All-in-one solution for single gene disorders with diverse mutational spectrum

Thalassemia

Background

Thalassemia is a group of inherited hemolytic disorders characterized by reduced or absent production of globin chains, involving a spectrum of globin gene defects (SNVs, InDels, recombination, CNVs, etc.). It significantly impacts regions in Southeast Asia, the Mediterranean, and the Middle East.

Thalassemia carries **a high risk of missed cases** with routine blood tests

Sequential hematological screen MCV + MCH and HbA2		
	Sensitivity	Specificity
α-thalassemia	16.53%	97.24%
β-thalassemia	73.74%	96.10%

Information derived from reference [1]

Due to the complex nature of thalassemia genetic variants, conventional molecular analysis methods cannot provide a comprehensive solution, potentially leading to missed diagnoses, misdiagnoses, or delays in the diagnostic process.

Conventional PCR-based methods, such as PCR-RDB and Gap-PCR, typically focus on a limited range of major or common variants. Although next-generation sequencing (NGS) expands the coverage of variants, its ability to detect structural variants and rare deletions is still constrained by the technical limitations of short-read sequencing.

Comprehensive Analysis of Thalassemia Alleles (CATSA)

shapes the future of thalassemia screening

With single molecule real-time (SMRT) sequencing, a comprehensive solution for thalassemia genetic analysis has been developed — CATSA. This innovative approach simplifies the diagnostic process into a single solution, eliminating the need for multiple tests and significantly reducing diagnostic time.

Patent (China): ZL 202110329821.X

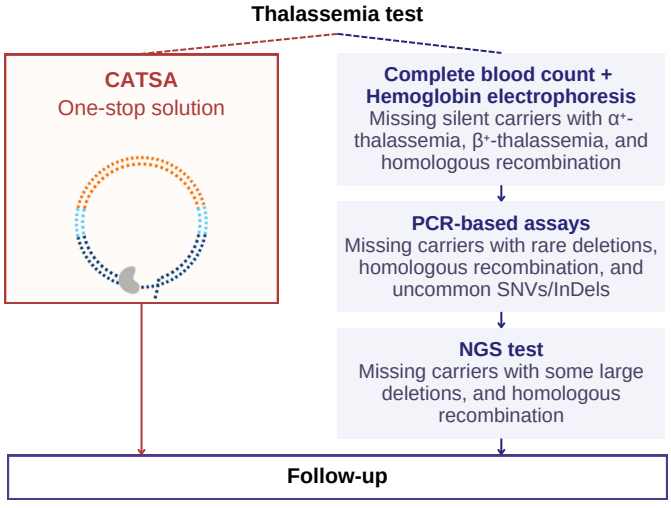
Technology: Single molecule real-time (SMRT) sequencing
Platform: PacBio Vega, Sequel II, and Sequel IIe system
Sample type: Dried blood spot (DBS), gDNA, blood, buccal swab, and amniotic fluid
Operation hour: 77 hours
(starting from sample preparation to report generation)

- Covers >2,200 variants to reliably identify rare carriers across high-diversity and isolated communities
- Determines *cis*/*trans* configuration to resolve phasing ambiguity, ensuring accurate zygosity reporting in multi-mutation cases

Expert consensus officially endorsed as a diagnostic and screening tool by the Medical Genetics Branch of the Chinese Medical Doctor Association (2025) [2]

	PCR-based assays				Sequencing	
	Gap-PCR	PCR-RDB	§Melting curve	+MLPA	NGS	**CATSA**
Deletions	✓	✓	✓	✓	✓	✓
Point Mutations	×	✓	✓	×	✓	✓
Homologous Recombinations	×	×	×	✓	×	✓

\+ Applicable only for large deletion
§ Applicable only for common deletions & point mutations for α-thalassemia as well as common point mutations for β-thalassemia



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Comprehensive Analysis of Thalassemia Alleles

Category	Basic panel	Expanded panel	Comprehensive panel	Prenatal comprehensive panel
α-thalassemia	30 Deletions	30 Deletions	30 Deletions	30 Deletions
	4 Homologous recombination	4 Homologous recombination	5 Homologous recombination	5 Homologous recombination
	80 *HBA1* SNVs/InDels; 139 *HBA2* SNVs/InDels	80 *HBA1* SNVs/InDels; 139 *HBA2* SNVs/InDels	80 *HBA1* SNVs/InDels; 139 *HBA2* SNVs/InDels	80 *HBA1* SNVs/InDels; 139 *HBA2* SNVs/InDels
β-thalassemia	28 Deletions	28 Deletions	28 Deletions	28 Deletions
	340 *HBB* SNVs/InDels	340 *HBB* SNVs/InDels	340 *HBB* SNVs/InDels	340 *HBB* SNVs/InDels
Hemoglobinopathy	--	324 *HBA1* SNVs/InDels; 386 *HBA2* SNVs/InDels	324 *HBA1* SNVs/InDels; 386 *HBA2* SNVs/InDels	324 *HBA1* SNVs/InDels; 386 *HBA2* SNVs/InDels
		694 *HBB* SNVs/InDels	694 *HBB* SNVs/InDels	694 *HBB* SNVs/InDels
Others	--	--	160 *HBD* SNVs/InDels	160 *HBD* SNVs/InDels
			102 SNVs/InDels in the *HBA1/2* and *HBB* genes that are low frequency, not clearly associated	*HBA1/2* and *HBB* variants that are low-frequency, not clearly associated

Performance backed by published data

The new gold standard

In a prospective multicenter study, CATSA demonstrated 100% accuracy in detecting pathogenic thalassemia variants among 1,159 individuals with abnormal hemoglobin parameters. [3] Additionally, in a separate study with 1,122 individuals, CATSA outperformed NGS by identifying and correcting discordant results with 100% accuracy, driving a 2.28% improvement in overall detection yield. [4]

Improved pregnancy outcomes

In 278 at-risk amniotic fluid samples, CATSA outperformed PCR-based assays by accurately identifying all genotypes, and correcting the predicted phenotype severity in 8 fetuses. Notably, 2 cases were reclassified from thalassemia trait to intermedia and one from intermedia to trait. [5]

Case study: A couple undergoes thalassemia carrier screening before giving birth

1. Post-test genetic counselling: low-risk and regular follow-up

	Mother	Father
Complete blood count	Anemia (Low MCH and MCV)	Normal
PCR test	β-thalassemia carrier ($\alpha\alpha/\alpha\alpha$; $\beta^{CD71/72}/\beta^{N}$)	α-thalassemia carrier ($-\alpha^{3.7}/\alpha\alpha$; β^{N}/β^{N})

2. However, their baby shows severe thalassemia symptoms at 8 months old.

- PCR results show baby genotype is concordant with parental genotypes
- Parents are also different types of thalassemia carrier

Question: Why is the baby exhibiting thalassemia symptoms when the genotype suggests he should not?

3. After having an advanced CATSA test, it is clear that **the incorrect results from the father led to misdiagnosis**.

	Father	Baby
PCR test	$-\alpha^{3.7}/\alpha\alpha$; β^{N}/β^{N}	$-\alpha^{3.7}/\alpha\alpha$; $\beta^{CD71/72}/\beta^{N}$
CATSA	$-\alpha^{3.7}/\alpha\alpha\alpha^{anti3.7}$; β^{N}/β^{N}	$-\alpha^{3.7}/\alpha\alpha\alpha^{anti3.7}$; $\beta^{CD71/72}/\beta^{N}$

This complex case of β-thalassemia heterogeneous ($\beta^{CD71/72}/\beta^{N}$) with α-triplicate ($\alpha\alpha\alpha^{anti3.7}$) enlarge the imbalance of α/β globin ratio, leading to β-thalassemia intermedia.

- The previous tests cannot detect α-triplicate ($\alpha\alpha\alpha^{anti3.7}$)
- This couple has 25% chance of getting β-thalassemia intermedia offspring

References: [1] He J, Song W, Yang J, et al. Next-generation sequencing improves thalassemia carrier screening among premarital adults in a high prevalence population: the Dai nationality, China. *Genet Med*. 2017;19(9):1022-1031. [2] Consortium For The Application Of Single-Molecule Real-Time Sequencing For The Precision Medicine And Control Of Thalassemia, Group Of Clinical Genetics Medical Genetics Branch Of Chinese Medical Doctor Association, Wu L. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2025;42(4):385-396. [3] Liang Q, Gu W, Chen P, et al. A More Universal Approach to Comprehensive Analysis of Thalassemia Alleles (CATSA). *J Mol Diagn*. 2021;23(9):1195-1204. [4] Huang R, Liu Y, Xu J, et al. Back-to-Back Comparison of Third-Generation Sequencing and Next-Generation Sequencing in Carrier Screening of Thalassemia. *Arch Pathol Lab Med*. 2024;148(7):797-804. [5] Liang Q, He J, Li Q, et al. Evaluating the Clinical Utility of a Long-Read Sequencing-Based Approach in Prenatal Diagnosis of Thalassemia. *Clin Chem*. 2023;69(3):239-250.
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