Chapter 7

The Mutation of Transient Receptor Potential Vanilloid 4 (TRPV4) Cation Channel in Human Diseases

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1. Introduction

The transient receptor potential vanilloid 4 (TRPV4) cation channel, a member of the TRP vanilloid subfamily, is expressed in a broad range of tissues, in which it contributes to the generation of Ca^{2+} signals and/or depolarization of membrane potential. TRPV4 is a polymodal Ca^{2+}-permeable cation channel with a length of 871 amino acids. It shows very prominent outward rectification, rarely opening upon hyperpolarization. Mutational analyses suggest that outward rectification is governed by a gating mechanism independent of the main intracellular gates [1-4]. The predicted TRPV4 structure harbors six membrane-spanning domains with a pore loop, an N-terminal domain with at least three ankyrin repeats, and a C-terminal domain residue within the cytoplasm [3-5]. These characters are common features in all six TRPVs (TRPV1–6). However, although the TRPV family shows similar characteristics (Fig. 1), each member has its own distinguishable functions from other TRPVs.

The participation of TRPV4 in osmo and mechanotransduction is relevant to several important functions, including cellular and systemic volume homeostasis, arterial dilation, nociception, bladder voiding, and the regulation of ciliary beat frequency. TRPV4 channel activity can be sensitized by coapplying a variety of stimuli and by the participation of a number of cell signaling pathways, which suggests the presence of different regulatory sites. In this regard, several proteins have been proposed to modulate TRPV4 subcellular localization and/or function: microtubule-associated protein 7, calmodulin, F-actin, and pacsin3 [5, 6]. Other studies have demonstrated a functional and physical interaction between inositol trisphosphate receptor 3 and TRPV4, which sensitizes the latter to the mechano and osmotransducing messenger 5'-6'-epoxieicosatrienoic acid. TRPV4 is also

responsive to temperature, endogenous arachidonic acid (AA) metabolites, and phorbol esters, including 4-α phorbol 12, 13-didecanoate(4-αPDD), and participates in receptor-operated Ca^{2+} entry; thus, showing multiple activation modes [1-7]. However, the precise manner in which TRPV4 is regulated in the cell by these protein interactions, chemicals, and stimuli remains to be clearly established.

2. Naturally occurring TRPV4 mutants and genetic disorders

Few naturally occurring TRPV4 mutants have been identified. Interestingly, most of these mis-sense and nonsense point mutations are linked with the development of genetic disorders in humans and a detailed list of naturally occurring TRPV4 mutations and related disease has been documented (Table 1 and Fig. 1). Here, I discuss some of these mutations that have gained importance in terms of genetic diseases [4-6].

2.1. Serum sodium level quantitative trait locus (hyponatremia)

Tian et al. (2009) demonstrated that the rs3742030 single nucleotide polymorphism in the TRPV4 gene (P19S) is significantly associated with serum sodium concentration. After this discovery, hyponatremia was defined as serum sodium < 135 mEq/L in non-Hispanic Caucasian male populations. In heterologous expression studies in HEK293 cells, P19S mutant channels show a diminished response to hypotonic stress and to the osmotransducing lipid epoxyeicosatrienoic acid compared to that in wild-type channels. The P19S polymorphism affects TRPV4 function *in vivo* and likely influences systemic water balance on a population wide basis [8].

2.2. Chronic obstructive pulmonary disease (COPD)

COPD is characterized by airway epithelial damage, bronchoconstriction, parenchymal destruction, and mucus hypersecretion. Upon activation by a broad range of stimuli, TRPV4 functions to control airway epithelial cell volume and epithelial and endothelial permeability; it also triggers bronchial smooth muscle contraction and participates in autoregulation of mucociliary transport [9, 10]. These TRPV4 functions may be important for regulating COPD pathogenesis; thus, TRPV4 is a candidate COPD gene. The TRPV4 P19S mutant, which is also characterized as the cause of hyponatremia, is observed in patients with COPD.

2.3. Brachyolmia type 3 (BRAC3) [MIM:113500]

BRAC3 has been characterized using linkage analysis and candidate gene sequencing. Rock et al. found that some patients affected with brachylomia have a TRPV4 missense mutation, specifically at positions R616Q or V620I [11]. These mutations are located in the fifth transmembrane region, which is part of the functional pore. Each of these two mutations increases basal level activity when compared to the wild-type TRPV4. Additionally, the response to 4-αPDD (a TRPV4 specific agonist) is greater in mutants when compared with

that in the wild-type [11]. This result also indicates that these two mutations preferably stabilize TRPV4 in its "open stage", resulting in constitutive channel activity. BRAC3 constitutes a clinically and genetically heterogeneous group of skeletal dysplasias characterized by a short trunk, scoliosis, and mild short stature. BRAC3 is an autosomal dominant form in which patients have severe kyphoscoliosis and flattened, irregular cervical vertebrae[11].

BRAC3, causing a R616Q gain-of-function channel, was examined and found to increase whole-cell current densities compared with that in wild-type channels. A single-channel analysis revealed that R616Q channels maintain mechanosensitivity but have greater constitutive activity and no change in unitary conductance or rectification [12]. BRAC3 ranges from mild autosomal-dominant BO, diagnosed by a shortened spine with characteristic vertebral defects and minor defects in the long bones to metatropic dysplasia characterized by more prominent spine defects as well as pronounced abnormalities in the articular skeleton resulting in short dumbbell-shaped long bones, which leads to prenatal lethality in its severest form [13].

2.4. Metatropic dysplasia (MTD) [MIM:156530]

MTD is a clinical heterogeneous skeletal dysplasia characterized by short extremities, a short trunk with progressive kyphoscoliosis, and craniofacial abnormalities that include a prominent forehead, midface hypoplasia, and a squared-off jaw [14]. Dominant mutations in the gene encoding TRPV4, a calcium permeable ion channel, have been identified in all 10 of a series MTD cases, ranging in severity from mild to perinatal lethal [14]. MTD is also called metatropic dwarfism. Metatropic dysplasia is a severe spondyloepimetaphyseal dysplasia characterized by short limbs, enlarged joints, and usually severe kyphoscoliosis [15]. Radiological features include severe platyspondyly, severe metaphyseal enlargement, and shortening of long bones. TRPV4 I331F and P799L mutants induce MTD [16, 17]. As all the above mentioned mutants are naturally occurring, these mutants are not embryonically lethal (as most lethal mutants are naturally excluded from the population). It is also important to note that none of these mutants show complete loss of their prime function, i.e., ion conductivity [12].

Several experimental results suggest that some of these mutants even have enhanced channel opening. These results demonstrate that the lethal form of the disorder is dominantly inherited and suggest locus homogeneity in the disease. Furthermore, electrophysiological studies have shown that the mutations activate the TRPV4 channel, indicating that the mechanism of the disease may result from increased calcium in chondrocytes [12, 16, 17].

Histological studies in two cases of lethal MTD revealed markedly disrupted endochondral ossification, with reduced numbers of hypertrophic chondrocytes and the presence of islands of cartilage within the primary mineralization zone [16]. These data suggest that altered chondrocyte differentiation in the growth plate leads to the clinical findings of MTD [18].

2.5. Distal spinal muscular atrophy congenital non-progressive (DSMAC) [MIM:600175]

DSMAC (also called hereditary motor and sensory neuropathy, Type IIC; HMSN2C) is a clinically variable, neuromuscular disorder characterized by a congenital lower motor neuron disorder restricted to the lower part of the body[19]. Clinical manifestations include nonprogressive muscular atrophy, thigh muscle atrophy, weak thigh adductors, weak knee and foot extensors, minimal jaw muscle and neck flexor weakness, flexion contractures of the knees and pes equinovarus. However, tendon reflexes are normal [20].

Inheritance is autosomal dominant. The R315W mutation has been identified in an unrelated family that also had HMSN2C [21]. Auer-Grumbach et al. identified two additional TRPV4 mutations (R269H and R316C) in affected members of three additional families with these three phenotypes, indicating that they are allelic disorders [22]. All three mutations occurred at the outer helices of the ANK4 and ANK5 domains, in the N-terminal cytoplasmic domain (Fig. 1). *In vitro* functional expression studies in HeLa cells show that the mutant protein forms cytoplasmic aggregates and has reduced surface expression, as well as an impaired response to stimulus-dependent channel activity. These results suggest that the mutations interfere with normal channel trafficking and function [21, 22]. Furthermore, Auer-Grumbach et al. identified a different heterozygous mutation in the TRPV4 gene (R315W; 605427.0008) in a patient with congenital distal SMA whose other family members with the same mutation had phenotypes consistent with hereditary motor and sensory neuropathy-2 or scapuloperoneal spinal muscular atrophy; thus, proving that these are allelic disorders with overlapping phenotypes[21, 22].

2.6. Spondyloepiphyseal dysplasia Maroteaux type (SEDM) [MIM:184095]

SEDM is a clinically variable spondyloepiphyseal dysplasia with manifestations limited to the musculoskeletal system [23]. Clinical features of SEDM include short stature, brachydactyly, platyspondyly, short and stubby hands and feet, epiphyseal hypoplasia of the large joints, and iliac hypoplasia; however, the patients have normal intelligence [23, 24]. Genetic mapping of patients affected with this disease show a missense mutation in TRPV4, either E183K, Y602C, or E797K [25]. Channel activity of the TRPV4 E797K mutant in HEK293 cells is constitutively active, consistent with the argument that the effects in TRPV4 are the cause SEDM [25]. SEDM is a clinically variable spondyloepiphyseal dysplasia with manifestations limited to the musculoskeletal system. Clinical features include short stature, brachydactyly, platyspondyly, short and stubby hands and feet, epiphyseal hypoplasia of the large joints, and iliac hypoplasia [26]. Both SEDM and parastremmatic dysplasia are part of the TRPV4 dysplasia family and TRPV4 mutations show considerable variability in phenotypic expression resulting in distinct clinical-radiographic phenotypes.

2.7. Parastremmatic dwarfism (PSTD) [MIM:168400]

PSTD is also characterized by defects in TRPV4 which is a bone dysplasia characterized by severe dwarfism, kyphoscoliosis, distortion, and bowing of the extremities, and contractures

of the large joints [27]. The disease is radiographically characterized by a combination of decreased bone density, bowing of the long bones, platyspondyly, and striking irregularities of endochondral ossification with areas of calcific stippling and streaking in radiolucent epiphyses, metaphyses, and apophyses [27].

In a 7-year-old girl with PSTD, Nishimura et al. (2010) analyzed the TRPV4 candidate gene and identified heterozygosity for a missense mutation (R594H; 605427.0003), which had previously been found in patients with the Kozlowski type of spondylometaphyseal dysplasia **(SMDK;** 184252)[25]. However, in patients with the Kozlowski type of spondylometaphyseal dysplasia (SMDK; 184252), Krakow et al. (2009) identified a 1781G-A transition in exon 11 of the TRPV4 gene, resulting in an arg594-to-his (R594H) substitution in the cytoplasmic S4 domain [12]. Thus, both PSTD and SMDK, which are caused by a TRPV4 mutation, seem to be associated with increased basal intracellular calcium ion concentration and intracellular calcium activity [12, 16, 25]. However, the Kozlowski type of spondylometaphyseal dysplasia **(SMDK;** 184252) is different from SEDM at TRPV4 mutation sites (E183K Y602C or E797K) [23-25].

2.8. Charcot–Maries–Tooth disease type 2C (CMT2C) and scapuloperoneal spinal muscular atrophy (SPSMA) [MIM:606071]

CMT2C is an axonal form of Charcot–Marie–Tooth disease, a disorder of the peripheral nervous system, characterized by progressive weakness and atrophy, initially of the peroneal muscles and later of the distal muscles of the arms [28]. Charcot–Marie–Tooth disease is classified into two main groups based on electrophysiological properties and histopathology: primary peripheral demyelinating neuropathies (designated CMT1 when they are dominantly inherited) and primary peripheral axonal neuropathies (CMT2) [29]. CMT2 group neuropathies are characterized by signs of axonal regeneration in the absence of obvious myelin alterations, normal or slightly reduced nerve conduction velocities, and progressive distal muscle weakness and atrophy [28, 29]. Nerve conduction velocities are normal or slightly reduced. CMT2C and SPSMA are also known as hereditary motor and sensory neuropathy type 2 (HMSN2C) [30, 31]. Patients with SPSMA are characterized by weakness of the scapular muscle and bone abnormalities. CMT2C leads to weakness of distal limbs, vocal cords, and often impairs hearing and vision [32]. Genetic analyses of these patients show the presence of TRPV4 missense mutations, particularly at the R269H, R315W, and R316C positions. [31, 33]

2.9. Familial digital arthropathy-brachydactyly (FDAB)

FDAB is a dominantly inherited condition that is characterized by aggressive osteoarthropathy of the fingers and toes and consequent shortening of the middle and distal phalanges [34]. Lamandé *et al*. showed that FDAB is caused by mutations encoding p.Gly270Val, p.Arg271Pro, and p.Phe273Leu substitutions in the intracellular ankyrin-repeat domain of the TRPV4 cation channel. The TRPV4 mutant in HEK-293 cells shows that the

mutant proteins have poor cell-surface localization. TRPV4 mutations that reduce channel activity cause a third phenotype, inherited osteoarthropathy, and show the importance of TRPV4 activity in articular cartilage homeostasis. Thus, the TRPV4 mutant (G270V, R271P, Y273L) also seems to be related with FDAB [34].

3. Conclusions and perspective

The TRPV4 functional Ca2+ channel consists of homo tetramer subunits [35]. TRPV4 and TRPC1 can coassemble to form heteromeric TRPV4–C1 channels [36, 37]. Because the TRPV4 ankyrin repeat is responsible for its channel selfassembly in the cell line, mutations in the TRPV4 ankyrin domain also seem to affect channel assembly in humans, as shown in the many genetic disorders (Fig. 1 and Table 1).

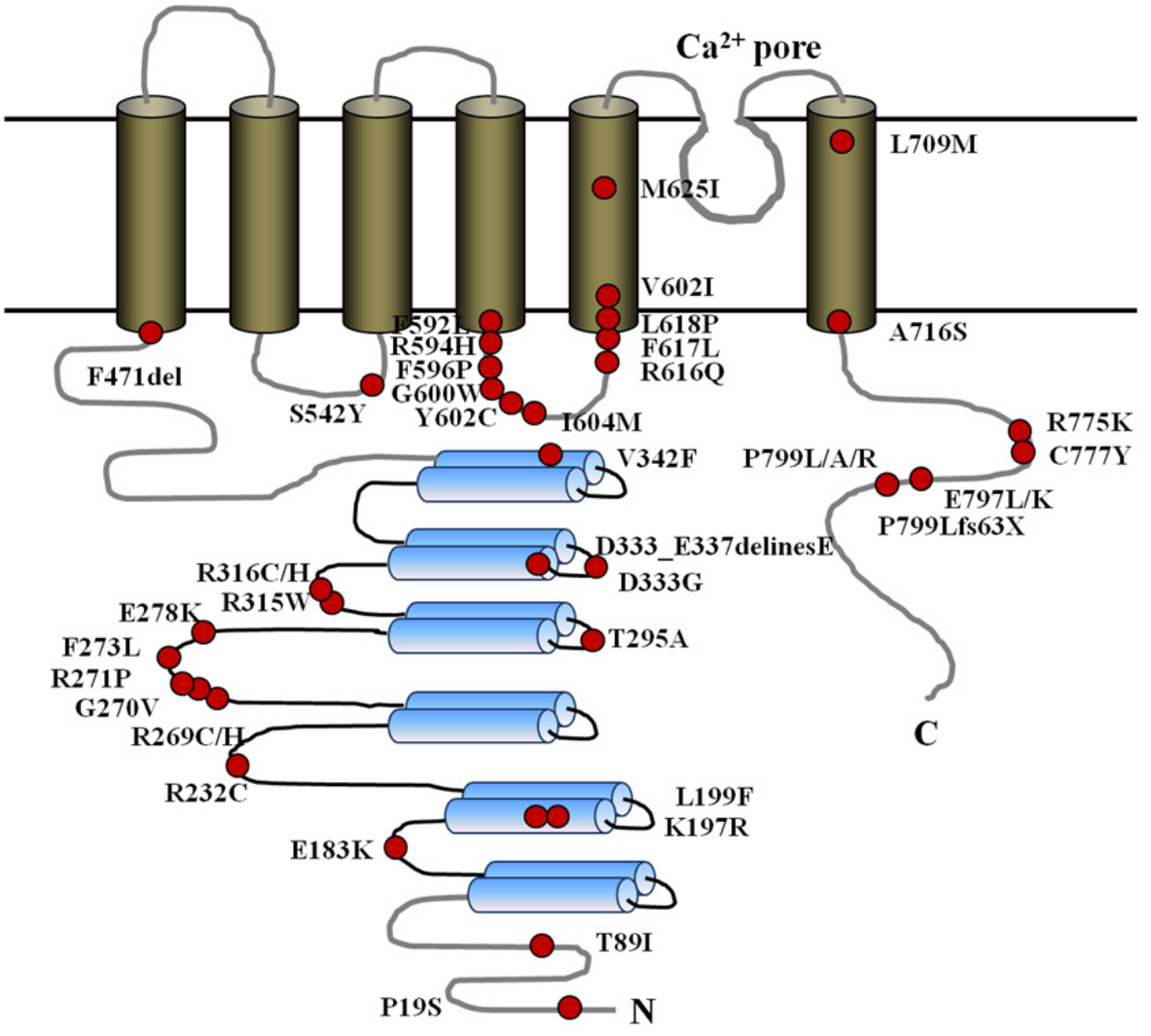

Figure 1. The naturally mutation sites on human TRPV4.

Mutation		Residue	Change in charge	Domain/motif effected	Effects on ion conductivity	Genetic disorder
1	C144T (exon 2)-	P19S	Nonpolar to polar	N-terminal	Less conductivity	Hyponatermia COPD
2	C366T (exon 2)	T89I	Polar (uncharged) to nonpolar	N-terminal	Not done	Metatropic dysplasia
3	G547A (exon 3)	E183K	Negative to plus	ARD1	Not done	SEDM-PM2
4	A590G (exon 4)	K197R	Plus to plus	ARD2	Not done	Metatropic dysplasia
5	-	L199F	Nonpolar to aromatic	ARD2	Not done	Metatropic dysplaisa
6	G806A (exon 5)	R269H	Plus to plus	ARD3	Less conductivity	SMA
7	G806A (exon 5)	R269H	Plus to plus	ARD3	More conductivity	CMT2C
8	G806A (exon 5)	R269H	Plus to plus	ARD3	More conductivity	CMT2C
9	G806A (exon 5)	R269C	Plus to polar un charged	ARD3	More conductivity	CMT2C
10		G270V	Nonpolar to polar	ARD3	Not done	FDAB
11		R271P	Plus to nonpolar	ARD3	Not done	FDAB
12		F273L	Aromatic to nonpolar	ARD3	Not done	FDAB
10	-	E278K	Negative to plus	ARD3	Not done	SMDK
11	-	T295A	Polar (uncharged) to nonpolar	ARD4	Not done	Metatropic dysplaisa
12	C943T (exon 6)	R315W	Plus to aromatic	ARD4	Less conductivity	HMSN2C
13	C946T (exon 6)	R316C	Plus to polar (uncharged)	ARD4	Less conductivity	HMSN2C
14	A1080T (exon 6)	I331F	Nonpolar to aromatic	ARD5	Not done	Metatropic dysplasia
15	-	I331T	Nonpolar to polar (uncharged)	ARD5	Not done	Metatropic dysplasia
16	A992G (exon 6)	D333G	Negative to nonploar	ARD4	More conductivity	SMDK
17	-	V342F	Nonpolar to aromatic	ARD5	Not done	Metatropic dysplasia
18	-	F592L	Aromatic to nonpolar	TM4	Not done	Metatropic dysplasia
19	G1781A (exon 11)	R594H	Plus to plus	TM4	More conductivity	SMDK
20	A1805G (exon 11)	Y602C	Aromatic to polar	TM4-TM5	Not done	SEDM-PM2
21	C1812G (exon 11)	I604M	Nonpolar to nonpolar	TM4-TM5	Not done	Metatropic dyslpasia

Mutation		Residue	Change in charge	Domain/motif effected	Effects on ion conductivity	Genetic disorder
22	G1847A (exon 12)	R616Q	Plus to polar uncharged	TM5, pore region	More conductivity	Brachylomia
23	C1851A (exon 12)	F617L	Aromatic to nonpolar	TM5, pore region	Not done	Metatropic dysplasia
24	T1853C (exon 12)	L618Q	Nonpolar to polar (uncharged)	TM5, pore region	Not done	Metatropic dysplasia
25	G858A (exon 12)	V620I	Nonpolar to nonpolar	TM5, pore region	More conductivity	Brachylomia
26	-	M625I	Nonpolar to nonpolar	TM5, pore region	Not done	SMDK
27	-	L709M	Nonpolar to nonpolar	TM5, pore region	Not done	SMDK
28	C2146T (exon 13)	A716S	Nonpolar to polar	Cytoplasmic side of TM6	Same as wild type	SMDK
29	-	R775K	Plus to plus	C-terminal region	Not done	Metatropic dysplasia
30	-	C777Y	Polar (uncharged) to aromatic	C-terminal region	Not done	SMDK
31	-	E797K	Negative to plus	C-terminal region	Not done	SEDM-PM2
32	-	P799R	Nonpolar to plus	C-terminal region	Not done	Metatropic dysplasia
33	-	P799S	Nonpolar to polar (uncharged)	C-terminal region	Not done	Metatropic dysplasia,
34	-	P799A	Nonpolar to non polar	C-terminal region	Not done	Metatropic dysplasia
35	C2396T (exon 15)	P799L	Nonpolar to nonpolar	C-terminal	Not done	SMDK

The disease abbreviation means below:

Serum Sodium Level Quantitative Trait Locus (Hyponatermia) (the # of MIM is not available)

Chronic obstructive pulmonary disease (COPD) (the # of MIM is not available)

Brachyolmia type 3 (BRAC3) [MIM:113500]

Metatropic dysplasia (MTD) [MIM:156530];

Distal spinal muscular atrophy congenital non-progressive (DSMAC) [MIM:600175]. (DSMAC is also called as Hereditary Motor and Sensory Neuropathy, Type IIC; HMSN2C)

Spondyloepiphyseal dysplasia Maroteaux type (SEDM) [MIM:184095].

Parastremmatic dwarfism (PSTD) [MIM:168400]

Charcot-Maries-Tooth disease type 2C (CMT2C) and Scapuloperoneal Spinal Muscular Atrophy (SPSMA) [MIM:606071]

Familial digital arthropathy-brachydactyly (FDAB): (the # of MIM is not available)

Kozlowski type of spondylometaphyseal dysplasia (SMDK): [mim:184252]

*MIM : Mendelian Inheritance in Man

Table 1. The Summary of the naturally occurring TRPV4 mutations and human diseases.

Our recent observations indicate that TRPV4 is modulated by phosphorylation of the Ser824 residue as a positive regulation loop [7, 38]. However, the TRPV4 C-terminal domain near serine residue 824 seems to regulate its function by an unknown controlling mechanism beyond a phosphorylation modification, such as a protein-protein interaction with CaM. TRPV4 C-terminal domain mutations also seem to affect protein-protein interactions, resulting in the genetic disorders listed in Fig. 1 and Table 1. In the future, TRPV4 mutant knockdown in an animal model will be helpful to elucidate how the TRPV4 mutations cause the genetic disorders.

TRPV4 was originally shown to be activated by hypotonicity, but later studies have demonstrated that activation can also be achieved by phorbol esters, AA, and moderate heat. TRPV4 appears to be an important player in pathological sensory perception and bone growth [1-6]. The potential effect of mutations on TRPV4 function, which are related to human diseases through its altered function, remains to be elucidated. Furthermore, the role of TRPV4 in the pathogenesis of several diseases should be characterized and how the channel protein contributes to the specific disease must be understood. This information may be useful to cure or alleviate the human diseases caused by TRPV4 mutations.Transmembrane topology of the human TRPV4 (871aa length). Indicated are the three ankyrin-binding repeats (ANK; blue bar), the six trans-membrane regions (TM1–TM6), the Ca^2 pore and the mutation site (WT; Gene Bank #. BC127052). The putative cytoplasmic region of N-terminal (1-471 aa) and C-terminal (718-871aa) of TRPV4 are indicated with N and C. Two "hot spots" in TRPV4 sequences are prominent, one at the pore region and the other one in the ARDs. (del: deletion, delines: deletion or insertion extra sequence, fs: fame shift)

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