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Case report: Whole exome sequencing identified a novel mutation (p.Y301H) of *MAF* in a Chinese family with congenital cataracts

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Background: Congenital cataracts stand as the primary cause of childhood blindness globally, characterized by clouding of the eye's lens at birth or shortly thereafter. Previous investigations have unveiled that a variant in the *V-MAF avian musculoaponeurotic-fibrosarcoma oncogene homolog* (*MAF*) gene can result in Ayme-Gripp syndrome and solitary cataract. Notably, *MAF* mutations have been infrequently reported in recent years.

Methods: In this investigation, we recruited a Chinese family with non-syndromic cataracts. Whole exome sequencing and Sanger sequencing were applied to scrutinize the genetic anomaly within the family.

Results: Through whole exome sequencing and subsequent data filtration, a new mutation (NM_005360, c.901T>C/p.Y301H) in the *MAF* gene was detected. Sanger sequencing validated the presence of this mutation in another affected individual. The p.Y301H mutation, situated in an evolutionarily preserved locus, was not detected in our 200 local control cohorts and various public databases. Additionally, multiple bioinformatic programs predicted that the mutation was deleterious and disrupted the bindings between *MAF* and its targets.

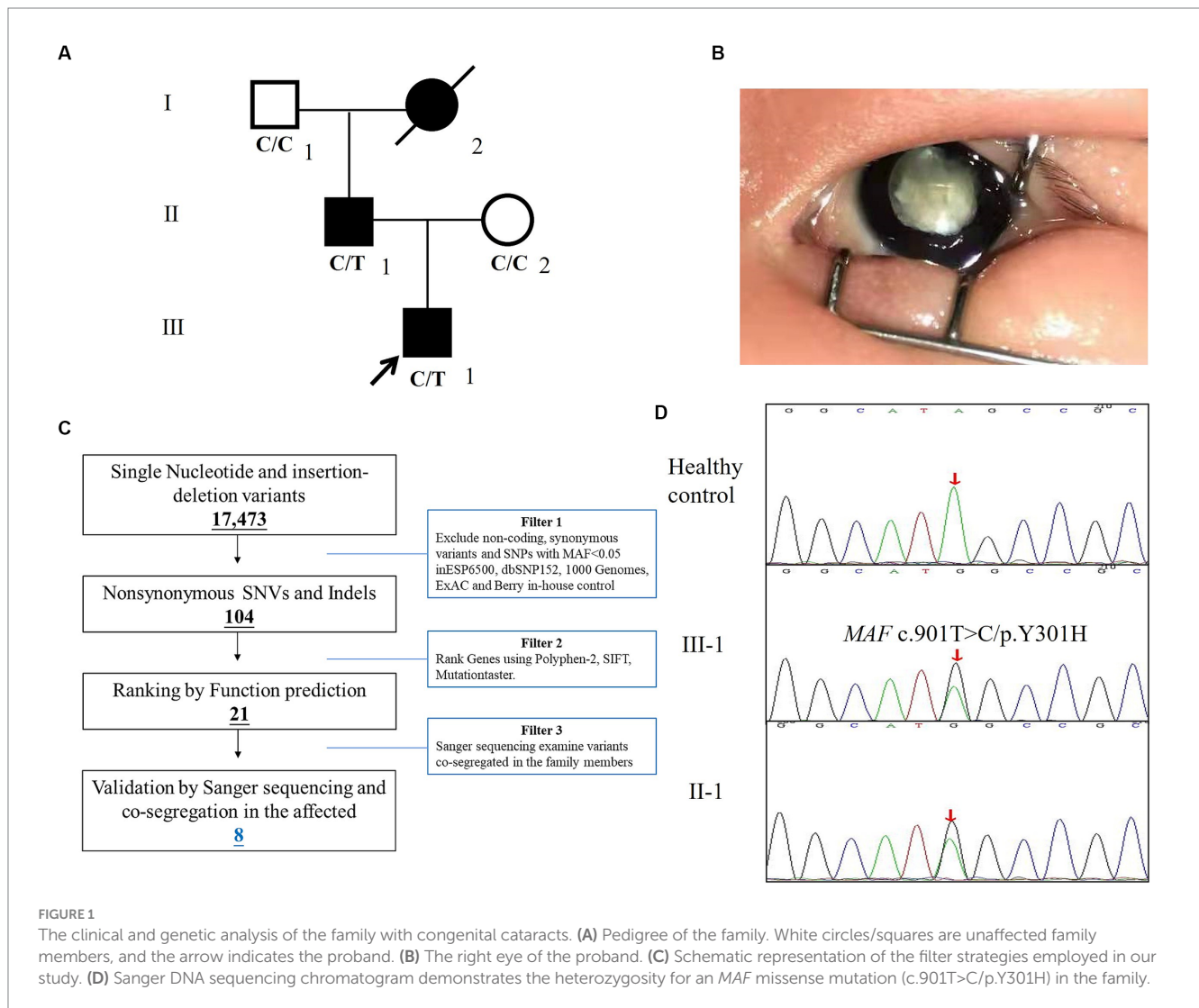
Conclusion: Hence, we have documented a new *MAF* mutation within a Chinese family exhibiting isolated congenital cataracts. Our study has the potential to broaden the spectrum of *MAF* mutations, offering insights into the mechanisms underlying cataract formation and facilitating genetic counseling and early diagnosis for congenital cataract patients.

KEYWORDS

congenital cataract, inherited cataract, *MAF*, whole exome sequencing, missense mutation

Introduction

Congenital cataracts, an ophthalmic disease presented at birth or developing in infancy, can lead to a clouding in the lens of the eye that can cause blurry vision or blindness (1–3). As the predominant cause of visual impairment and blindness among children, congenital cataracts affect approximately 200,000 children worldwide, with an estimated prevalence



ranging from three to six per 10,000 live births (4, 5). The current studies believe that multiple factors including genetics, infections, radiation exposure, toxic agents, and metabolic disturbance underlie the occurrence of congenital cataracts (3). To date, over 40 genes responsible for the molecular etiology of isolated or syndromic congenital cataracts, featuring autosomal dominant or autosomal recessive inheritance patterns, have been identified (1, 6).

The *V-MAF avian musculoaponeurotic-fibrosarcoma oncogene homolog (MAF)* gene, also known as MAF bZIP transcription factor (OMIM#177075), is situated on chromosome 16q23.2, spanning approximately 6.9 kilobases (7). As a DNA-binding transcription factor with a leucine zipper motif that can control the activity of target genes, MAF can serve as a transcriptional activator or repressor, regulating diverse cellular processes, including embryonic lens fiber cell development, heightened T-cell susceptibility to apoptosis, and chondrocyte terminal differentiation (8–10). In 2002, Jamieson et al. (11) initially reported the association of *MAF* with cataracts, ocular anterior segment dysgenesis, and coloboma. Subsequently, approximately 30 *MAF* mutations have been detected in patients with Ayme-Gripp syndrome and isolated cataracts (7).

Here, we recruited a Chinese family affected by isolated congenital cataracts. Utilizing whole exome sequencing and Sanger sequencing, we sought to uncover the genetic abnormalities in the affected individuals.

Case presentation

Here, we enrolled the family from Hebei province, China (Figure 1A). The affected proband, a four-year-old boy was admitted to Hebei General Hospital and diagnosed as a total congenital cataract of the right eye (Figure 1B). A medical history survey suggested that the patient suffered from poor vision in dim light at approximately 3 years old but did not arouse parents' attention, and the symptoms of the child developed to lens complete opacification from pupil gray appearance quickly during this year. Finally, the patient agreed to undergo surgery for cataract extraction and implantation for the posterior chamber intraocular lens, and the eye vision is gradually recovering. A study of the family history indicated that his father also suffered from cataracts and underwent cataract extraction in infancy. The proband's grandmother was blind and died several years ago.

TABLE 1 The gene list of Sanger sequencing validation and co-segregation analysis.

Gene	Chromosome position	Variant	Genotype	ACMG analysis	Diseases in OMIM
RRM2B	Chr 8:103220407	NM_015713: c.1010T>C, p.M337T	Het	Uncertain significance	AR, mitochondrial DNA depletion syndrome; AR, rod-cone dystrophy and sensorineural deafness
DNA2	Chr 10:70209793	NM_001080449: c.931C>T, p.R311C	Het	Uncertain significance	AR, Seckel syndrome; AD, progressive external ophthalmoplegia
AGPS	Chr 2:178257534	NM_003659: c.17C>G, p.A6G	Het	Uncertain significance	AR, rhizomelic chondrodysplasia punctata
GDF3	Chr 12:7842818	NM_020634: c.751G>A, p.A251T	Het	Uncertain significance	AD, microphthalmia
RDH11	Chr 14:68162398	NM_016026: c.23T>C, p.L8P	Het	Uncertain significance	AR, retinal dystrophy, juvenile cataracts, and short stature syndrome
MAF	Chr 16:79632899	NM_005360: c.901T>C, p.Y301H	Het	Likely pathogenic	AD, cataract; AD, Ayme-Gripp syndrome
COL1A2	Chr 6:33154514	NM_080680: c.688G>T, p.G230W	Het	Uncertain significance	AD, Ehlers-Danlos syndrome; AD, osteogenesis imperfecta
CRB1	Chr 1:197398616	NM_201253: c.2714G>A, p.R905Q	Het	Uncertain significance	AR, leber congenital amaurosis; AD, pigmented paravenous chorioretinal atrophy; AR, Retinitis pigmentosa

AD, autosomal dominant; AR, autosomal recessive; Het, heterozygotes.

Laboratory investigations

Whole peripheral blood samples of the patient and his family were obtained and stored in EDTA/citrate tubes. Genomic DNA was extracted by GenElute blood genomic DNA extraction kit (Sigma-Aldrich, NA 2010). Whole Exome sequencing (WES) was mainly conducted by Berry Genomics (Beijing, China) and Agilent SureSelect Human All Exon V6 kits and Illumina HiSeq2500 (Illumina Inc., San Diego, United States) and matched to Human Reference Genome (hg19). GATK online software¹ was used to detect SNP, Indel, and variants, and the Annovar (Annotate Variation) tool was used to functionally annotate genetic variant results in detail.

The strategies of data filtering are as follows (12, 13): (a) non-coding and synonymous variants, SNPs, or frameshift-causing INDELS with an alternative allele frequency >0.05 in the NHLBI Exome Sequencing Project Exome Variant Server (ESP6500), dbSNP152,² the 1,000 Genomes project,³ the ExAC database,⁴ or in-house exome databases of BerryGenomics (2000 exomes) were excluded; (b) the filtered SNVs and INDELS, predicted by SIFT,⁵

Polyphen2,⁶ and MutationTaster⁷ to be causing damage remained; (c) co-segregation analysis was conducted in each family.

The filtered mutations validation and co-segregation analysis were performed by Sanger sequencing. The primer pairs (the sequence of primers will be provided upon request) were designed by Primer 5. The sequences of the primers were: 5'-3' TCAGCAAGGAGGAGGTGAT and 3'-5' CTGCTCACCACTTC TCGTATT. The sequence of the polymerase chain reaction products was determined using the ABI 3100 Genetic Analyzer (ABI, United States).

After the abovementioned data filtering and Sanger sequencing validation (Figure 1C), a new mutation (NM_005360, c.901T>C/p.Y301H) of *MAF* was discerned in the proband (Table 1). No other meaningful mutations related to cataracts were detected. Co-segregation analysis indicated that the new mutation was present in the affected family members and was not detected in unaffected family members and healthy controls as well as 200 local control cohorts (Figure 1D). Three programs for analyzing protein functions, polyphen2, SIFT, and MutationTaster, predicted that the p.Y301H variants are probably damaging (1.0), deleterious (0.00), and disease-causing (0.99), respectively. Cross-species alignment analysis of *MAF*

1 www.broadinstitute.org/gatk

2 <http://www.ncbi.nlm.nih.gov/projects/SNP/index.html>

3 <http://www.1000genomes.org/>

4 <http://exac.broadinstitute.org>

5 <http://sift.jcvi.org/>

6 <http://genetics.bwh.harvard.edu/pph2/>

7 <http://www.mutationtaster.org/>

amino acid sequences revealed that this mutated site was highly evolutionarily conserved (Figure 2A). Swiss-Model and alphafold2 online software (14) found that the p.Y301H mutation changed the surface hydrophobic area and surface charge of MAF (Figure 2B).

Discussion

Congenital cataracts represent a highly diverse ocular disorder both clinically and genetically (3). Mutations in MAF have been linked to various types and severities of human congenital cataracts (Table 2) (32). MAF proteins play a pivotal role in eyes and lens

development, regulating the expression of crystallin genes, MIP (major intrinsic protein of the ocular lens fiber membrane), and other genes expressed in lens fiber cells from the formation of the lens pre-placode to the development of lens fiber cells and lens epithelium (8–10). In C57BL/6J mice, homozygous deletion of MAF results in embryonic lethality, but the lens fiber cell MAF condition knockout mice (MAF^{ΔTAM}) develops abnormal lens structure, and the expression of crystallin genes in MAF^{ΔTAM} mice eyes are reduced compared to WT mice (33). The mice data were consistent with human genetic studies, highlighting the essential role of MAF in the differentiation and cell cycle arrest of lens fiber cells. Although the first mutation of MAF was reported in 2002 (11), the MAF novel

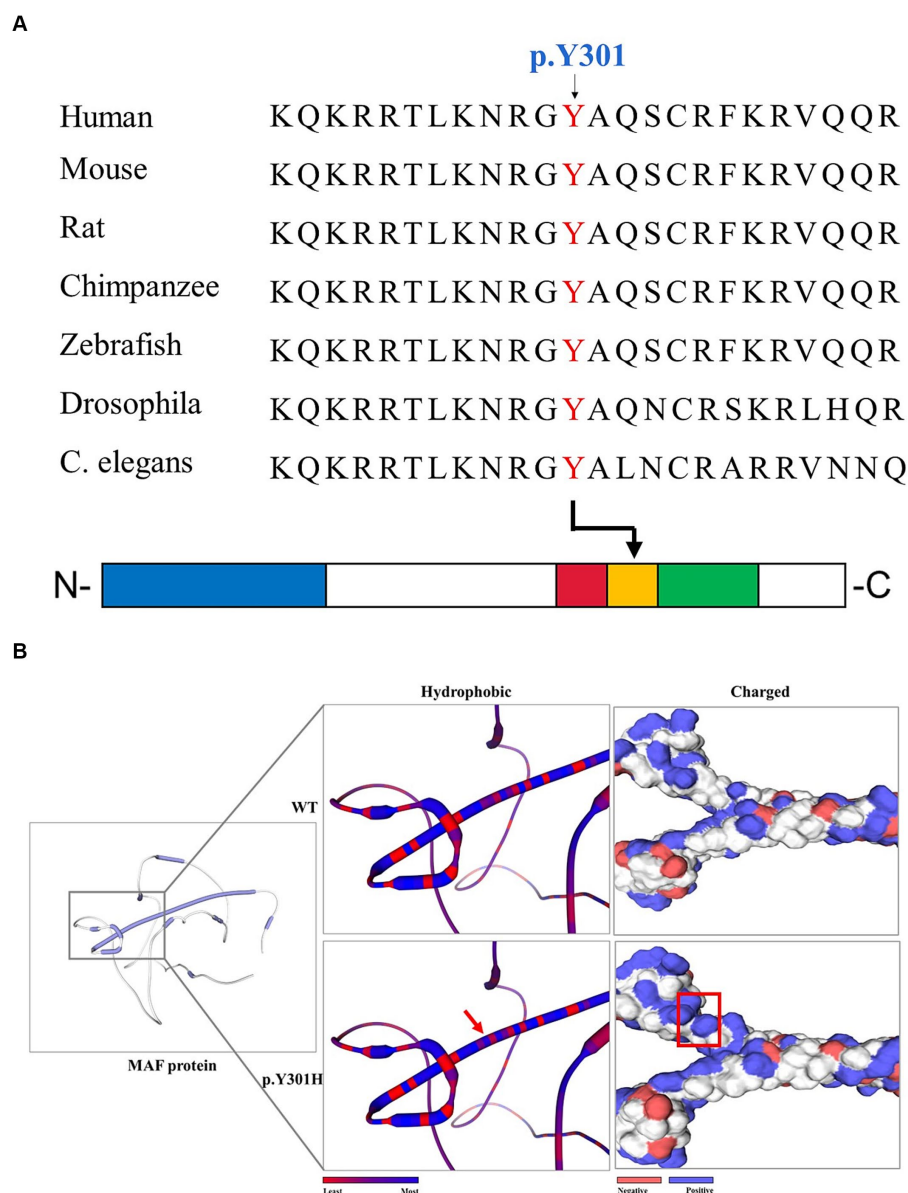


FIGURE 2
 The bioinformatics analysis of the MAF p.Y301H mutation. **(A)** Alignment of multiple MAF protein sequences across species. The Y301-affected amino acid is located in the highly conserved amino acid region in different mammals (from Ensembl). The red column shows the Y301 site. Blue square: transactivation domain. Red square: extended homology region. Orange square: basic region motif. Green square: leucine zipper motif. **(B)** The hydrophobic surface area and surface charge of the WT and mutated MAF were predicted by SWISS-MODEL and alphafold2. The red arrow and red square indicate the differences between WT and mutated protein.

TABLE 2 The summary of reported mutations in *MAF* gene.

No	Mutation	Domain	Phenotypes	Reference
1	p.Ser54Leu	TAD	Cataracts	Niceta et al. (15)
2	p.Ser54Trp	TAD	Ayme-Gripp syndrome	Amudhavalli et al. (16)
3	p.Ser57Phe	TAD	Ayme-Gripp syndrome	Niceta et al. (17)
4	p.Thr58Ala/Ile	TAD	Cataracts	Niceta et al. (15)
5	p.Pro59Leu/His	TAD	Cataracts	Niceta et al. (15)
6	p.Pro59Arg	TAD	Ayme-Gripp syndrome	Javadiyan et al. (18)
7	p.Thr62Arg	TAD	Cataracts	Niceta et al. (15)
8	p.Pro63Arg	TAD	Ayme-Gripp syndrome	Amudhavalli et al. (16)
9	p.Ser66Trp	TAD	Ayme-Gripp syndrome	Amudhavalli et al. (16)
10	p.Ser66Leu	TAD	Ayme-Gripp syndrome	Niceta et al. (17)
11	p.Pro69Arg	TAD	Cataracts	Niceta et al. (15)
12	p.Ala169Ser	EHR	Cataracts	Liu et al. (19)
13	p.Phe261Ser	EHR	Cataracts	Jackson et al. (20)
14	p.Ser270Tyr	EHR	Cataracts	Dudakova et al. (21)
15	p.Val271Glu	EHR	Cataracts	Si et al. (7)
16	p.Glu273Asp	EHR	Cataracts	Ma et al. (22)
17	p.Arg288Pro	BR	Cataracts	Jamieson et al. (11)
18	p.Arg294Trp	BR	Cataracts	Sun et al. (23)
19	p.Lys297Arg	BR	Cataracts	Vanita et al. (24)
20	p.Asn298Tyr	BR	Cataracts	Patel et al. (25)
21	p.Arg299Ser	BR	Cataracts	Hansen et al. (26)
22	p.Tyr301His	BR	Cataracts	This study
23	p.Gln303Pro	BR	Cataracts	Narumi et al. (27)
24	p.Cys305Trp	BR	Cataracts	Ma et al. (22)
25	p.Arg306Gly	BR	Cataracts	Ma et al. (28)
26	p.Glu317Gly	LZM	Cataracts	Li et al. (29)
27	p.Lys320Glu	LZM	Cataracts	Hansen et al. (30)
28	p.Pro366Argfs*8	LZM	Cataracts	Ziats et al. (31)

TAD, transactivation domain; HER, extended homology region; BR, basic region motif; LZM, leucine zipper motif.

mutation was rarely reported in recent years. Here, we identified a new variant (NM_005360, c.901T>C/p.Y301H) of *MAF* in a Chinese family with congenital cataracts via whole exome sequencing and Sanger sequencing. Our study expanded the mutation spectrum of *MAF* and further proved that mutations in *MAF* may lead to congenital cataracts.

The *MAF* protein consists of an N-terminal transactivation domain with a regulatory function and a C-terminal DNA binding domain (18). The C-terminal domain is further divided into three conserved regions (Figure 2A): extended homology region, basic region motif, and leucine zipper motif (15, 34). Earlier studies have indicated that the N-terminal variants may result in Ayme-Gripp syndrome which presents with cataracts, hearing loss, epilepsy, intellectual disability, etc., while most of the C-terminal mutation carriers only showed ocular diseases such as cataracts (Table 2) (7). Here, the mutation (p.Y301H) is also situated in the C-terminal of *MAF*, which provides more evidence that C-terminal mutations are responsible for isolated cataracts.

Furthermore, the p.Y301H mutation is in the BR motif of the C-terminal, which is the mutational hot spot region of *MAF* (7). Previous studies have suggested that the BR motif is responsible for binding the specific target promoters of crystallin genes including *CRYGA*, *CRYAA*, *CRYBA1*, and *CRYBA4*, which are associated with inherited cataracts (32, 35). Additionally, ChIP-seq studies have identified several non-crystallin genes crucial for maintaining lens transparency as direct targets of *MAF* (36, 37). Hence, the p.Y301H mutation may disrupt the bindings between *MAF* and the target genes such as crystallin genes, and finally disrupt the expression of promoters of crystallin genes, leading to congenital cataracts. Following the ACMG guideline (38), the p.Y301H mutation is likely pathogenic (PM1 + PM2 + PP1 + PP2 + PP3).

Congenital cataracts persist as a leading cause of global blindness, and early surgical intervention, prolonged postoperative amblyopia training, and visual reconstruction constitute the primary therapeutic approaches for the disease (39, 40). Early diagnosis is paramount, particularly in the era of precision medicine, where technologies such as

PCR, Sanger sequencing, high-throughput sequencing, and gene editing have facilitated the discovery of numerous pathogenic genes linked to congenital cataract development. This advancement enhances our understanding of the disease's pathogenesis and lays the groundwork for genetics-based treatments (6, 28). In the future, we can develop a genetic detection panel that contains all the reported mutations of *MAF* including the p.Y301H, and the panel may contribute to the genetic counseling and early diagnosis of congenital cataract patients.

Conclusion

Hence, we detected a new mutation (NM_005360, c.901T>C/p.Y301H) of *MAF* in a Chinese family with congenital cataracts by employing whole exome sequencing and Sanger sequencing. Our study not only explores the genetic lesion of the family and broadens the spectrum of *MAF* mutations but also confirms that the *MAF* mutation was linked to non-syndromic total congenital cataracts and facilitates genetic counseling and early diagnosis for congenital cataract patients. Certainly, there were still some limitations in this study, for example, the sample size was small and population specificity was not excluded.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Hebei General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

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Author contributions

Z-JL: Data curation, Formal analysis, Writing – original draft. J-YL: Formal analysis, Writing – review & editing. JL: Resources, Writing – review & editing. F-NW: Resources, Writing – review & editing. WC: Resources, Writing – review & editing. LZ: Formal analysis, Funding acquisition, Writing – original draft. Y-LL: Funding acquisition, Resources, Writing – original draft. L-LF: Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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