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A Novel Germline SUFU Variant in a Child with Medulloblastoma

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Abstract

Medulloblastoma is the most frequent malignant brain tumor in children, with a median presentation age of 7 years and predominance in males. Germline *SUFU* pathogenic variants have been demonstrated to increase susceptibility to sonic hedgehog (SHH)- activated medulloblastoma. However, only a limited number of germline *SUFU* variants associated with medulloblastoma have been reported to date.

We report on a 1-year-old boy diagnosed with SHH-β subtype medulloblastoma. A novel germline *SUFU* variant was detected by next-generation sequencing, in accordance with current recommendations to perform genetic analysis of germline DNA in all patients with SHH medulloblastoma, especially in young children. Computational analysis and protein structure modeling were used to assess the potential impact of the variant on SUFU function.

Whole exome sequencing of blood DNA revealed a rare heterozygous *SUFU* variant NM_016169.4:c.619G > A, NP_057253.2:p.(Glu207Lys). Loss of heterozygosity in *SUFU* was revealed in the proband's tumor DNA. In the protein structure, the altered residue is located in the helix bundle at the boundary between two SUFU domains. Substitution p.(Glu207Lys) changes the charge of the amino acid, and thus might influence the domain movement that is necessary for protein function. Despite a successful initial treatment with neurosurgery and chemotherapy, the patient experienced disease recurrence and unexplained neurotoxicity, leading to a poor outcome.

This report aims to highlight a possible connection between a novel germline *SUFU* missense variant and an aggressive pediatric medulloblastoma.

INTRODUCTION

Medulloblastoma, an embryonal tumor of the cerebellum, is the most frequent malignant brain tumor in children, with a median presentation age of 7 years and predominance in males.[1] The World Health Organization classifies medulloblastomas into four molecular subgroups: wingless (WNT)-activated, sonic hedgehog (SHH)-activated and *TP53*-wildtype, SHH-activated and *TP53*-mutant, and non-WNT/non-SHH [2]. The SHH-activated tumors are most frequent in infants and young adults and account for approximately 30% of all medulloblastomas [3]. The SHH-activated group has also been shown to be heterogeneous, with four subtypes. The SHH α subtype is associated with *TP53* pathogenic variants and *MYCN* and *GLI2* amplifications. SHH β tumors mostly affect infants and usually result in poor outcomes. The SHH γ subtype is also frequent in infants but has a better prognosis. In contrast, SHH δ tumors are mostly found in adults [4].

Although most often medulloblastomas arise sporadically due to somatic pathogenic variants, they can also be associated with various germline pathogenic variants, especially within the SHH molecular subgroup [5]. Multiple factors contribute to the SHH pathway, including the inactivation of Suppressor Patched 1 (*PTCH1*) and Suppressor of Fused (*SUFU*). The SHH pathway plays a crucial role in normal cerebellar development and is disrupted in various malignancies [6]. The association of the SHH

pathway with medulloblastoma was initially established by the discovery of germline pathogenic variants in *PTCH1* in individuals with Gorlin syndrome, characterized by a combination of skin tumors, craniofacial abnormalities, and an increased risk of SHH-activated medulloblastomas [7–9]. Individuals with germline *SUFU* pathogenic variants are also predisposed to medulloblastoma, predominantly occurring before the age of 3 years. These patients usually present without odontogenic jaw keratocysts characteristic of Gorlin syndrome, but basal cell carcinoma and meningioma can occur [10]. Familial medulloblastoma was reported in patients with other genetic syndromes, including Li-Fraumeni syndrome (MIM 151623), caused by pathogenic variants in *TP53* (MIM 191170), constitutional mismatch repair deficiency syndrome (MIM 276300, 619097), associated with biallelic variants in *MLH1 (MIM 120436)*, *MSH2* (MIM 619096), *MSH6* (MIM 600678), and *PMS2* (MIM 600259), and Fanconi anemia (MIM 605724, 610832), associated with biallelic variants in *BRCA2* (MIM 600185) and *PALB2* (MIM 610355). Germline pathogenic variants in *APC* (MIM 611731), *ELP1* (MIM 155255), and *GPR161* (MIM 612250) have also been reported as possible medulloblastoma predisposition genes [5, 11–15].

Gaining a deeper understanding of the etiology and risk factors of medulloblastoma is crucial for advancements in treatment and increasing survival rates. Therefore, identifying and highlighting newly discovered DNA variants possibly associated with medulloblastoma development is important. We describe a child with medulloblastoma and a germline *SUFU* missense variant that has not been documented before.

CLINICAL SUMMARY

A 1-year-old boy was admitted to the pediatric neurology ward due to a sudden loss of coordination and inability to sit or eat after 3 days of febrile fever. The boy received a third dose of the pneumococcal conjugate vaccine and the meningococcal B vaccine 11 days before hospitalization. His medical history was otherwise unremarkable. Upon admission, the patient presented with a profound lack of responsiveness to tactile and auditory stimuli, absence of oculomotor pursuit, and a fixed lateral head position, paralysis of the right leg, spasticity of the right hand, and generalized hypotonia on the left side. The Babinski sign was positive bilaterally. Magnetic resonance imaging (MRI) revealed a 46 x 43 x 38 mm non-homogeneous, contrast-accumulating infratentorial tumor with a cystic component (Fig. 1). Imaging features were compatible with medulloblastoma, with morphology and enhancement pattern raising suspicion for the SHH molecular subgroup (including a possible SUFU-associated subtype). Complete obstruction of the fourth ventricle resulting in severe obstructive hydrocephalus with associated periventricular edema and mild mass effect on the brainstem, without imaging evidence of significant peritumoral vasogenic edema, was noted. Cranial and spinal imaging showed no evidence of dissemination. A suboccipital craniotomy was conducted along with the placement of external ventricular drainage. After the surgery, the patient lapsed into a coma. Tumor resection was incomplete: MRI showed postoperative lesions, a cerebral and vermis defect, hydrocephalus, ischemic lesions, and a residual tumor mass of approximately 13 x 20 x 10 mm. Cerebrospinal fluid was negative for tumor cells, and MRI revealed no metastases.

Twenty-seven days post-surgery, an Ommaya reservoir was implanted, and serial CSF draining punctures improved the patient's condition. The preliminary pathology report was consistent with medulloblastoma. The patient was discussed with HIT-MED study coordination as part of the twinning project TREL [16] within the framework of the ERN PaedCan tumor board for children with central nervous system tumors.[17] The SKK chemotherapy regimen, according to the HIT-MED Guidance for Patients with newly diagnosed Medulloblastoma, Ependymoma, and Pineoblastoma Version 5.2, was initiated. The definitive pathology and genetic analysis confirmed an SHH-β subtype medulloblastoma (described in detail below). The entire course of treatment consisted of 3 SKK cycles plus 2 modified SKK cycles as published within the HIT2000-SKK trial [18], and was concluded after 10 months. A complete remission was documented on the control MRI at the end of chemotherapy. However, a follow-up MRI four months after the completion of therapy demonstrated local recurrence – a newly developed, contrast-enhancing mass measuring approximately 24 x 15 x 26 mm. A non-radical surgical excision of the recurrent tumor was performed. Subsequently, chemotherapy was started according to the HIT-REZ 2005 protocol [19]. After two cycles of chemotherapy with a 96-hour infusion of Carboplatin 200 mg/m^2/d and Etoposide 100 mg/m^2/d and intrathecal Etoposide, the tumor significantly decreased in size. The TREL multidisciplinary team considered the response to reinduction successful. Consolidation with high-dose chemotherapy with an autologous stem cell rescue after the fourth cycle was foreseen. During the third cycle, the patient developed a tremor, presumably consistent with chemotherapy-induced neurotoxicity. After managing the symptoms, the boy underwent the fourth cycle of chemotherapy, but the tremor progressed along with body spasms. A differential diagnostic workup revealed Epstein-Barr virus in the cerebrospinal fluid. Despite therapeutic efforts, the patient’s condition continued to deteriorate. Repetitive MRI did not reveal any sign of tumor progression. Chemotherapy was discontinued due to the unstable neurological condition. After a thorough discussion with the family and approval from the institutional ethics board, mesenchymal stem cells were used as a last-resort therapy to relieve neurotoxicity. However, it had no positive effect on the patient’s condition, leaving palliative treatment as the only option. The tumor eventually progressed, which resulted in brain herniation and a fatal outcome 30 months after initial diagnosis at the age of 3 years and 7 months.

PATHOLOGICAL AND MOLECULAR FINDINGS

Morphological analysis of the tumor confirmed histologically defined desmoplastic/nodular medulloblastoma G4 (Fig. 2), and molecularly defined medulloblastoma SHH-β subtype by DNA methylation profiling (cs 0.99) [20]. Molecular karyotyping by single-nucleotide polymorphism arrays revealed deletions of 8q, 9p, and 20p. The histological examination results of the recurrent tumor were consistent with the primary medulloblastoma.

Whole-exome sequencing

Whole-exome sequencing (WES) of proband’s blood DNA was performed using Human Core Exome Kit (Twist Bioscience) as previously described [21]. Genes associated with childhood solid tumors were

analyzed. Variants were classified following the guidelines of the American College of Medical Genetics and Genomics (ACMG) [22]. Only variants that passed quality and coverage filters and showed > 99.9% detection reliability were analyzed.

Post-Sequencing Data Analysis

Protein sequence was taken from the UniProt database (UniProt AC: Q9UMX1) [23]. Experimental structures and structural data on SUFU interactions were queried using PPI3D web server [24]. Protein domain organization was analyzed using ECOD and InterPro [25, 26]. Initial structure models were downloaded from the AlphaFold Database [27]. A mutant structure model was produced using AlphaFold 2 via ColabFold [28, 29]. Contacts in structures were analyzed using the VoroContacts server [30].

RESULTS

WES revealed a *SUFU* variant NM_016169.4:c.619G > A, NP_057253.2:p.(Glu207Lys), which was heterozygous in the blood DNA. The variant has not been described in the literature previously and has no entries in ClinVar, HGMD, or other databases [31, 32]. *SUFU* variant NM_016169.4:c.619G > A has not been observed in the gnomAD v4.1 dataset, or an in-house database of over 2000 samples [33]. *In silico* analysis indicates that c.619G > A missense variant has a deleterious effect on protein structure and function (SIFT: 0, PolyPhen: 0.998, CADD: 32, AlphaMissense: 0.9992). This sequence change results in the substitution at position 207 of SUFU, a residue that is highly conserved in mammals and across evolutionarily distant species. However, only a few missense pathogenic variants are known in *SUFU*. Based on these data, we classified *SUFU* variant c.619G > A as a variant of uncertain significance (PP3, PM2_SUP).

Sanger sequencing of the proband's tumor DNA revealed a homozygous genotype of the variant, indicating loss of heterozygosity in *SUFU.* Segregation analysis showed that the variant was inherited from the mother, who had no oncological conditions or clinical features of Gorlin syndrome (Fig. 3).

To estimate the effect of the missense variant on the protein structure and function, computational analysis of available structural data was performed. SUFU protein contains two structural domains and a disordered region (Fig. 4, A). Upon interaction with GLI1 peptides, structural changes were observed when the N-terminal and C-terminal domains were brought together, and both interacted with the peptide, forming a "closed" conformation of the protein (Fig. 4, A) [34, 35]. The mutated residue, Glu207, is located in a three-helix bundle at the boundary between domains. In the case of p.(Glu207Lys), a negatively charged glutamic acid residue is substituted with a positively charged lysine. In the wild-type structure, Glu207 participates in a network of hydrogen bonds and/or salt bridges with residues from other helices, especially with the positively charged Arg240. The change of charge upon introducing the lysine residue abolishes these interactions (Fig. 4, B). Therefore, it is likely that the dynamics of the protein can be significantly altered, resulting in functional changes.

DISCUSSION

SUFU is a tumor suppressor gene encoding an inhibitor of the SHH signaling cascade, which takes place in the nucleus and cytoplasm. Homozygous or compound heterozygous alterations of the SUFU protein led to impaired interaction with GLI transcription factors in the cell. Therefore, they remain constantly active, leading to enhanced signaling of the SHH pathway, thus accelerating cell proliferation and the development of malignant tissue. Heterozygous germline *SUFU* variants were first associated with childhood medulloblastoma in 2002 [10]. Most SUFU germline pathogenic variants are protein-truncating, and loss of function is a known mechanism of the disease, often in conjunction with a somatic pathogenic variant in tumor DNA. Nevertheless, five of reported *SUFU* variants were missense variants, including c.422T > G, p.(Met141Arg) and c.544G > T, p.(Asp182Tyr) variants detected in patients with medulloblastoma, c.367C > T, p.(Arg123Cys) variant segregating in relatives with meningiomas, and c.293T > G, p.(Leu98Arg) as well as c.1390T > C, p.(Trp464Arg) variants for which the tumor was not specified [36–40]. *SUFU* variant c.619G > A, p.(Glu207Lys) detected in our patient, and all previously reported *SUFU* missense variants except c.1390T > C, were located in SUFU domain (PF05076), whose primary biochemical function is to bind directly to the GLI transcription factors and silence targeted genes (31). Most germline pathogenic variants in ClinVar are protein truncating, except missense variant c.527A > G, p.(His176Arg), associated with Joubert syndrome. To date ClinVar database contains 550 entries of missense variants in the *SUFU* gene. Most of them (506) are classified as variants of unknown significance. Verification of the pathogenicity of the missense variant unquestionably requires further *in silico* and functional analysis. Impairment of domain motion has been demonstrated for these pathogenic variants using molecular dynamics [41]. In our patient, the substitution of a negatively charged Glu residue with a positively charged Lys at a boundary between domains changes the hydrogen bonding and salt bridges. Therefore, it is expected to also influence the domain motions required for binding GLI peptides.

Waszak et al. in 2018 reported a study involving 1022 patients diagnosed with medulloblastoma, which showed that 6% of all affected individuals had a germline pathogenic variant in *SUFU*, *TP53*, *APC*, *PTCH1*, *BRCA2*, or *PALB2*. The SHH subgroup had the highest prevalence of genetic predisposition. Germline pathogenic variants in either *SUFU* or *PTCH1* were found in 2% of all individuals with medulloblastomas. Patients with germline *SUFU* or *PTCH1* pathogenic variants were generally diagnosed at a median age of 2 years and had a five-year combined progression-free survival of 56% [42]. In *PTCH1* pathogenic variant carriers, the incidence of medulloblastoma is estimated to be lower than 2%. In *SUFU* pathogenic variant carriers, the exact prevalence is difficult to evaluate due to the small number of individuals described to date, but it is expected to be much higher than for those with *PTCH1* pathogenic variants [36, 38]. Genetic testing is recommended for individuals with SHH-activated medulloblastomas, particularly for patients under 3 years old, due to the high incidence of germline variants [43]. Germline *SUFU* pathogenic variant carriers have an increased risk of developing malignant tumors over their lifespan. Therefore, detecting these germline variants is important, particularly in infancy [37].

Standard-risk medulloblastoma patients have 80% survival rates and a generally good prognosis [44]. The overall prognosis for SHH medulloblastoma in infants is good, although there are substantial differences among the four subtypes. 5-year survival rates range from 67% for SHH β tumors to 88% for SHH δ tumors [4]. A recent study shows that the prognosis of germline *SUFU*-associated medulloblastoma is worse than the general prognosis within the SHH group, with a 5-year overall survival of 66% and a 5-year disease-free survival of 37,5% in germline *SUFU* pathogenic variant carriers. This contrast in survival rates can be explained by more frequent local relapse of *SUFU*-associated medulloblastoma [36]. Additionally, *SUFU*-related tumors are mostly desmoplastic/nodular medulloblastomas and medulloblastomas with extensive nodularity, which might interfere with successful treatment [45]. However, no inferior survival rates were observed in the HIT series of patients with Gorlin syndrome and medulloblastoma.[46]

Surgery plays a vital role in the treatment of medulloblastomas, and the degree of tumor removal significantly influences the prognosis. In children younger than three years old, aggressive chemotherapy typically serves as the primary treatment until they are old enough to tolerate radiation [3]. In our patient, the surgery and standard chemotherapy were not effective enough, and the tumor progressed despite successful first-line treatment. The patient experienced a recurrence of the tumor and received a salvage chemotherapy regimen. The boy suffered from chemotherapy-induced neurotoxicity, which led to discontinuation of the treatment. This suggests that adjustments in chemotherapy schemes may be crucial in *SUFU*-related medulloblastoma. So far, treatment recommendations for children with Gorlin syndrome include omission of radiotherapy, but do not differ regarding medical treatment from recommendations for infant SHH-medulloblastoma without SUFU-alterations. Thus, optimal treatment for young children with *SUFU* medulloblastoma is an area for discussion and further prospective evaluation.

Conclusions

This study demonstrates that germline *SUFU* missense variant NM_016169.4(SUFU):c.619G > A, NP_057253.2:p.(Glu207Lys) shows a possible association with pediatric medulloblastoma. Our report also suggests that medulloblastoma with the novel *SUFU* missense variant may be associated with a worse prognosis compared with the SHH-activated group and may not respond to standard treatments. Clinical and molecular characterization of new *SUFU* variants may enhance our understanding of *SUFU*-related disorders and guide personalized clinical management, risk assessment, and genetic counseling.

Declarations

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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Informed Consent Statement

This research was conducted in accordance with the Declaration of Helsinki and was approved by the Vilnius Regional Biomedical Research Ethics Committee of Lithuania (protocol Nr. 2020/10-1274-753). Informed consent was obtained from the family.

Author Contribution

M.Č. and I.K. conceptualized the study, performed the initial investigation, and wrote the main manuscript text. J.D. performed the computational structural analysis of the variant. G.P. and D.P. performed the molecular/pathological analyses and prepared the figures. I.A., and S.Ro. provided clinical data, managed patient care, and contributed to clinical interpretation. S. Ru., M.S., K.W. and T.v.O.H. contributed to clinical and genetic variant interpretation. J.R. and E.P. supervised the study and revised the manuscript. All authors reviewed and approved the final manuscript.

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Figures

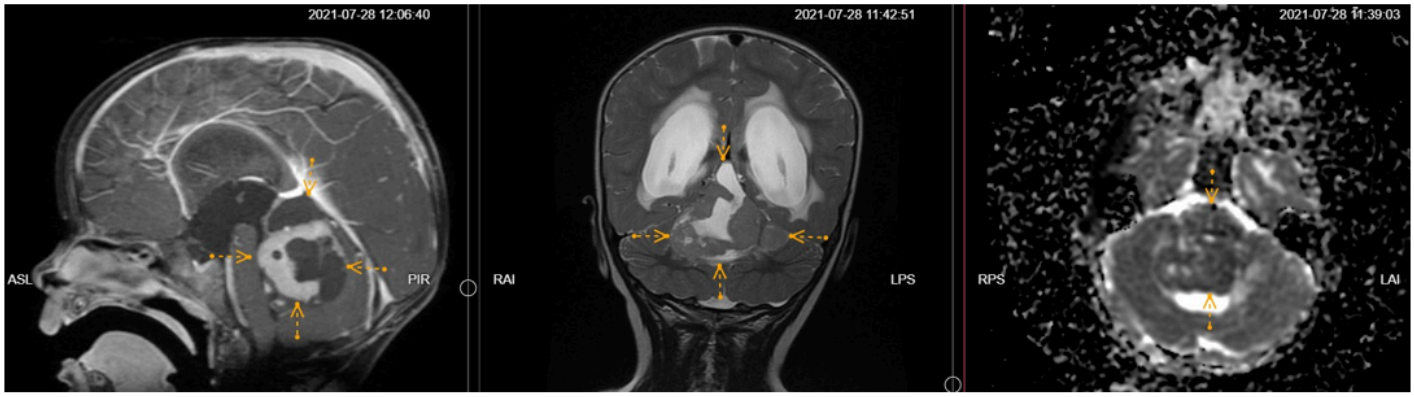


Figure 1

MRI scan of the brain (from the left to the right: T1 with fat sat and c/m, T2 cor, ADC map): Large, well-defined heterogeneous enhancing posterior fossa mass (arrows) of high cellularity centered in the fourth ventricular region with a cystic component.

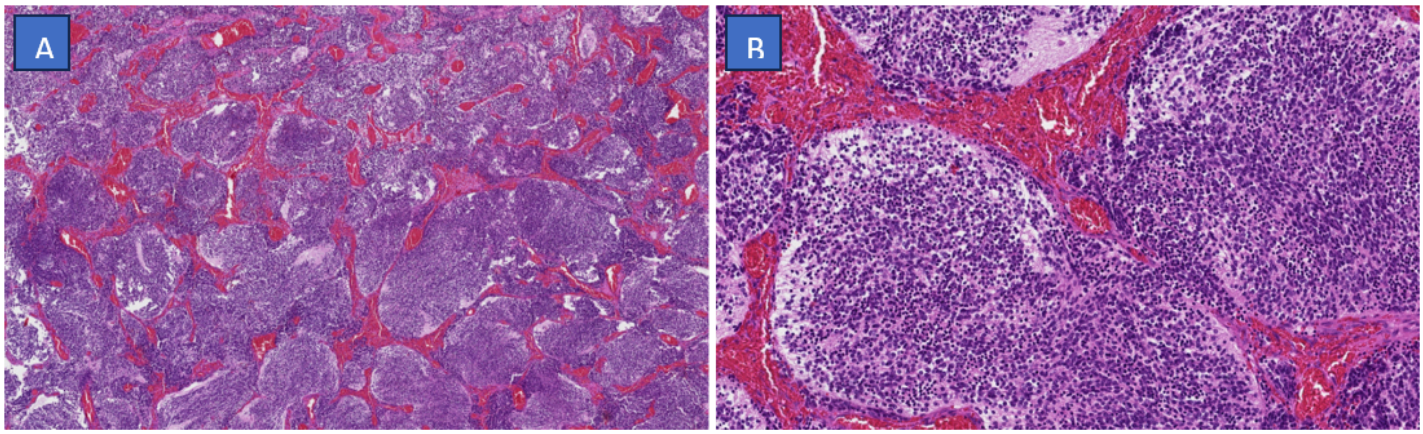


Figure 2

Nodular pattern of the medulloblastoma histology in magnification x 40 (A) and x 400 (B), stained with hematoxylin and eosin.

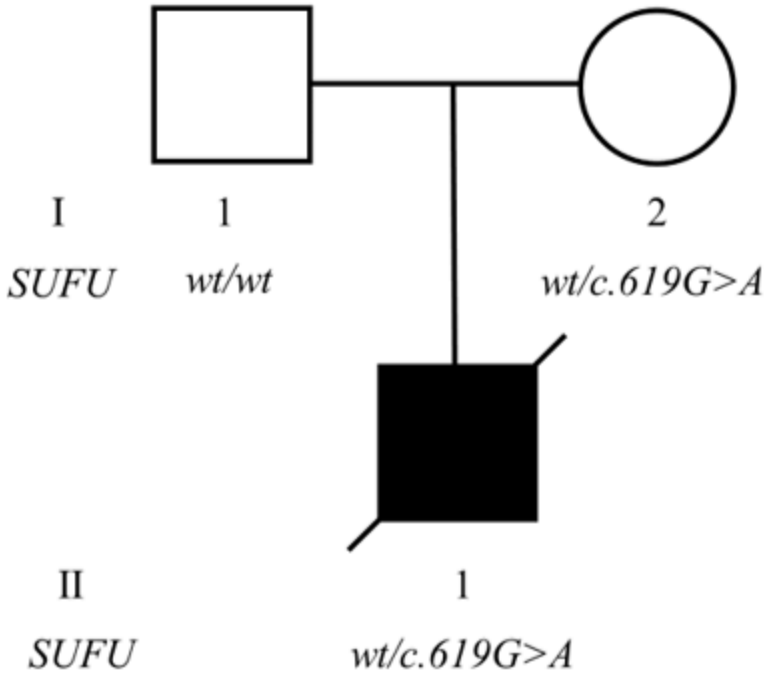


Figure 3

The genealogy of the family presents the affected proband (II-1). The heterozygous *SUFU* variant was detected in the proband and the unaffected mother (I-2).

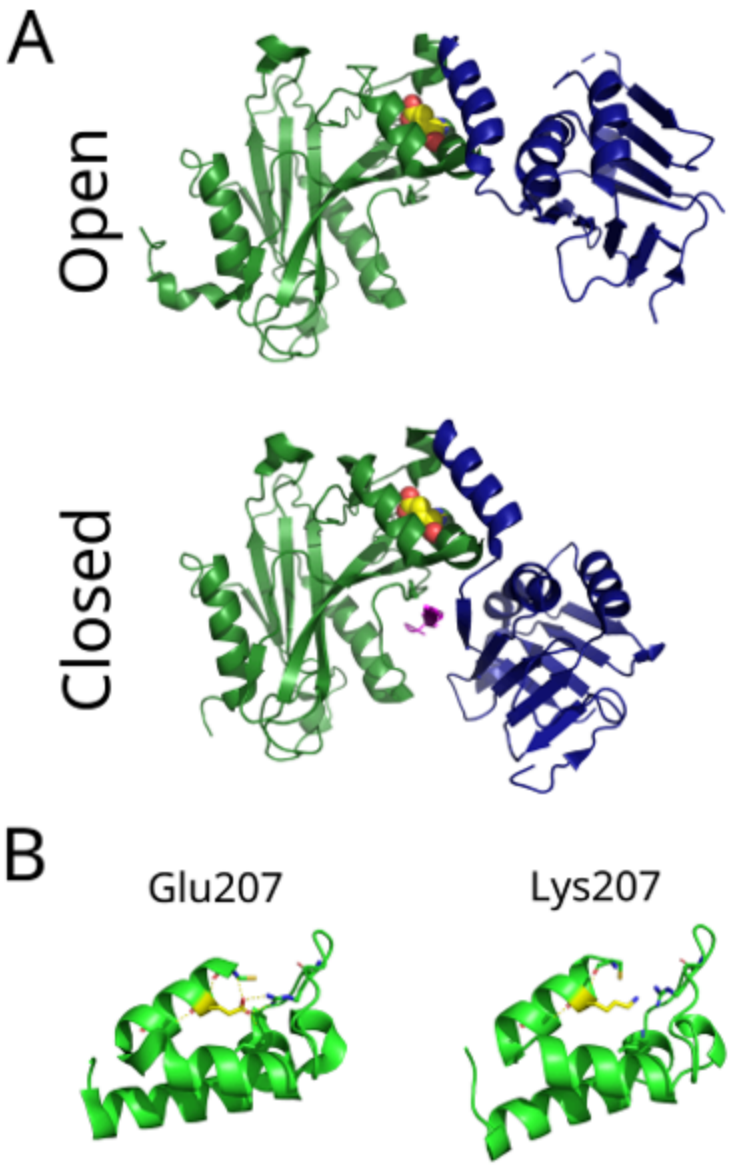


Figure 4

(A) The structure of *SUFU* in open (top, PDB: 4KM8) and closed (bottom, PDB: 4KMD) conformations. N-terminal domain is green, C-terminal domain is blue, bound GLI1 peptide is in magenta, and residue Glu207 is in yellow spheres. (B) Changes in hydrogen bonding in the helix bundle upon substitution Glu207Lys (left: experimental wild-type structure, PDB: 4KMD, right: a model of the altered structure with lysine residue, residue 207 is coloured in yellow).