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HELQ in cancer and reproduction

Minireview

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Helicase POLQ-like (HELQ), an ATP-dependent 3'-5' DNA helicase, plays pivotal roles in DNA processing, such as DNA replication, recombination and repair. The recent discovery of HELQ in mouse model and human cancer cell reveal that genetic alteration of HELQ is involved in cancer susceptibility and subfertility. Here we review the origin, function and mechanisms of HELQ in maintaining genomic stability. Furthermore, we also summarize the known roles of HELQ in human carcinogenesis and reproduction. Importantly, we review that HELQ releases DNA replication block at interstrand cross-linking sites in cellular tolerance to cross-linking agents during DNA repair process. It may provide new avenues to develop novel therapies for enhancing efficacy of conventional chemotherapy.

Key words: HELQ, helicase, DNA interstrand cross-linking, chemotherapy

Helicases, a ubiquitous group of motor enzymes crucial for genomic stability maintenance, translocate along 3→5 or 5→3 directions and catalyze the separation of duplex nucleic acid (eg, DNA-DNA, DNA-RNA, RNA-RNA) in a nucleoside triphosphate (NTP) -dependent manner. According to the targeted type of nucleic acid substrates, helicases are generally classified into DNA helicases and RNA helicases. DNA helicases are involved in many steps of DNA metabolism, including replication, transcription, translation, repair, recombination and ribosome biogenesis, while RNA helicases are implicated in all aspects of RNA metabolism, including RNA splicing, transport, editing and degradation [1]. Helicases have been revealed by extensive computer-assisted sequence analyses of helicases from a variety of collection organisms [2, 3], characterized by short, conserved amino acid sequence called as "helicase motifs". Based on the number of motifs and amino acid sequence, helicases are classified into two larger superfamilies (SF1-SF2) and four smaller superfamilies (SF3-SF6). SF6 is totally composed of RNA helicases while the other SFs contain both RNA and DNA helicases. All the helicases superfamilies share common helicase motifs involved in NTP binding and hydrolysis that are similar to Walker A and Walker B box of ATPase, as well as at least one domain similar to the ATP-binding core of RecA recombination protein (RecA-like domain). SF1 and SF2 contain at least seven conserved motifs and two RecA-like domains, acting as monomer and dimer. SF3-SF6 helicases, by contrast, have fewer conserved motifs and RecA-like or AAA+ domain, acting as ring-shaped hexamers that are composed of six monomers [4, 5]. The characteristics of each SF are summarized in Table 1 [6-35].

SF2 is the largest helicase superfamily, with its members exist in almost all organisms. They are characterized by the presence of the following nine conserved motifs, including: Q, I, Ia, Ib, II, III, IV, V and VI. According to the sequence homology, SF2 is subdivided into RecQ-like, RecG-like, Rad3/XPD, Ski2-like, type I restriction enzyme, RIG-I-like, NS3/NPH-II, DEAH/RHA, DEAD-box and Swi/Snf families, among which DEAD-box family is the important member. Recently, coding gene mutations and abnormal expression of SF2 helicases have been linked to many diseases, including cancer, genetic disorders, development defects and neurodegenerative diseases. Mutations in WRN and BLM, two members of RecQ family in SF2, are respectively linked to Werner syndrome [36] and Bloom syndrome [37] that con-

Table 1. Characteristics of six helicase families

SF	members	organism	motif	protein fold	polarity	function
SF1	UvrD/Rep family Pif1-like family Upf1-like family	bacteria [6] Eukaryote[6]	Q, I, Ia, Ib, II, III, IV, V and VI	RecA-like	3'→5' 5'→3'	DNA translocate, unwinding [7, 8] DNA replication, recombination and repair [9-11] maintenance of telomeres [12-14], processing of Okazaki fragments[15],
SF2	RecQ-like family RecG-like family Rad3/XPD family Ski2-like familytype I restriction enzyme family RIG-I-like family NS3/NPH-II family DEAH/RHA family DEAD-box family Swi/Snf family	diverse orginasm, including virus, bacteria and human[6]	Q,I, Ia, Ib,II, III, IV, V and VI	RecA-like	3'→5'	DNA/RNA unwinding [16], DNA repair [17], recombination [18], replication [19], transcription and translation [20], chromatin remodeling [21], ribosome synthesis[22], RNA maturation, splicing, nuclear export holliday junction movement [23]
SF3	bovine papillomavirus(BPV-1) E1 helicase simian virus 40 (SV40) adeno-associated virus type 2(AAV2)	small DNA virus [24]	A,B ,B' and C	AAA+	3→5'	DNA unwinding, DNA replication [25-27]
SF4	the replicative DnaB SPP1 G40p T7gp4 TWINKLE	Bacteria [28] Bacteriophage [29, 30] Eukaryote [31]	H1,H1a,H2,H3 and H4	RecA-like	5'→3'	DNA replication, DNA unwinding and single-strand RNA(ssRNA) packing [32]
SF5	Rho protein	Bacteria [33]		RecA-like	5'→3'	RNA translocation, DNA/RNA unwinding, transcription termination [34]
SF6	Mini chromosome maintenance (MCM) RuvA, RuvB and RuvC	Eukaryote, archaea [35] bacteria		AAA+	5'→3'	DNA unwinding, DNA replication [35]

fer susceptibility to cancer. Mutations of XPD, a member of Rad3/XPD family in SF2, are implicated in various genetic diseases, including xeroderma pigmentosum with Cockayne syndrome, cerebro-oculo-facial-skeletal syndrome (COFS) and trichothiodystrophy (TTD) [38, 39]. DDX5 (P68), an identified RNA helicase of DEAD-box family in SF2, plays viral roles in RNA metabolism, including transcription, miRNA maturation and procession [40]. Additionally, it serves as transcriptional co-activator of many cancer-associated transcriptional factors. It is revealed that DDX5 is upregulated in various cancers, such as colorectal [41], prostate [42] and breast cancer [43], and promotes cancer proliferation [44]. EIF4A, another member of DEAD-box RNA helicase, is required for translation initiation [45], with expression increased in melanoma [46] and hepatocellular carcinoma [47] but decreased in glioma [48], colon [49], lung [50] and breast cancer [51]. These findings suggest that members of SF2 helicases play important roles in tumorigenesis and cancer progression. Besides the participation in cancer, SF2 helicases also play a part in embryonic development. For example, deficiency of DEAD-box RNA helicase Gemin3 in mice leads to death at early embryonic stage [52]. Moreover, loss of another member of DEAD-box RNA helicase family, DDX11, has been identified to associated with embryonic lethality and development defects [53]. DDX6 is present in nuage and non-nuage structure as well as nuclei, suggesting it might exert important roles in spermatogenic cells [54]. RecQL4, one member of RecQ family in SF2, is often involved in aging. Several studies revealed the functional roles for RecQL4 in three mechanisms associated with aging, including oxidative DNA damage repair, telomeres maintenance, and mitochondrial dysfunction [55].

Helicase POLQ-like (HELQ) is an ATP-dependent 3'-5' DNA helicase belonging to Ski2-like family in SF2, first isolated in 2002 through its homologous to the helicase domain of mus308 in *D. melanogaster* [56]. In human, HELQ is expressed in the heart, skeletal muscle, testes and ovaries [57, 58]. It is a newly identified cancer-associated and reproduction-related helicase. In the present review, we summarize the gene and protein information, function, and roles of HELQ in cancer and reproduction, trying to outline the significance of HELQ in physiological and pathological processes.

The structure of HELQ

HELQ gene has been cloned by its homology to helicase domain of *mus 308*, a *Drosophila* gene usually involved in conferring hypersensitivity to cross-linking reagents. *HELQ*

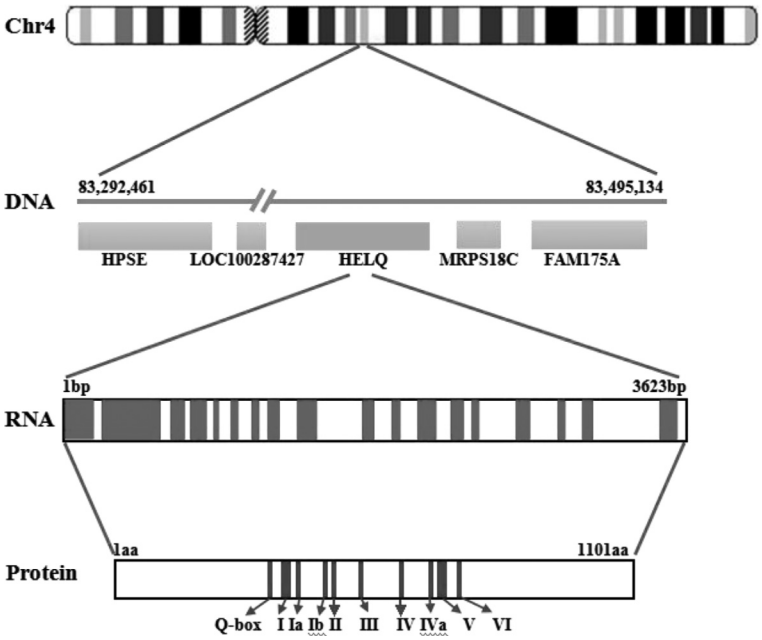

Figure 1. Nucleotide and protein information of human HELQ gene. HELQ gene is located at chorosome 4q21.23.The upstream and downstream genes of HELQ are LOC10028747 and MRPS18C, respectively, which are shown in blue. The longest transcript variant 1 and the encoded protein isoform are illustrated in the figure. HELQ gene contains 18 exons, shown in red. The full-length HELQ protein contains seven conserved motifs including Q-box, I, Ia,Ib, II, III, IV, V and VI, shown in brown.

gene is 8667 bp long, located at chromosome 4q21.23 [59]. Seven transcript variants have been identified for *HELQ* gene (http://www.ncbi.nlm.nih.gov/nuccore/?term=HELQ)(see in Figure 1), among which transcript variant 7 is a non-coding gene [60]. The information of each transcription variant and the corresponding encoded protein are summarized in Table 2. HELQ protein is classified into MUS 308 subfamily that affiliated to Ski2-like family of SF2. It highly conserves from archaea throughout to eukaryotes. Human HELQ and Drosophila Mus308 share 40% identity and 55% similarity over the helicase domain [61]. Human HELQ also has 40% identity and 55% similarity with another human Mus308 homolog

Table 2. Seven transcript variants of HELQ and the encoded protein

HELQ mRNA	RefSeq#	Transcript	Protein	Notes
Variant 1	NM_133636.3	3,623 bp	1101 aa	Full length
Variant 2	NM_001297755.1	3,422 bp	1034 aa	249-255aa missing 265-289aa missing 295-302aa missing 356-364aa missing 388-391aa missing 406-424aa missing 427-428aa missing 435aa missing
Variant 3	NM_001297756.1	3,636 bp	604 aa	1-498aa missing
Variant 4	NM_001297757.1	3,525 bp	557 aa	1-544aa missing
Variant 5	NM_001297758.1	2,469 bp	316 aa	63-100aa missing 338aa missing 346-351aa missing 361-1101aa missing
Variant 6	NM_001297759.1	2,580 bp	353 aa	338aa missing 346-351aa missing 361-1101aa missing
Variant 7	NR_123737.1	2,708 bp	-	-

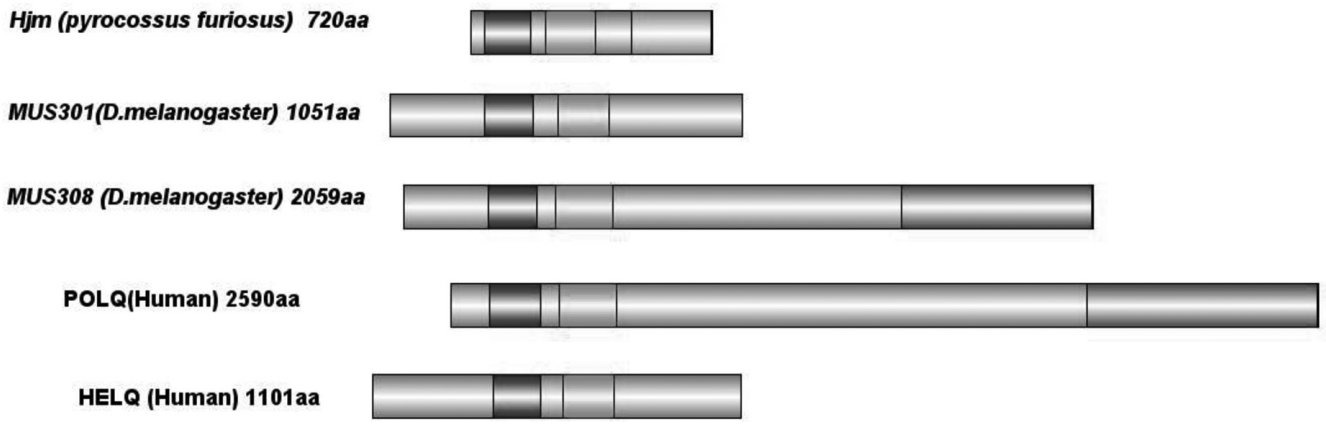

Figure 2. Schematic diagram of selected members of MUS308 subfamily of DNA helicases. The C-terminal of helicase domain was divided into DEXDc domain (purple) and HELIC domain (green).The N-terminal polymerase domain of MUS308 and POLQ were depicted in grey blue, and the sec63 domain of Hjm was shown in yellow.

POLQ that contains 2590 amino acid and belongs to A type family of DNA polymerases [62]. But human HELQ only contains C-terminal helicase domain, while human POLQ has both C-terminal helicase domain and N-terminal polymerase domain (Figure 2).

HELQ protein contains ten motifs including: I, Ia, II, III, IV, V and VI motifs conserved in SF1 and SF2 helicases and Q-box, Ib and IVa motifs only existing in some members of SF2 [63] (Figure 1). These motifs exert different biological function. Motifs I and II are similar to Walker A and Walker B ATPase motifs, respectively, playing important roles in catalyzing ATP hydrolysis reaction. It is worth mentioning that mutations in motif II significantly decreases ATP hydrolysis and helicase activity, but has no effect on DNA binding capability [64]. Motifs Ia, Ib, IV, IVa and V facilitate interaction of HELQ with phosphodiester backbone of DNA. Motifs III and VI are involved in nucleotide binding of helicase, confer high affinity of nucleic acid to HELQ, and transduce energy from ATP hydrolysis [65, 66]. Q box is often involved in conferring specificity to ATP for HELQ [4].

The crystal structure of HELQ from crenarchaeote Sulfolobus solfataricus is proposed to be a five-domain monomer protein that surrounds DNA and separates DNA duplex using the energy from ATP hydrolysis [67]. Domain 1 and 2 are the classical ATP-binding motor domains, also known as RecA-like domains, which act as transducers converting energy produced by ATP hydrolysis into 3'-5'directional motion along DNA. The conserved motifs are distributed in these two domains, among which motifs Q box, I, Ia, Ib, II and III are located in domain 1 while motifs IV, IVa, V and VI are located in domain 2. Located at the interface between two RecA-like domains, I, II, III, VI and Q box motifs form an ATP binding pocket when the two domains are brought close proximity upon ATP binding. HELQ also possesses three accessory domains including winged helix (WH) domain, seven helix bundle domain (also called as "Ratchet" domain) and helix-loop-helix domain (HLH domain). WH domain locates nearest to motor core formed by domain 1 and 2, sharing a topology composed of four helices and two parallel β-strands forming a body that is flanked by two "wings" or linkers that connect the α/β core. This domain facilitates the tight binding of HELQ to macromolecules, such as DNA or proteins. It also functions as a "hinge" for communicating between ATPase activity of two RecA domain and helicase activity of ratchet domain [68]. "Ratchet" domain is involved in DNA duplex strand seperation by the pin structure formed through an insertion of β-hairpin motif between V and VI motifs in the motor domains [16, 69]. HLH domain, locating at C-terminal of HELQ, acts as a "molecular brake" that limits the processivity of HELQ on branched substrate since deletions or mutations in this domain significantly enhances processivity of HELQ [69]. Taken together, two motor domains control ATP binding and hydrolysis, and transduce energy from ATP to 3'-5' direction motion along DNA, while the other three accessory domains orient HELQ to DNA substrate and couple translocation of HELQ along these substrates to self -limit helicase activity [70]. This domain facilitates the tight binding of HELQ to macromolecules.

The function and mechanisms of HELQ

HELQ catalyzes the unwinding of double-stranded DNA (dsDNA) with the 3'→5' polarity in an ATP-dependent manner. Initially, the unwinding activity of HELQ is activated by 2bp DNA binding in an ATP independent manner, and further driven by ATP binding and hydrolysis. In addition, HELQ preferably unwinds branched DNA structure, specially the substrates resembling stalled replication fork the structure. This feature is highly conserved through archaea to human. The processivity of DNA unwinding by HELQ can be significant stimulated in the presence of single-strand DNA-binding protein (RPA) in vitro [59]. However, the detailed

mechanisms mediating the helicase activity of HELQ remains largely undefined.

Additionally, HELQ contributes to repair of replication blocking lesion induced by cross-linking agents. Human cells lacking HELQ display hypersensitivity to crosslinking reagent such as mitomycin C (MMC) and camptothecin (CPT) [71]. In *Caenorhabditis elegans*, HELQ is recruited to replication forks under crosslinking conditions. HELQ localizes at stalled replication fork and unwinds parent strands, sequentially restarts DNA replication following CPT treatment [72]. These findings indicate that HELQ participates in DNA crosslinking repair and restarts DNA replication. Several pathways are involved in DNA interstrand cross-linkings (ICLs) repair, including the Fanconi anaemia (FA) regulatory network, homologous recombination (HR), mismatch repair (MMR), nucleotide excision repair (NER) and translesion DNA synthesis (TLS) [73-77]. The correlation between HELQ and FA pathway has received extensive attention but the results have been contradictory. FA pathway is composed of an upstream core complex containing Fanconi anaemia complementation group A/B/C/E/F/G/L/M (FANCA/B/C/E/F/G/L/M), that is required to monoubiquitinat of the downstream Fanconi anemia group D2 (FANCD2) and Fanconi anemia complementation group I (FANCI) [78], which coordinates multiple DNA repair activities required for the resolution of ICLs [79]. The studies of *Caenorhabditis elegans* show the epistatic relationship between *helq*, an orthology of human *HELQ*, and *fcd-2*, an orthology of human *FANCD2*, under crosslinking condition [80]. HELQ deficient mouse cells present sustained FANCD2 monoubiquitination, indicating HELQ is dispensable for this modification [81]. In addition, HELQ co-localizes at the loci of collapsed replication fork along with FANCD2 after treatment with CPT [72]. Mass spectrometry further identifies that HELQ directly interacts with FANCD2/FANCI heterodimer [81], mediating the activation of FA pathway in DNA repair [82]. On the contrary, no alteration of FANCD2 mono-ubiquitination is found when *HELQ* deficiency MEFs exposed to either MMC or aphidicolin (APH) by Luebben et al [58]. The group puts forward that *HELQ* and *FANCC* are not epistatic to each other in restart of stalled replication fork, especially in the unchallenged S phase, implying the role of HELQ involved in maintaining genomic stability might be dependent on a mechanism different from FA pathway. Since the interaction of HELQ and FA pathway in genomic maintenance remains controversial, experiments that seek to define the relationship between HELQ and FA pathway still be of urgent need.

Recent studies report the involvement of HELQ in ICL repair process based on the cellular co-localization of ATM- and Rad3-Related (ATR). ATR, a phosphoinositide 3-kinase related protein kinase (PIKK), can induce monoubiquitination of FANCD2 through phosphorylating FA protein FANCI, then activate FA DNA repair pathway [83]. ATR is also capable of phosphorylating and then activating serine/threonine specific protein kinase checkpoint kinase 1 (CHK1) [84, 85], resulting in initiation of cell cycle checkpoints, G2/M cell cycle arrest, DNA repair and cell death to prevent damaged cells from progressing through the cell cycle. *In vitro*, HELQ deficient cells show reduced CHK1 Ser345 phosphorylation and decreased G2/M cell population after treatment with MMC for 24 h, implying a role of HELQ in activation of CHK1 during ICL repair process [86].

In addition to FANCD2 and ATR, there are other HELQ-associated proteins, among which Rad51 and its paralogs are the most widely studied candidates. Rad 51 is a critical element in DNA repair and functions via homologous recombination pathway. HELQ co-localizes with Rad51 at the sites of CPT-induced replication fork block [43]. Rad51 paralogs including Rad51B, Rad51C, Rad51D, XRCC2 and XRCC3 transduce DNA damage signals to effector kinases, facilitating Rad 51 assembly at the sites of DSB and promoting chromatid recombinational repair [87]. In Drosophila, the collaboration of Rad51-like gene (Spn-A, Spn-B, Spn-D) and Mus301, an orthology of human HELQ, in the formation of stable recombination intermediates is crucial for efficient double strand break (DSB) repair [88]. Recently, a physical interaction between HELQ and RAD51 paralogs subcomplex "BCDX2" which contains Rad51B, Rad51C, Rad51D and XRCC2 was confirmed by immunoprecipitation assay [81, 86]. BCDX2 subcomplex binds preferentially to single-stranded DNA and to single stranded region or nicks in duplexed DNA [89], participating in the homologous recombination repair not only at early stage by promoting the formation of RAD51 nucleoprotein filaments on ssDNA [90], but also in the late step via Holliday junction process [91]. Of note, the association between HELQ and the other Rad51 paralogues subcomplex CX3 consisting of Rad51C and XRCC3 was not detected in vitro, perhaps because RAD51C-XRCC3 subcomplex functions in a manner different from BCDX2 subcomplex [92]. Replication protein A (RPA1) is another HELQ-associated protein. It is a single-strand DNA-binding protein, playing important roles in multiple DNA metabolic processes including DNA repair, replication and recombination [93]. Recent study reveals HELQ structurally interacts with RPA [81] which promotes the activity of HELQ to unwind DNA duplex region [59] and then facilitate DNA replication.

Taken together, HELQ carries out essential functions via interacting with FANCD2 or forming macromolecular complex with other proteins, such as Rad51 paralogues subcomplex "BCDX2", ATR and RPA. Further studies are still ongoing to detail the mechanisms of HELQ function in ICL repair.

HELQ and cancer

HELQ gene is located in 4q where genetic alterations frequently happened in oral squamous cell carcinoma[94], hepatocellular carcinoma [95], ductal pancreatic adenocarcinoma [96], and gastric cancer [97]. In ovarian cancer, deletion of 4q21 is the most common genetic alteration, detected in

54% of ovarian carcinoma [98]. This genetic alteration makes oncologists explore why this region is deletion and what genes misregulated in this region during tumorigenesis.

A 4q21 variant rs1494961 located in *HELQ* has been identified to be associated with upper aerodigestive tract (UADT) cancers in a Genome-Wide Association Study (GWAS) [99]. Another GWAS study has reportedrs1494961 not only to confer susceptibility to head and neck squamous cell carcinoma (HNCSS), but also to modify the relationship between smoking-pack years and HNCSS [100]. Catalogue of somatic mutations in cancer (COMS), a public database recording somatic mutation information and related details of genes in multiple human cancers (http://cancer.sanger.ac.uk/cosmic/gene/analysis?ln=HELQ#dist) summarized a total of 101 *HELQ* mutations including substitution nonsense, substitution missense, substitution synonymous, insertion frameshift and deletion frameshift mutations, and missense substitution accounts for 70.3% of all the mutations. The distribution of *HELQ* mutations is listed in Figure 3. Moreover, analysis of 569 ovarian cystadenocarcinoma cases in TCGA database shows

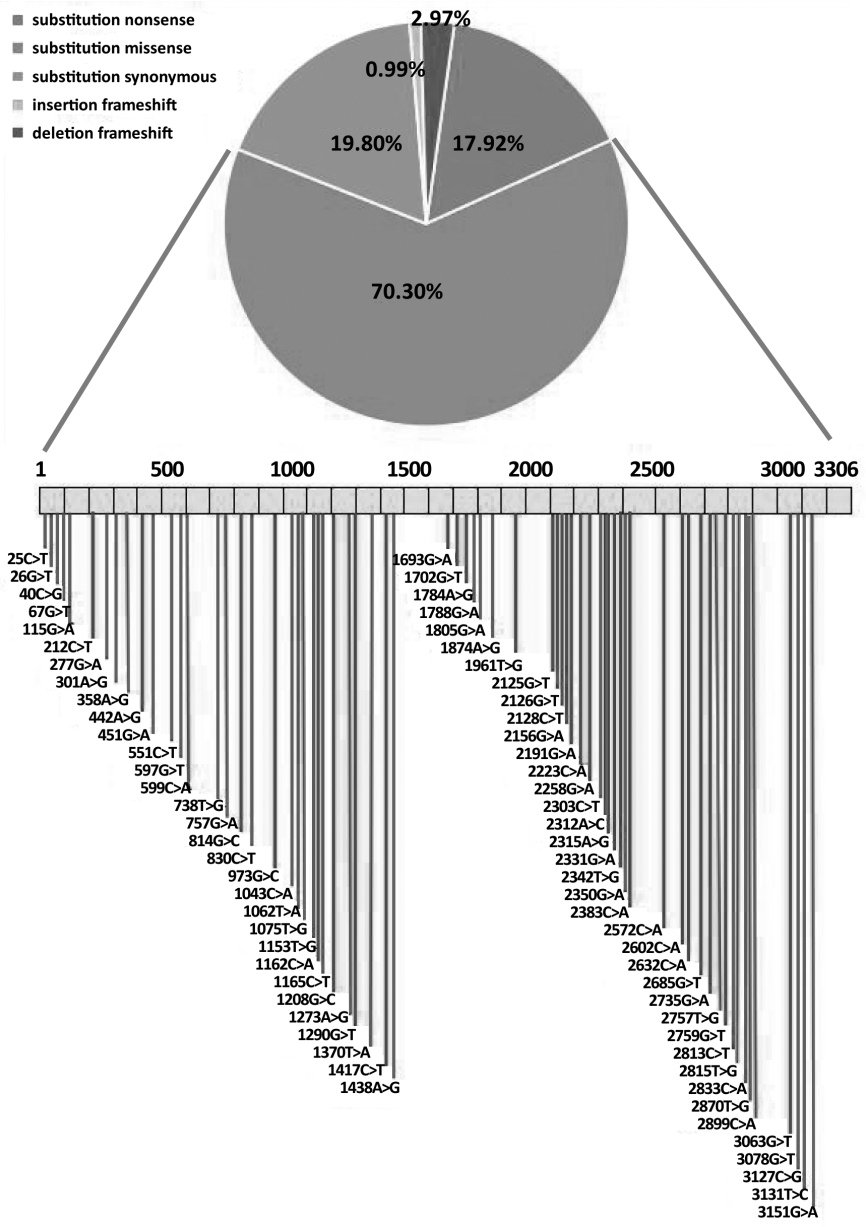

Figure 3. The distribution of HELQ mutations (substitution missense, nonsense,synonymous, insertion frame shift and deletion frame shift) is illustrated in the pie graph, in which the substitution missense mutations located in cDNA strands(3306nucleotides) of HELQ are depicted. All the data are derived from the catalogue of somatic mutations in cancer (COSMIC). (http://cancer.sanger.ac.uk/cosmic/gene/ analysis?ln=HELQ#dist).

the copy number decrease of *HELQ* and *Rad51 paralogues* (Rad51B, C, D, XRCC2 and XRCC3) confer susceptibility to ovarian cancer [101-103], implying *HELQ* might act as a tumor suppressor for ovarian cancer. In support of this, *Helq* deficient mice established by insertion of β-Geo, a fusion gene of the β-galactosidase and neomycin resistance gene, into intron between exon 11 and 12 exhibit high susceptibility to pituitary tumor, gastric cancer and ovarian cancer [81]. Although theses evidence indicated genetic deletion and mutation of HELQ is correlated to tumorigenesis, it still unclear the potential roles and underlying mechanisms of HELQ in tumorigenesis and tumor development. First it remains unknown whether the protein level of HELQ correspondingly altered along with the genetic alterations in tumorigenesis. Additionally, no evidence showed what roles HELQ plays in tumor development. Moreover, emerging evidence revealed that HELQ deficiency sensitized human culture cells to DNA damaging agents, but the mechanism of the possible chemopreventive action of HELQ is not comprehensively understood. In the future, more efforts must be taken to explore these problems.

Of note, helicases targeted -siRNA not only inhibits tumor cell growth and proliferations, but also sensitizes cancer cells to chemotherapy, indicating DNA helicases might be act as both potential target in cancer therapy and a novel neoadjuvant chemotherapy. To date, there are several DNA helicase inhibitors are exploited from screening chemical libraries and use either alone or in combination with other chemotherapy agents to inhibit solid tumors growth and proliferation in vitro. A small molecule ML216 has been identified to inhibit the helicase activity of BLM. Exposure of human culture cells to ML216 dramatically impaired culture cell growth and proliferation in a BLM dependent-manner. Moreover, ML216 treatment of PSNF5 cells sensitized cells to DNA damaging agents, suggesting ML216 as a candidate therapeutic agent for cancers [104]. Additionally, NSC19630, another helicase inhibitor developed for specifically inhibiting helicase activity of WRN shows similar anticancer effects in vitro [105, 106]. So what can HELQ do in cancer therapy? Recent work shows that silence of HELQ by targeting the first exon with zinc finger nucleases (ZFNs) in U2OS cells confers sensitivity to ICL agents including MMC and cisplatin [86] that are already widely used in a variety of cancer therapy. Knockdown of HELQ in U2OS by siRNA causes similar effects [81]. It is reasonably to hypothesize that HELQ-suppressive reagents might be developed as a adjunctive therapeutics. Alternatively, since HELQ executes its biological function by interacting with multiple counterparts mentioned above via its helicase domain, targeting its helicase domains might enhance the effectiveness of chemotherapy. Considering the tumor suppressive effects of HELQ in tumorigenesis and the protective effects of HELQ in other systems, such as aging and neurodegeneration, there are concern about if HELQ inhibitor treatment may actually increase the secondary malignancies and other disease (neurodegenerative diseases, aging and hypogonadism). No relevant report can be found at present. Thus, further researches are needed to evaluate the effectiveness and safety of silencing HELQ by siRNA or inhibitors in cancer chemotherapy.

HELQ and reproduction

The roles that HELQ play in reproduction in mouse model have been reported. In these studies, the helqgt/gt model is a mouse in which exon 12-23, translated into three conserved helicase domains (domain 3-5), are removed by inserting β-Geo into intron between exon 11 and 12, producing a truncated protein that is fused with β-Geo at C-terminal [58, 81]. Helqgt/gt male mice show smaller testis, atrophied seminiferous tubules, loss of spermatocytes and spermatogonia that are associated with hypogonadism, while female mice exhibit smaller ovaries and reduced number of follicles that are correlated to sterile [58]. Coincidentally, a recent study mentions the similar role for HELQ in reproduction and attributes the role to replication-coupled DNA repair [81].

Of note, HELQ is linked to age of natural menopause in a meta-analysis of 22 genome-wide association studies [107]. This kind of correlation provides insight into HELQ and its role in female reproduction, since menopause is a cessation of ovary reproductive function and directly reflects ovary aging in female. However, little is known regarding its significance in human reproduction. Further studies are needed to define the roles and underlying mechanisms in reproduction.

As discussed, HELQ interacts with FANCD2, ATR, Rad51 and its paralogs proteins and appear to be an key molecular in preservation of genome stability by its involvement in DNA repair. While the relationship between HELQ and cancer or reproduction have been uncovered, the molecular mechanisms of HELQ plays in tumorigenesis and reproduction subfertility are not completely understood. Further research is warranted to elaborate the functional pathways and targets manipulated by HELQ. Importantly, with HELQ's emergence as an important genome caretaker in response to DNA damage agents, more efforts must be taken to explore HELQ as a potential target for clinical and therapeutic strategies.

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