

SHORT REPORT

Open Access



# A novel mutation of *ABHD5* gene in a Chanarin Dorfman patient with unusual dermatological findings

Ali Haydar Eskiocak<sup>1</sup>, Sara Missaglia<sup>2,3</sup>, Laura Moro<sup>4</sup>, Murat Durdu<sup>1†</sup> and Daniela Tavian<sup>2,3\*†</sup> 

## Abstract

**Background:** Chanarin Dorfman Syndrome (CDS) is a rare autosomal recessive disorder characterized by the multisystemic accumulation of neutral lipids inside the cytoplasmic lipid droplets. This condition is caused by mutations in the abhydrolase domain containing 5 gene (*ABHD5*). In CDS the skin involvement is the prevalent and always observed clinical feature, consisting of a non-bullous congenital ichthyosiform erythroderma (NCIE). Moreover, a variable involvement of the liver and neuromuscular system can be also observed. In this report, we aimed to perform the clinical and genetic characterization of a patient affected by CDS with atypical dermatological findings, considering this rare inborn error of neutral lipid metabolism.

**Methods:** Genomic DNA samples obtained from patient and his parents were used to perform the sequencing of the *ABHD5* exons and their intron/exon boundaries. Bioinformatic analyses were performed to investigate the possible effect of the identified mutation on protein structure.

**Results:** Here we present the case of a 29-year-old male patient with CDS, who, for long time, has been misdiagnosed as pityriasis rubra pilaris (PRP). He has a history of increasing hyperlipidemia; hepatomegaly associated with hepatosteatosis was also detected. *ABHD5* molecular analysis revealed a novel missense mutation, the c.811G > A (p.G271R). Bioinformatic investigations showed that the variant has a deleterious effect on *ABHD5* function, probably causing an incorrect folding of the mutant protein.

**Conclusions:** These results highlight the importance of genetic testing for *ABHD5* in unresolved cases of patients presenting unusual skin lesions, that resemble PRP, associated with a history of hyperlipidemia and nonalcoholic fatty liver.

**Keywords:** Chanarin-Dorfman syndrome, Ichthyosis, Lipid disorder, Liver involvement, Pityriasis rubra pilaris, Hyperlipidemia

## Background

Chanarin Dorfman syndrome (CDS; MIM: 275630) is a rare neutral lipid storage disease, characterized by the intracellular accumulation of triacylglycerol (TG) in numerous tissues including skin, liver, skeletal muscle, eyes, ears, central nervous system and bone marrow [1]. The clinical diagnosis is based on detection of Jordans'

bodies (JBs), characteristic cytoplasmic vacuoles in the granulocytes of patients [2]. To date, 150 cases have been described worldwide [3, 4]. Many of them have been reported from the Mediterranean and Middle-East region, especially Turkey, where consanguineous marriages are still common [5]. Mutations in *ABHD5* have been demonstrated as the responsible defect of CDS [6]. They cause the impairment of *ABHD5* function, leading to an abnormal accumulation of TG stored into lipid droplets (LDs) in many tissues [7]. Indeed, *ABHD5* acts as a coactivator for adipose triglyceride lipase (ATGL), which hydrolyzes the first fatty acid from TG [8]. Non bullous-congenital ichthyosiform erythroderma (NCIE)

\* Correspondence: [daniela.tavian@unicatt.it](mailto:daniela.tavian@unicatt.it)

<sup>†</sup>Murat Durdu and Daniela Tavian contributed equally to this work.

<sup>2</sup>Laboratory of Cellular Biochemistry and Molecular Biology, CRIBENS, Catholic University of the Sacred Heart, p.z Buonarroti 30, 20145 Milan, Italy

<sup>3</sup>Department of Psychology, Catholic University of the Sacred Heart, Largo Gemelli 1, 20123 Milan, Italy

Full list of author information is available at the end of the article



is the dominant feature of CDS, but additional clinical features can include liver damage, myopathy, neurosensory hearing loss, subcapsular cataracts, nystagmus, strabismus and mental retardation. It has been recently demonstrated that NCIE is caused by the impairment of ABHD5 function which does not depend by ATGL lipase activity. Besides ATGL, ABHD5 is able to activate PNPLA1, which catalyzes the final step of  $\omega$ -O-acylceramide production, an essential lipid for correct skin barrier formation in human keratinocytes [9] (Fig. 1).

Here we report one more CDS family where the affected patient presents a peculiar skin phenotype resembling

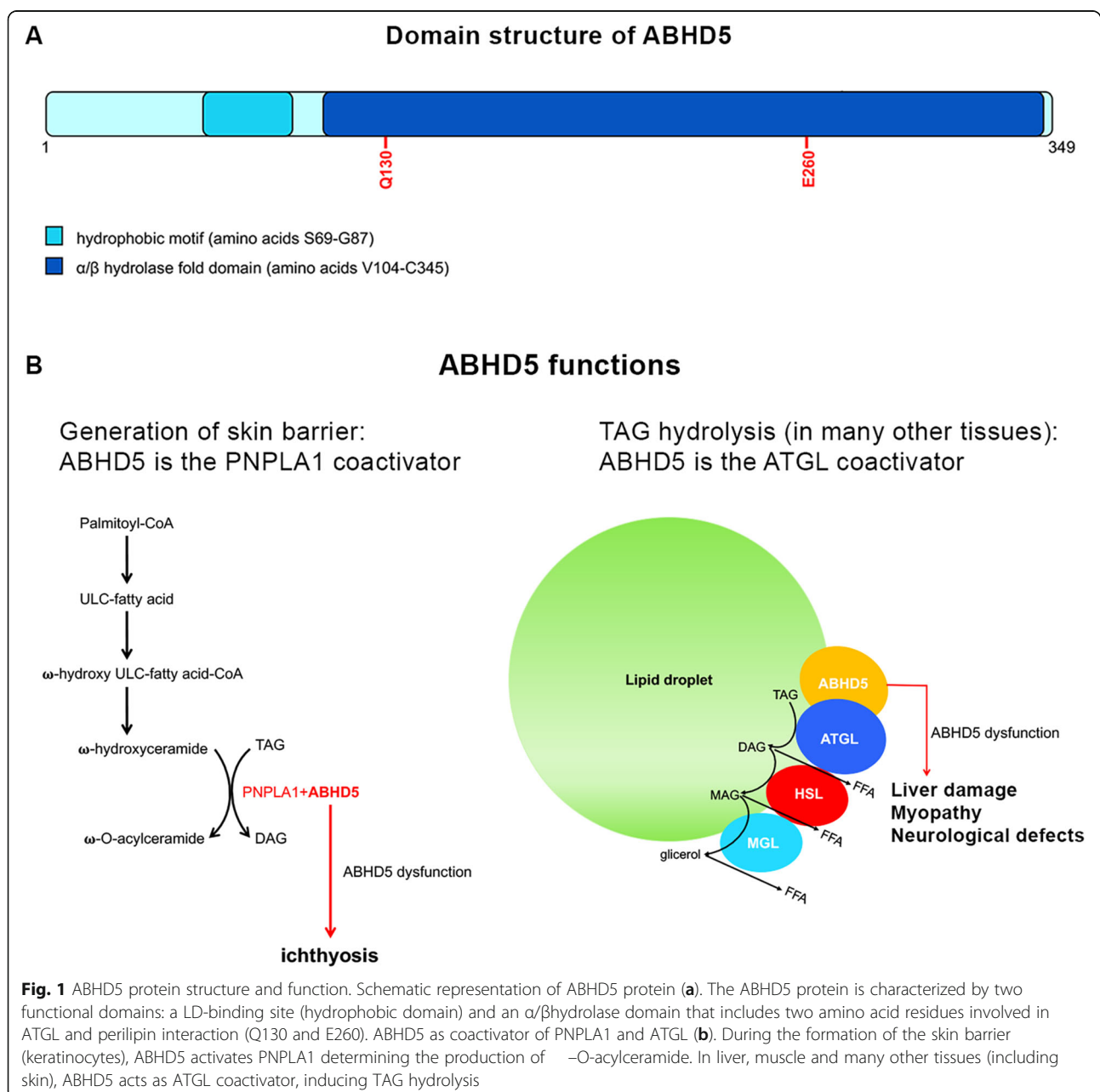
pityriasis rubra pilaris and, for this reason, he had been misdiagnosed for long time.

## Methods

### Histopathologic examination

A punch biopsy was fixed in formalin. The histologic sections for light microscopy were stained with haematoxylin and eosin.

Fresh EDTA-treated peripheral blood sample from patient, was centrifugated at 3300 g for 10 min. Buffy coat was collected, smeared onto slides glasses, dried and stained with May-Grünwald Giemsa (MGG) stain.



### Molecular analysis

To evaluate *ABHD5* exons sequences and their intron/exon boundaries, genomic DNAs of patient and his parents were amplified as previously reported [7]. All PCR products were purified using Nucleo Spin Extract kit (Mcherey-Nagel) and sequenced on 3730 DNA Analyzers by the BigDye® Terminator V1.1 Cycle Sequencing Kit (Applied Biosystems). Informed consent was obtained from all participants and analyses were performed in accordance with the Declaration of Helsinki principles.

### Bioinformatic investigation of *ABHD5* missense mutation

NCBI reference sequence of the human *ABHD5* protein (NP\_001342115.1) was used as template to evaluate possible effects of the identified missense mutation on *ABHD5* function by ClustalW, PolyPhen and Mutation Tasting. *ABHD5* wild-type and *ABHD5* (G271R) 3D models were generated using I-Tasser, an in silico protein modeling tool.

## Results

### Case presentation

A-29-year old man was admitted to our outpatient clinic for erythematous scaly lesions that had been present since the age of 2 years. He had been previously biopsied twice and was diagnosed with pityriasis rubra pilaris. He received oral acitretin treatment for a long time but he did not respond to treatment. His parents were non-relatives and no one else in his family had a similar disease. Most recently, a dermatological examination performed in our clinic, revealed extensive erythematous patch and plaques on all parts of the body accompanied by fine scaling especially on lower limbs (Fig. 2a, b). The scaling was evident on border of the erythematous plaques. Strikingly, there were unaffected areas between the plaques on the back and the limbs. His face and scalp

had seborrheic dermatitis-like mild erythema and fine scales. Ectropion, nail dystrophy or palmoplantar involvement was not detected. Histopathologic examination of punch biopsy revealed orthohyperkeratosis (Fig. 3a), focal parakeratosis, flattening and merging of rete ridges and mild perivascular lymphocytic infiltration (Fig. 3b). Dilated follicular infundibulum with hyperkeratotic plug, a histopathologic feature of pityriasis rubra pilaris, was not detected. Notably, lipid vacuoles were observed in the cytoplasm of basal keratinocytes (Fig. 3c).

Muscle strength was normal and electromyographic (EMG) examination showed no signs of myopathy. Patient denied any hearing or visual problem. The mental status and neurologic examination were normal. Liver transaminases, creatine kinase (CK) and serum TG levels were elevated (alanine transaminase: 132 U/L, normal 5–35 U/L; aspartate transaminase: 83 U/L, normal 5–17 U/L; CK: 580 U/L, normal 22–200 U/L; TG: 381 mg/dl, normal 35–130 mg/dl). Abdominal ultrasonography was compatible with hepatomegaly associated with hepatosteatosis.

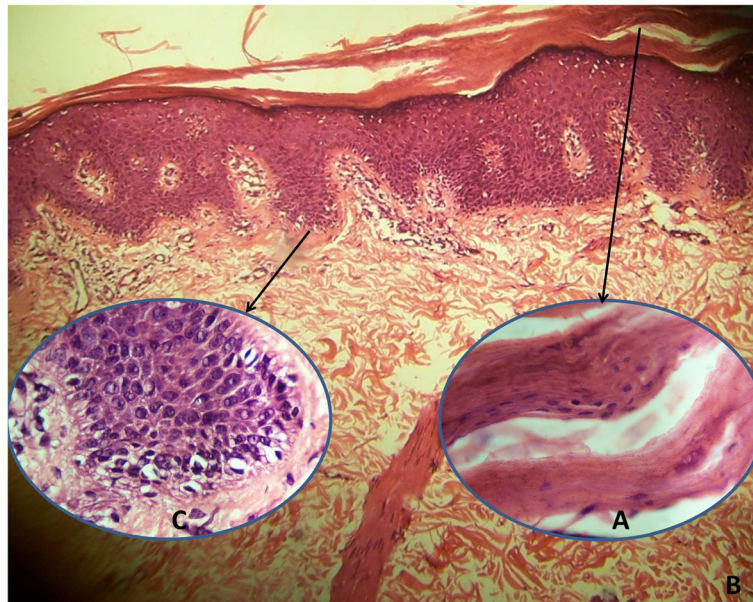
As our patient had a history of hyperlipidemia associated with hepatomegaly and his skin lesions got worse when serum triglyceride levels increased, CDS was suspected. Therefore, peripheral blood smear was performed and prominent intracytoplasmic vacuoles (JBs) were detected in neutrophils when stained with MGG (Fig. 2c).

### Genetic investigation

Molecular analysis revealed a novel *ABHD5* disease-causing variant (c.811G > A) in homozygous status (Fig. 4a), confirming the patient's clinical diagnosis. The mutant sequence was submitted to GenBank (accession number MN242826). This pathogenic variant was not found in 100 healthy controls. It causes the substitution of a single amino-acid in position 271 of the *ABHD5* protein (p.G271R). Bioinformatic analyses were carried out to



**Fig. 2** Clinical presentation of CDS patient. Erythematous and scaly lesions on back (a) and lower limbs (b) with uninvolved areas. Intra-cytoplasmic vacuoles (Jordans' bodies) in neutrophil of peripheral blood smear (c) (May-Grunwald-Giemsa X1000)



**Fig. 3** Histopathologic examination shows orthokeratosis, focal parakeratosis (a), flattening and merging of rete ridges (b), and vacuolar appearance in the cytoplasm of basal keratinocytes (c) (H&E, A and C  $\times$  1000; B  $\times$  100)

evaluate the impact of the p.G271R mutation on ABHD5 function. The alignment of ABHD5 protein sequences in eleven vertebrates revealed that the amino acid G271 is located in a highly conserved site. Moreover, investigation performed by PolyPhen-2 and Mutation Taster showed that p.G271R mutation probably has a deleterious effect on ABHD5 function. Finally, I-Tasser tool revealed that secondary structure of p.G271R ABHD5 presents conformational changes at positions 171, 218 and 269 (Fig. 4b). These modifications probably correlate with an incorrect 3D folding of the mutant protein (Fig. 4c).

## Discussion

CDS is an autosomal recessive neutral lipid disease that affects the skin, eyes, central nervous system, skeletal muscle, liver and bone marrow. While the extracutaneous manifestations are heterogeneous both in characteristics and in severity, ichthyosiform erythroderma is usually present in all patients, since birth. The typical features of ichthyosis in CDS are extensive scaly lesions on erythematous background [10]. However, the clinical appearance of CDS may, in rare cases, imitate other skin diseases with erythema and scales. Indeed, a case of erythrokeratoderma variabilis-like CDS, presenting patches of normal skin alternating with erythematous scaly patches, has been reported in the literature [11]. The cutaneous lesions of our patient developed at the age of 2 years. Moreover, he presented uninvolved areas between wide plaques with no alternating lesions. In this sense the clinical picture resembled pityriasis rubra pilaris in which the uninvolved areas are the typical feature [12].

The different clinical appearance of skin led to a long delay in reaching the correct diagnosis.

Liver involvement and hiperlipemia are common findings in CDS, occurring in more than 80% of cases. Currently, there is *no specific treatment for CDS*. However, a diet low in fatty acids with medium chain triglycerides (MCT) supplementation was reported to decrease hepatomegaly and normalize hepatic enzymes, especially when early initiated in combination with vitamin E and ursodeoxycholic acid [4, 7, 13–15]. Although our patient is now 29 years old, after molecular testing, we have recommended a fat-restricted diet+MCT because he presented hepatomegaly, hepatosteatosis and elevation in liver function tests. CK was also elevated in our patient, but myopathy was not detected in EMG and clinically there was no muscle weakness. However, muscle damage has been reported only in 40% of affected subjects [16].

In our CDS family, genetic analysis displayed a novel ABHD5 missense variant (p.G271R). Bioinformatic investigation, performed with two different predictive tools for missense mutations, showed that glycine to arginine substitution at position 271 may affect protein activity. Moreover, to clarify whether p.G271R can also alter ABHD5 protein folding, tridimensional (3D) structures of native and mutant proteins were generated. The analysis, obtained by I-Tasser software, revealed that the p.G271R substitution causes a modification of the secondary structure of the protein in 3 different regions. These alterations can determine dramatic 3D conformational changes of the ABHD5 protein affecting its ability to bind lipid droplet surface and to interact with



distinct type of ichthyosiform skin lesions, expanding the spectrum of clinical phenotype for CDS. As CDS is an extremely rare genetic disorder and its pathophysiology is largely unclear, it is important to emphasize the accurate description of novel patients in order to improve the knowledge of the natural history and explore genotype-phenotype correlation.

#### Abbreviations

CDS: Chanarin Dorfman Syndrome; CK: Creatine kinase; EMG: Electromyographic examination; LD: Lipid droplet; MCT: Medium chain triglycerides; MGG: May-Grünwald-Giemsa; NCIE: Non-bullous congenital ichthyosiform erythroderma; PRP: Pityriasis rubra pilaris; TG: Triacylglycerol; UV: Ultra violet

#### Acknowledgements

We are grateful to patient and his parents for their kind cooperation.

#### Authors' contributions

MD was responsible for patient care; genetic analysis was performed by SM; bioinformatic analysis was carried out by LM; detailed clinical data and materials for molecular studies were provided by AHE and MD; the paper was written by AHE, SM and DT; the study was designed and coordinated by DT and MD. All authors read, critically revised and approved the final manuscript.

#### Funding

The publication of this article was supported by Università Cattolica del Sacro Cuore (Milan, Italy). This work was supported by PRIN Grant 2017A5TXC3 (Italy).

#### Availability of data and materials

Data obtained during this study are included in the article.

#### Ethics approval and consent to participate

Informed consent was obtained from the study participants. This manuscript reports the description of a subject who presented with CDS clinical symptoms and his parents. No experiments were performed and no hypothesis were tested for this study. This case report does not constitute systematic research, therefore no ethics approval was necessary.

#### Consent for publication

Written informed consent was obtained from patient for publication of this Short report and any accompanying images.

#### Competing interests

The authors declare that they have no competing interest.

#### Author details

<sup>1</sup>Department of Dermatology, Baskent University Faculty of Medicine, Adana Hospital, Adana, Turkey. <sup>2</sup>Laboratory of Cellular Biochemistry and Molecular Biology, CRIBENS, Catholic University of the Sacred Heart, pz Buonarroti 30, 20145 Milan, Italy. <sup>3</sup>Department of Psychology, Catholic University of the Sacred Heart, Largo Gemelli 1, 20123 Milan, Italy. <sup>4</sup>Department of Pharmaceutical Sciences, University of Piemonte Orientale, Novara, Italy.

Received: 4 October 2019 Accepted: 23 December 2019

Published online: 28 December 2019

#### References

- Missaglia S, Coleman RA, Mordente A, Tavian D. Neutral Lipid Storage Diseases as Cellular Model to Study Lipid Droplet Function. *Cells*. 2019; 8 pii: E187.
- Tavian D, Colombo R. Improved cytochemical method for detecting Jordans' bodies in neutral-lipid storage diseases. *J Clin Pathol*. 2007;60:956–8.
- Nur BG, Gencpinar P, Yuzbasoglu A, Emre SD, Mihci E. Chanarin-Dorfman syndrome: genotype-phenotype correlation. *Eur J Med Genet*. 2015;58:238–42.
- Gupta N, Gothwal S, Satpathy AK, Missaglia S, Tavian D, Das P, Timila D, Kabra M. Chanarin Dorfman syndrome: a case report with novel nonsense mutation. *Gene*. 2016;575:359–62.
- Durdu M, Missaglia S, Moro L, Tavian D. Clinical and genetic characterization of a Chanarin Dorfman syndrome patient born to diseased parents. *BMC Med Genet*. 2018;19:88.
- Lefevre C, Jobard F, Caux F, Bouadjar B, Karaduman A, Heilig R, Lakhdar H, Wollenberg A, Verret JL, Weissenbach J, Ozguc M, et al. Mutations in CGI-58, the gene encoding a new protein of the esterase/lipase/thioesterase subfamily, in Chanarin-Dorfman syndrome. *Am J Hum Genet*. 2001;69(5): 1002–12.
- Missaglia S, Valadares ER, Moro L, Fagundes E, Roque R, Giardina B, Tavian D. Early onset of chanarin-dorfman syndrome with severe liver involvement in a patient with a complex rearrangement of ABHD5 promoter. *BMC Med Genet*. 2014;15:32.
- Tavian D, Missaglia S, Redaelli C, Pennisi EM, Invernici G, Wessalowski R, Maiwald R, Arca M, Coleman RA. Contribution of novel ATGL missense mutations to the clinical phenotype of NLS-D: a strikingly low amount of lipase activity may preserve cardiac function. *Hum Mol Genet*. 2012;21: 5318–28.
- Ohno Y, Nara A, Nakamichi S, Kihara A. Molecular mechanism of the ichthyosis pathology of Chanarin-Dorfman syndrome: stimulation of PNPLA1-catalyzed ω-O-acylceramide production by ABHD5. *J Dermatol Sci*. 2018;92:245–53.
- Ujihara M, Nakajima K, Yamamoto M, Teraishi M, Uchida Y, Akiyama M, Shimizu H, Sano S. Epidermal triglyceride levels are correlated with severity of ichthyosis in Dorfman-Chanarin syndrome. *J Dermatol Sci*. 2010;57:102–7.
- Pujol RM, Gilaberte M, Toll A, Florensa L, Lloreta J, González-Enseñat MA, Fischer J, Azon A. Erythrokeratoderma variabilis-like ichthyosis in Chanarin-Dorfman syndrome. *Br J Dermatol*. 2005;153:838–41.
- Wang D, Chong VC, Chong WS, Oon HH. A review on Pityriasis Rubra Pilaris. *Am J Clin Dermatol*. 2018;19:377–90.
- Israeli S, Pessach Y, Sarig O, Goldberg I, Sprecher E. Beneficial effect of acitretin in Chanarin-Dorfman syndrome. *Clin Exp Dermatol*. 2012;37:31–3.
- Methre ST, Godbole RR, Nayar PS, Manchanda RV. Dorfman-ghanarin syndrome: a case report. *Indian J Hematol Blood Transfus*. 2012;28:50–3.
- Angelini C, Pennisi E, Missaglia S, Tavian D. Metabolic lipid muscle disorders: biomarkers and treatment. *Ther Adv Neurol Disord*. 2019;12: 1756286419843359.
- Pennisi EM, Arca M, Bertini E, Bruno C, Cassandrini D, D'amico A, Garibaldi M, Gragnani F, Maggi L, Massa R, Missaglia S, et al. Neutral lipid storage diseases: clinical/genetic features and natural history in a large cohort of Italian patients. *Orphanet J Rare Dis*. 2017;12:90.
- Aggarwal S, Maras JS, Alam S, Khanna R, Gupta SK, Ahuja A. Novel nonsense mutation of ABHD5 in Dorfman-Chanarin syndrome with unusual findings: a challenge for genotype-phenotype correlation. *Eur J Med Genet*. 2012;55: 173–7.

#### Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more [biomedcentral.com/submissions](https://biomedcentral.com/submissions)

