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CASE REPORT

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Identification of a pathogenic *SMCHD1* variant in a Chinese patient with bosma arhinia microphthalmia syndrome: a case report

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Abstract

Background Bosma arhinia microphthalmia syndrome (BAMS; MIM603457) is a rare genetic disorder, predominantly autosomal dominant. It is a multi-system developmental disorder characterized by severe hypoplasia of the nose and eyes, and reproductive system defects. BAMS is extremely rare in the world and no cases have been reported in Chinese population so far. Pathogenic variants in the *SMCHD1* gene (MIM614982) cause BAMS, while the underlying molecular mechanisms requires further investigation.

Case presentation In this study, a Chinese girl who has suffered from congenital absence of nose and microphthalmia was enrolled and subsequently submitted to a comprehensive clinical and genetic evaluation. Whole-exome sequencing (WES) was employed to identify the genetic entity of thisgirl. A heterozygous pathogenic variant, NM_015295, c.1025G > C; p. (Trp342Ser) of *SMCHD1* was identified. By performing very detailed physical and genetic examinations, the patient was diagnosed as BAMS.

Conclusion This report is the first description of a variant in *SMCHD1* in a Chinese patient affected with BAMS.Our study not only furnished valuable genetic data for counseling of BAMS, but also confirmed the diagnosis of BAMS, which may help the management and prognosis for this patient.

Keywords Bosma arhinia microphthalmia syndrome, *SMCHD1*, Whole-exome sequencing, Arhinia

Introduction

Arhinia, a congenital anomaly characterized by the total absence of the nose, is an exceedingly rare malformation with fewer than 100 cases reported to date [1]. This malformation can manifest as an isolated condition or may be accompanied by ocular defects and hypogonadotropic hypogonadism, which together form a potentially life-threatening triad known as Bosma arhinia microphthalmia syndrome (BAMS; MIM603457) [2]. BAMS is a rare genetic disorder, predominantly autosomal dominant. Arhinia is believed to arise from the failure of fusion between the maxillary and lateral nasal processes and the associated abnormal fusion of the cribriform plate during embryonic development [3]. Although the pathogenesis

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Table 1 Phenotypic Features of the patient with BAMS

Gender	Age	Consanguinity	Nose	Eyes	Reproductive system	Growth	Psychomotor development
Female	9 Y	Unknown	Complete arhinia	Microphthalmia; Normal eyesight	Normal	Normal	Normal

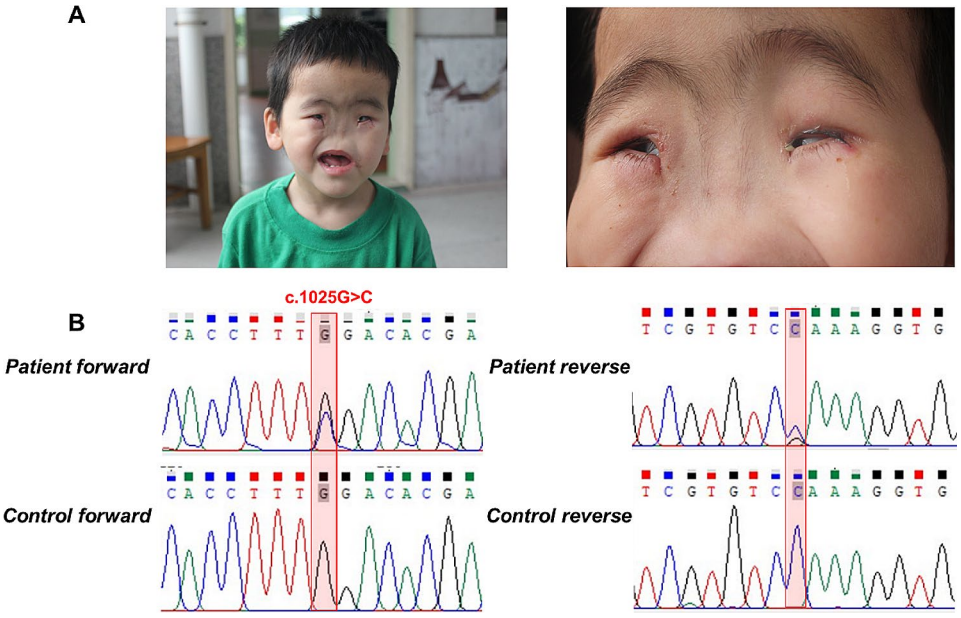

Fig. 1 The clinical and sequencing data of this patient. (**A**) Clinical features of this patient, including complete absence of nose and microphthalmia. Consent was obtained to publish patient images. (**B**) Sanger DNA sequencing chromatogram detected a heterozygous missense variant (NM_015295, c.1025G > C; p.Trp342Ser) of *SMCHD1* gene in the patient

of this condition is presumed to be genetic, the etiology of this severe abnormality remains unknown.

Structural Maintenance of Chromosomes Flexible Hinge Domain Containing 1 (*SMCHD1*, MIM614982), located in chromosome 18p11.32, encodes a 2005 amino acid protein. SMCHD1 is an atypical member of the SMC protein family, containing a C-terminal SMC hinge domain and an N-terminal ATPase domain [4–6]. SMCHD1 was previously shown to act as an epigenetic regulator of autosomal and X-linked genes that plays critical roles during development [7, 8]. In situ hybridization data has indicated regional expression of Smchd1 in the nasal cavity in E14.5 mice, and transcriptional profiling of mouse postnatal olfactory epithelium has revealed that Smchd1 is specifically expressed in immature olfactory sensory neurons [9, 10].

SMCHD1 function is highly relevant to human disease, including BAMS and facioscapulohumeral muscular dystrophy type 2 (FSHD2; MIM158901) [11]. Through a combination of whole-exome, whole-genome and targeted sequencing in an international cohort of 40 arhinia patients, Shaw et al. discovered a high prevalence (84%) of missense variants in the gene *SMCHD1* [1, 10]. Notably, truncation variants of *SMCHD1* have been found to be common in FSHD2, a rare, oligogenic form of muscular dystrophy [1, 12]. Nevertheless, little is currently known about the genes responsible for causing BAMS or the molecular mechanisms by which *SMCHD1* achieves its various functions.

Here, we reported the first case with BAMS in Chinese population. WES and Sanger sequencing were applied to identify the pathogenic genes of this girl.

Case presentation

Clinical manifestations

The patient, a 9-year-old girl, was born with congenital arhinia and raised at Guangzhou City Social Welfare Institute. Her physical and intellectual development was similar to that of normal peers but was too young to be sure of hypogonadotropic hypogonadism (Table 1). However, the combination of congenital nasal deformities and microphthalmia in this patient suggested a diagnosis of BAMS (Fig. 1A). Moreover, by performing a very detailed physical examination, it was determined that her visual refraction muscle strength and tone were all functioning normally. Unfortunately, we could not exclude a later onset of a muscle phenotype as first signs of FSHD are usually only visible at the end of the second decade of life. However, an MRI examination was not conducted due to the patient's preferences. Considering that the

patient had no signs of muscular dystrophy, the diagnosis of FSHD2 was ruled out for now. Based on these findings, it was concluded that the patient was suffering from BAMS.

Genetic analysis

Genomic DNA was extracted from the patient by QIAamp DNA Blood Mini Kit (250) (Qiagen, Valencia, CA, U.S.A). However, parental DNA of the patient were not available due to the unknown parentage. The WES analysis was mainly conducted in the Novogene Bioinformatics Institute (Beijing, China). All variants were formatted under HGVS nomenclature [13]. After data filtration (supplementary material), a pathogenic heterozygous variant of *SMCHD1*, NC_000018.10:g.2694678G>C, NM_015295.3:c.1025G>C, NP_056110.2:p.(Trp342Ser), was identified. Sanger sequencing was further performed to validate this variant (Fig. 1B). This variant results in a change in the amino acid sequence of the ATPase active structural domain of the SMCHD1 protein, which may lead to altered ATPase activity and hence affect the characteristics of the resulting protein. It was predicted to be "disease causing" by MutationTaster, SIFT and PolyPhen2, and also was not found in the 1,000 Genome Browser, The ExAC Browser, the Exome Variant Server and GnomAD. According to ACMG standards and guidelines [14], this variant was categorized as pathogenic (PM1, PM2, PS3, PP3, PP5) (Table 2). Although this variant was reported in a previous research, the pathogenic analysis was absent [10]. We further performed bioinformatics analysis of the variant. Alignment of SMCHD1 amino acid sequences was highly conserved across species (Fig. 2B). Also, ConSurfServer software predicted that the affected amino acid was slightly conserved (Fig. 2C). Furthermore, there reveals a difference between the normal and mutant protein models constructed with SWISS-MODEL software, which affect highly conserved residues and hence affect the SMCHD1 protein features (Fig. 2D). Considering the clinical phenotypes and genetic results, the patient was diagnosed as BAMS.

Discussion

In this study, we reported a Chinese girl who has suffered from congenital arhinia and microphthalmia. The patient was adopted by Guangzhou City Social Welfare Institute so that the genomic information of her parents is unknown. WES was conducted to identify the causative genes of this patient. A pathigenic heterozygous missense variant of *SMCHD1*, NM_015295: c.1025G>C: p. (Trp342Ser) was identified in the patient. Sanger sequencing subsequently confirmed this variant. Thus, the patient was further diagnosed as BAMS. Our study further confirms that variants of *SMCHD1* are associated with BAMS.

Consistent with prior researches, the p.(Trp342Ser) variant identified in this study is located in the ATPase activity domain of SMCHD1 protein. As shown in the Fig. 2A, variations in the affected residue of the SMCHD1 protein may lead to different alterations and subsequently impact its function. Although the underlying pathogenesis necessitates further investigation, a detailed functional analysis such as testing of the methylation level of the D4Z4 repeat as done for other BAMS-associated mutations, of the SMCHD1 protein with this heterozygous missense variant is recommended. Such an analysis may provide additional insights into the pathogenic mechanism of BAMS.

There is a lack of clarity on the cause of the different clinical outcomes of pathogenic *SMCHD1* variants. Although previous studies have highlighted the involvement of these pathogenic *SMCHD1* variants in FSHD2, recent reports have also implicated them in the pathogenesis of BAMS [1, 10]. To the best of our knowledge, no individual afflicted with BAMS has yet to exhibit clinical characteristics reminiscent of FSHD2. It has been reported that missense variants in *SMCHD1* were considerably prevalent in BAMS cases, while loss of function variants have been more frequently associated with the manifestation of FSHD2. As reported in published literature, all BAMS-related variants were missense alleles, localized to exons 3–13 of *SMCHD1*, which encodes the ATPase domain of SMCHD1 [1, 10, 15]. And yet in FSHD2, missense, nonsense, and deletion variants spanned the entire *SMCHD1* coding region [1, 11, 16]. Therefore, despite the overwhelming evidence that BAMS is caused by gain-of-function variants in *SMCHD1*, the loss-of-function versus gain-of-function dichotomy between FSHD2 and BAMS appears to be one-sided. It is more likely that both BAMS and FSHD2 are triggered by complex oligogenic or multifactorial mechanisms that only partially intersect at the level of *SMCHD1* [16, 17]. This highlights the need to probe the molecular mechanisms underlying how variations within

Table 2 The SMCHD1 variant identified by WES for the affected individual

Gene	CHR	RefSeq ID	AA Alteration	Genotype	Function	Database	MutationTaster	CADD	ACMG
SMCHD1	18p11.32	NM_015295	c.1025G>C; p.Trp342Ser	Het	Missense	Unknown variant	Disease causing	6.708873, 32	PM1 + PM2 + PS3 + PP3 + PP5 (Pathogenic)

CHR Chromosome, AA Amino Acids, Het Heterozygous, PVS Pathogenicity very strong, PM Pathogenicity moderate. The database included 1000G, ExAC and Exome Variant Server

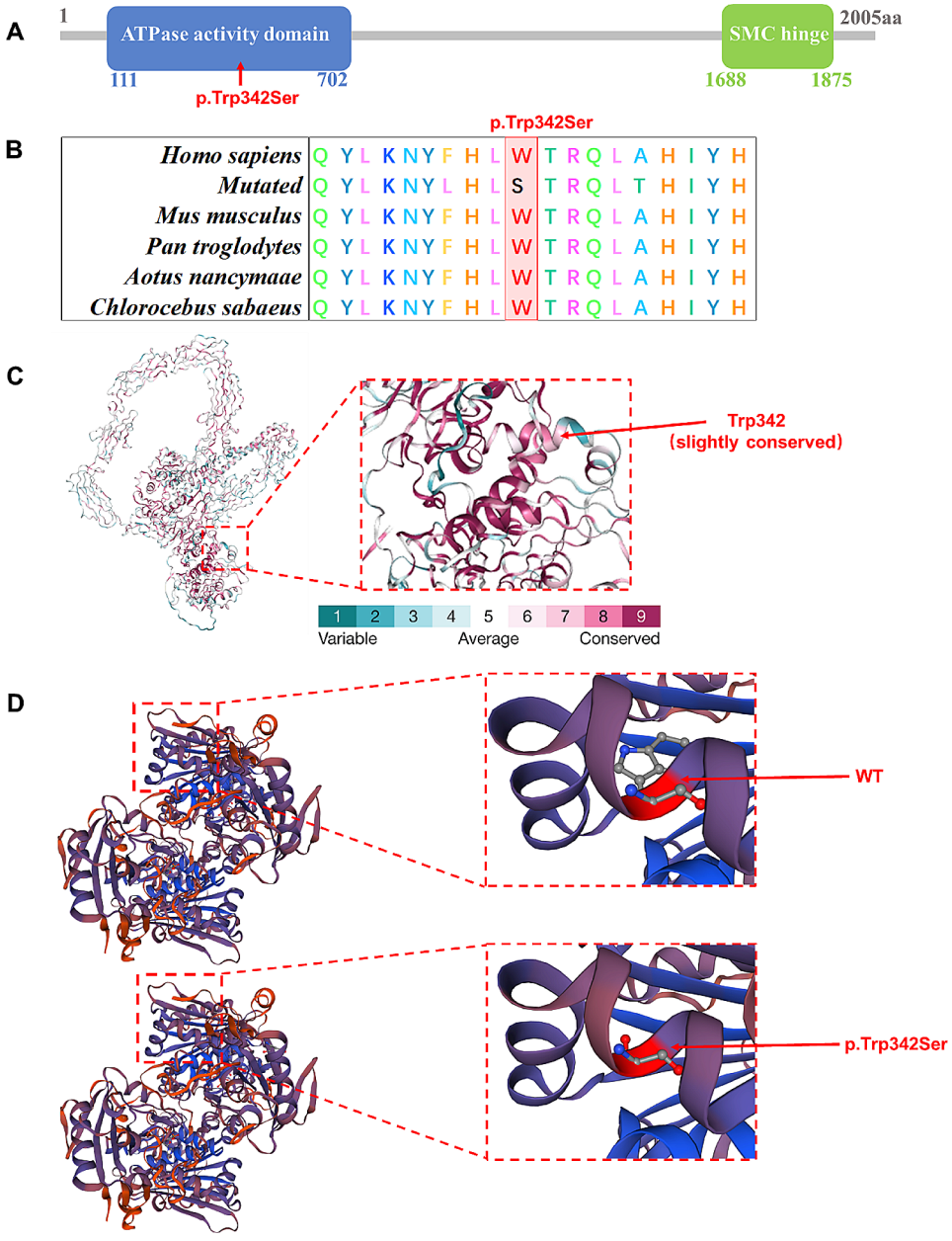

Fig. 2 The bioinformatics analysis of this variant. (**A**) The positions of this missense variant in SMCHD1 identified in the patient. Domains in SMCHD1 are indicated with different colored squares. (**B**) Alignment of multiple SMCHD1 protein sequences across species. Letters in red show the W342 site is evolutionarily conserved. (**C**) The conservation analysis of the W342 site amino acids was predicted by ConSurf Server software. (**D**) Structure prediction of wild type and mutant SMCHD1 protein. The wild type SMCHD1 (SMCHD1-WT) protein structure and the p.Trp342Ser mutant SMCHD1 (SMCHD1-p.Trp342Ser) protein structure were predicted by SWISS-MODEL online software

the same gene can give rise to distinct phenotypic manifestations. Furthermore, A previous study has proposed that the localisation of missense variants within the ATPase structural domain of SMCHD1 may account for the disparate phenotypic outcomes observed in BAMS and FSHD2 cases [18]. However, to fully decipher the impact of *SMCHD1* variants on its function, further studies incorporating structural and biochemical characterizations are warranted.

BAMS is a clinically heterogeneous disease, with a phenotypic spectrum spanning from the absence of craniofacial features to nasal hypoplasia and complete arhinia, rendering clinical diagnosis a challenging task. The findings in Xenopus model indicated that variants implicated in BAMS are associated with a reduced eye diameter, and in severe cases, anophthalmia may ensue [10, 15]. By identifying the relevant cell type (cranial placode) and mechanism of cell death (DUX4), Kaoru et al. proposed

that in patients with arhinia and related nasal phenotypes (e.g., anosmia and nasal hypoplasia), nasal morphogenesis is completely or partially arrested when *SMCHD1* missense mutations unleash DUX4 toxicity in cranial placode cells, leading to cell death [19]. Those findings suggested that SMCHD1 plays an important role in the development of craniofacial organs.

In conclusion, we used WES to explore the genetic entity in a Chinese girl who has suffered from congenital absence of nose and microphthalmia. A heterozygous missense variant, NM_015295:c.1025G>C:p.(Trp342Ser), of *SMCHD1* was identified in the patient with BAMS. Here we reported the first case with BAMS in Chinese population. Our investigation not only offers crucial genetic counseling data to the affected individual, but also furnishes characteristic clinical images of BAMS, which can aid in the accurate diagnosis of the disease in conjunction with genetic analyses.

Abbreviations

BAMS	Bosma arhinia microphthalmia syndrome
WES	Whole Exome Sequencing
SMCHD1	Structural Maintenance of Chromosomes Flexible Hinge Domain Containing 1
FSHD2	Facioscapulohumeral muscular dystrophy type 2
ACMG	American College of Medical Genetics and Genomics
PVS	Pathogenicity very strong
PM	Pathogenicity moderate
1000G	The 1000 Genomes Project

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12920-024-01907-6.

Supplementary Material 1

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Author contributions

ZP-T designed the study. ZP-T and YF-Y gathered clinical information from the patient. JL-Y wrote the main manuscript text and prepared the figures. JL-Y, H-G, ZZ-Y and XH-X performed the sequencing, as well as analyzed, and interpreted the WES data. ZP-T revised the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, and the carers of the patient gave informed consent.

Consent for publication

Written informed consent was obtained from the individual's legal guardian for the publication of any potentially identifiable images or data included in this article. A copy of the written consent is available for review by the editor of this journal.

Competing interests

The authors declare no competing interests.

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