaya, T.V. Gorodnova, et al., Value of bilateral breast cancer for identification of rare recessive at-risk alleles: evidence for the role of homozygous GEN1 c.2515_2519delAAGTT mutation, Fam. Cancer 12 (2013) 129–132.
[158] D.R. Barnes, A.C. Antoniou, Unravelling modifiers of breast and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: update on genetic modifiers, J. Intern. Med. 271 (2012) 331–343.

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