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Hb H Disease Caused by Uniparental Disomy: First Report of the $\alpha^{T-Saudi}\alpha$ Mutation in the Chinese Population

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To the editor.

Thalassemia is one of the most common monogenic disorders worldwide.¹ It shows an autosomal recessive Mendelian pattern of inheritance, which means that thalassemia patients should be homozygous or compound heterozygous of pathogenic mutations, and their parents should be heterozygotes of mutations.² However, in some families with thalassemia, the patient has only one parent who is a mutation carrier, which is discrepant with the Mendelian law. Other than non-paternity, this situation can be caused by two mechanisms: (i) A de novo mutation occurring in the child.^{2,3} In this status, the child is generally a compound heterozygote. (ii) Uniparental disomy (UPD), in which the child inherits a pair of chromosomes from only one parent. In this scenario, the child is always a homozygote. There are three patterns of UPD: a patient can have two identical copies of the same chromosome (uniparental isodisomy, iUPD), two homologous chromosomes from the same parent (uniparental heterodisomy, hUPD), or a mixture of iUPD and hUPD. A recent study estimated the overall prevalence of UPD at birth to be approximately 1/2000.⁴

Here, we reported a Chinese female with Hb H disease who was homozygous for the $\alpha^{T-Saudi}\alpha$ mutation as a result of UPD. We explored a possible mechanism for its generation as it displayed a relatively complex structure with uniparental maternal heterodisomy and isodisomy. Moreover, while the $\alpha^{T-Saudi}\alpha$ mutation is a well-known ethnic-specific variant in the Arabian population,⁵ this is the first time it has been detected in the Chinese population.

The patient (II-4) was a pregnant 25-year-old woman who lived in Guangdong Province in South China, a region of high thalassemia prevalence.⁶ However, she was born in Shanxi Province in northwest China, a region where thalassemia is not endemic. During the obstetrical examination process, she was diagnosed with Hb H disease on the basis of moderate anemia with

microcytosis and hypochromia, a reduced HbA₂ level, and the existence of the presence of Hb H and Hb Bart's in peripheral blood cells (**Table 1**). She had no symptoms of splenomegaly, hepatomegaly, jaundice or iron deficiency, and she did not receive any blood transfusions. A routine test for common mutations associated with α -thalassemia in a local hospital in Guangdong showed negative results. Her family (**Figure 1A**) was referred to our laboratory for further analysis. Written informed consent was obtained in accordance with the Declaration of Helsinki. A detailed family history was collected, and the pure Chinese origin of the family was confirmed at least 5 generations back, with no record of migration marriage.

The hematological data from this family are shown in **Table 1**. The patient's mother and three siblings all presented microcytic hypochromic parameters with normal hemoglobin levels and reduced or borderline Hb A₂ levels, consistent with the clinical characteristics of the α -thalassemia trait, while the father showed a normal phenotype. Sanger sequencing (**Figure 1B** and **Supplementary Figure 1**) revealed the presence of the $\alpha^{T-Saudi}\alpha$ mutation (*HBA2*: c.*94A>G) in this family, including a homozygous in the patient and a heterozygous result in her mother and three siblings, whereas a normal result in her father. $\alpha^{T-Saudi}\alpha$ is a non-deletional α -thalassemia mutation occurring in the poly-A signal of the $\alpha 2$ -globin gene (AATAAA>AATAAG). Previous research⁵ demonstrated that homozygotes for this mutation present with typical Hb H disease (Hb ranges: 74–97 g/L and Hb H level:7.5%-27.2%). Therefore, the α -globin genotype data of all family members are in accordance with their phenotypes. Puzzlingly, however, the patient is a homozygote, while her father does not carry this mutation. Multiplex ligation-dependent probe amplification (MLPA) analysis excluded the existence of deletions (data not shown). Therefore, we speculated that the homozygous state might have been caused by UPD. Genome-wide

single nucleotide polymorphism (SNP) genotyping analysis was performed using the Illumina Human Omni Zhonghua-8 BeadChip in the proband and her parents. UPD analysis of the patient was carried out using genotype data in a trio. The results (**Figure 1C**) showed

that there were two maternal heterodisomic regions and two maternal isodisomic regions on chromosome 16. Therefore, we confirm that this case of Hb H disease was caused by maternal UPD.

Table 1. Summary of hematological and genotype data.

Subject	Gender/age	Hb (g/L)	MCV (fL)	MCH (pg)	Hb A ₂ (%)	Hb H (%)	Hb Bart's (%)	α-Genotype
I-1	M/53	172	90.8	27.8	2.7	-	-	αα/αα
I-2	F/52	128	70.7↓	22.3↓	2.8	-	-	α ^{T-Saudi} α/αα
II-1	F/31	124	68.2↓	21.5↓	2.2↓	-	-	α ^{T-Saudi} α/αα
II-2	M/29	154	74.9↓	24.1↓	2.7	-	-	α ^{T-Saudi} α/αα
II-3	F/28	108↓	62.5↓	18.5↓	2.1↓	-	-	α ^{T-Saudi} α/αα
II-4	F/25	90↓	58.5↓	17.9↓	0.7↓	21.6↑	2.1↑	α ^{T-Saudi} α/α ^{T-Saudi} α

Hb: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; -: not detected. Reference value: Hb 130-175 g/L for males, 115-150 g/L for females; MCV 80-100 fL; MCH 27-34 pg; Hb A₂ 2.5-3.5%; Hb H 0%; Hb Bart's 0%.

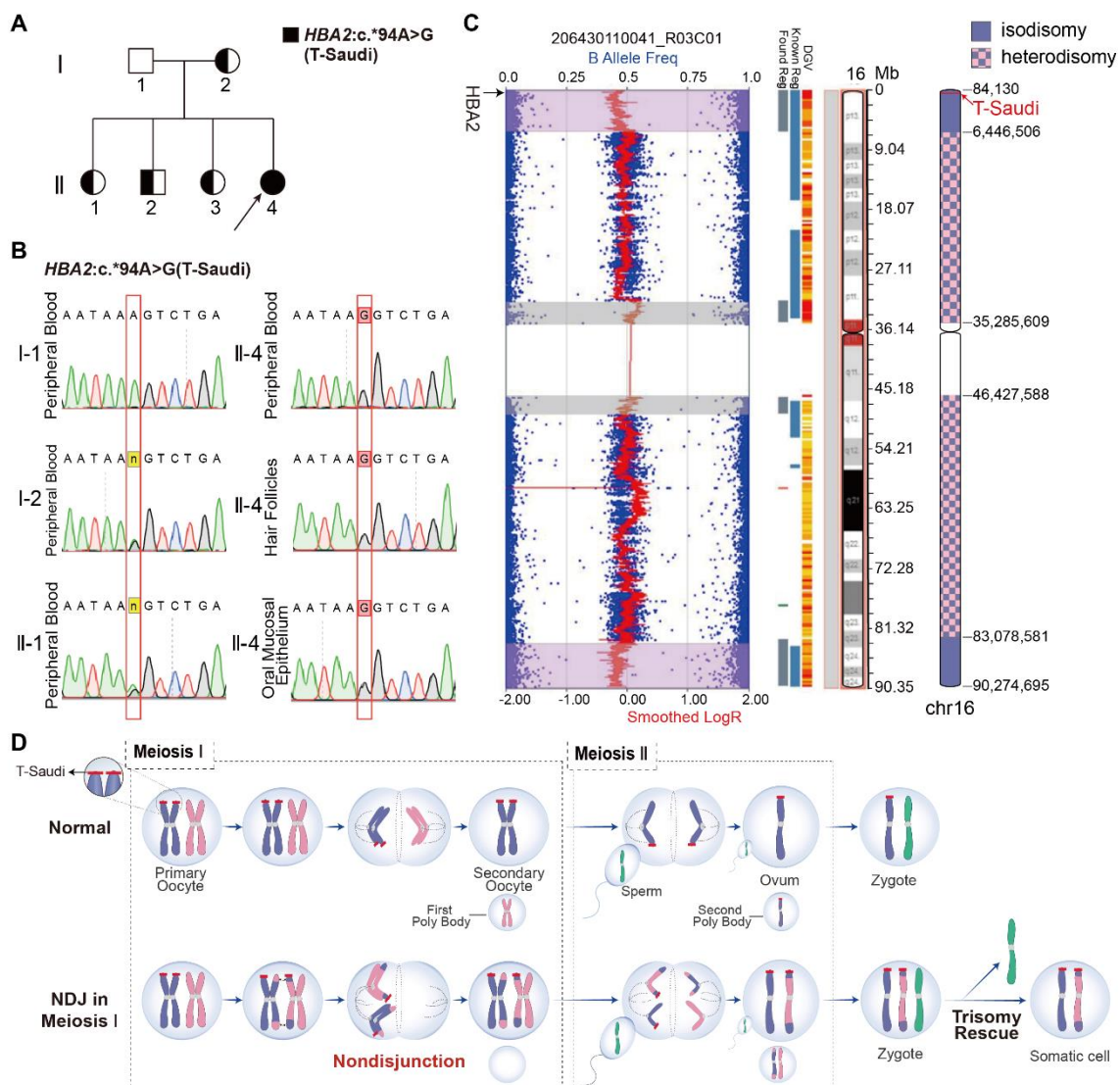


Figure 1. The patient is homozygous for the $\alpha^{T-Saudi}\alpha$ mutation, and her homozygous state is due to maternal UPD. (A) The pedigree of the family. The arrow indicates the patient (II-4.) (B) Sanger sequencing results for samples of peripheral blood cells (I-1, I-2, II-1 and II-4) as well as oral mucosal epithelium and hair follicles (II-4). The red box indicates the mutation site. (C) The SNP array result revealed maternal uniparental isodisomy and heterodisomy on chromosome 16. Smooth Log R ratio (red line) shows the SNP intensity and represents the allelic copy number. B-allele frequency (blue dots) displays genotyping information. (D) Possible mechanism to explain the formation of the UPD pattern in II-4. NDJ: nondisjunction.

To date, a total of 12 cases of hemoglobinopathy caused by UPD have been reported (**Supplementary Table 1**). Seven cases, comprising six cases of thalassemia major and one case of abnormal hemoglobin, were due to UPD on chromosome 11 encompassing the β -globin gene. Five cases, comprising three cases of Hb Barts hydrops foetalis, one case of Hb H disease (our case) and one case of abnormal hemoglobin, were due to UPD on chromosome 16 encompassing the α -globin gene.⁷⁻¹⁰ When comparing our data with previously published data, we inferred that our case is only one with iUPD at the distal p (short arm) and distal q (long arm) segment and hUPD at the pericentromeric region. In addition, among the 5 cases of UPD related to α -globin, 2 of them mentioned that possible mechanism leading to UPD is nondisjunction error at maternal meiosis I. Therefore, we further investigated the mechanism of UPD formation in our case.

Mechanisms that result in UPD include trisomy rescue, gamete complementation, monosomy rescue and somatic recombination.¹¹ Monosomy rescue leads to complete isodisomy, and gamete complementation produces complete heterodisomy. Considering that our case has partial heterodisomy and partial isodisomy, the above two mechanisms can be ruled out. Somatic recombination always results in mosaicism. Analysis of DNA from our patient's hair follicle and oral mucosal cell DNA was consistent with the testing of her blood cells, which excludes the existence of mosaicism in

somatic cells and indicates that trisomy rescue is the only possible mechanism.

Moreover, our case had heterodisomic and isodisomic regions, suggesting the occurrence of homologous recombination events at multiple sites and segregation error events in meiosis.¹² Nondisjunction error can occur in both meiosis I and meiosis II. Based on this situation, recombination occurs at distal short arm and distal long arm fragments if nondisjunction takes place in meiosis I. In contrast, if nondisjunction takes place in meiosis II, recombination occurs at pericentromeric fragments. Since the pericentromeric region is often suppressed for recombination, nondisjunction is very unlikely to occur in meiosis II. Therefore, we propose that nondisjunction can occur during meiosis I and then due to trisomy rescue, resulting in uniparental disomy, as shown in **Figure 1D**.

In previously published data, all known individuals carrying this mutation (**Supplementary Table 2**) were distributed either in countries in the Middle East or in countries with a large Arabian population (**Figure 2**). Previous studies have confirmed that the $\alpha^{T-Saudi}\alpha$ mutation is one of the major α -thalassemia determinants in the population of the Arabian Peninsula.⁵ Therefore, this mutation can be regarded as an ethnic-specific variant in the Arabian population. However, it is the first identification of the $\alpha^{T-Saudi}\alpha$ mutation in the Chinese population, and we speculated that it is population migration that results in ethnic-specific mutations spread to other populations.

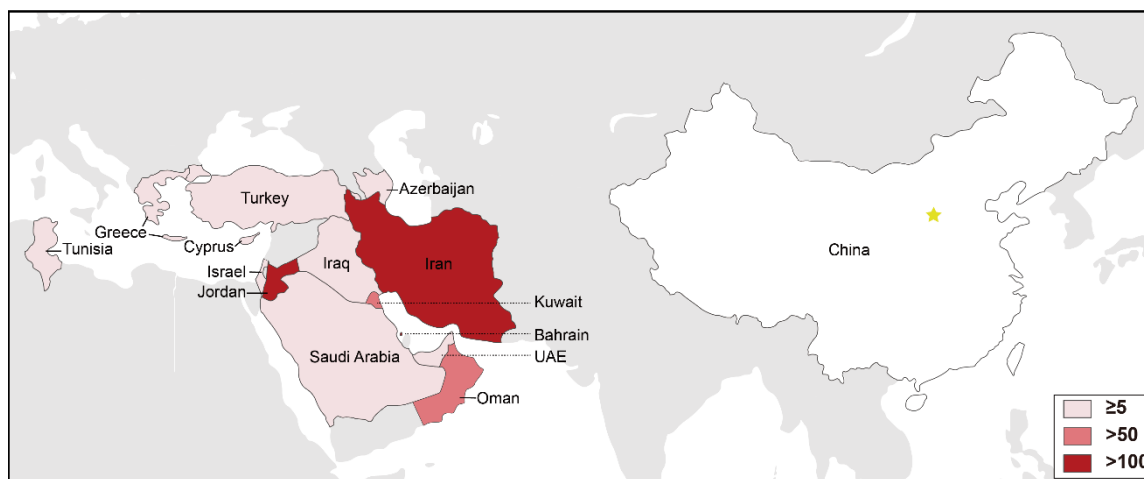


Figure 2. Geographic distribution of known individuals carrying the $\alpha^{T-Saudi}\alpha$ mutation. The yellow star represents the case in this study.

In summary, we have identified the detailed UPD pattern in this patient with Hb H disease and have analyzed the mechanism by which it originated. These data may be valuable for providing accurate diagnoses in similar cases. In addition, this case could be used as new evidence substantiating the gene flow between the Chinese population and another population in ancient times.

List of abbreviations and HGVS name of the variants. UPD, uniparental disomy; iUPD, uniparental isodisomy; hUPD, uniparental heterodisomy; SNP, single nucleotide polymorphism; MLPA, multiplex ligation-dependent probe amplification; NDJ, nondisjunction; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin. $--_{MED}$: including $--_{MED} I$ (NG_000006.1:g.24664_41064del16401) and $--_{MED} II$ (NG_000006.1:g.10864_40864del30001).

The reference sequence of HBA2 is from NC_000016.10, GRCh38.

[9/?q=HBA2:%20c.*94A%3EG&m=NM_000517.6\(HBA2\):c.*94A%3EG](https://www.ncbi.nlm.nih.gov/nuccore/9/?q=HBA2:%20c.*94A%3EG&m=NM_000517.6(HBA2):c.*94A%3EG)

Ethics approval and consent to participate. This study was approved by the Ethics Committee of Zhuhai Women and Children's Hospital (number IRB-2020081401). We certify that the study was performed in accordance with the 1964 Declaration of Helsinki and later amendments. Written informed consent was obtained from all the participants prior to enrollment in this study.

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Consent for publication. Written informed consent was obtained from the patient and her parents for publication of this Case report and any accompanying images.

CRedit authorship contribution statement. Ge Wang, Yuqiu Zhou: Resources. Hongting Xie: Conceptualization, Data curation, Methodology, Writing – original draft. Jun Zhang, Peng Huang, Min Liang: Formal analysis, DinaZhu, Qianqian Zhang: Validation. Xuan Shang: Conceptualization, Writing – review and editing.

Availability of data and materials. The data in the current study are available within the article and its supplementary materials. The variant has been submitted to ClinVar under Accession: VCV000375749.61 (<https://www.ncbi.nlm.nih.gov/clinvar/variation/37574>)

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