



Hereditary Disorders in Moderate-Altitude Taif, Saudi Arabia: Molecular Genetic Evidence and a Community Genomics Research Agenda

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Abstract: - Taif is situated at approximately 1,800 m above sea level, below the conventional threshold for high altitude but sufficiently elevated to justify investigation of oxygen-sensitive phenotypes. Its community-genetics profile is also shaped by consanguinity, family-specific founder variants, and a substantial burden of autosomal-recessive disease. This critical narrative review separates three related questions: the hereditary-disorder spectrum relevant to Saudi and Arab populations, the molecular biology of adaptation to severe high-altitude hypoxia, and the currently untested possibility that moderate-altitude residence modifies disease expression in Taif. Evidence from Saudi genomic programs supports family-based exome or genome sequencing, homozygosity mapping, segregation analysis, and population-specific variant interpretation. Priority clinical groups include neurodevelopmental disorders, inherited retinal disease, hemoglobinopathies, inborn errors of metabolism, mitochondrial disease, and congenital anomalies. Studies of Tibetan, Andean, and Ethiopian populations establish the importance of hypoxia-inducible factor signaling, particularly EPAS1 and EGLN1, but these findings cannot be transferred directly to Taif. Direct local human genomic evidence remains sparse, and the available Taif study of oxidative stress used an animal model rather than a resident population. We propose a staged community genomics program integrating a regional registry, standardized phenotyping, family-centered sequencing, ancestry-aware analyses, a lower-altitude Saudi comparison group, and clinically governed return of results. This approach could improve diagnosis, carrier screening, counseling, and precision prevention while testing whether moderate altitude modifies hematologic, cardiopulmonary, or metabolic phenotypes.

Keywords: Taif; community genetics; consanguinity; hereditary disorders; genomic medicine; moderate altitude.



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Introduction

Community genetics links genomic knowledge with population-level prevention, equitable service delivery, and informed reproductive and clinical choices (ten Kate et al. 2010). This perspective is particularly relevant in Saudi Arabia, where extended family structures, consanguineous unions, and regional founder variants can concentrate rare pathogenic alleles. The resulting disease burden spans neurodevelopmental syndromes, inherited retinal disorders, hemoglobinopathies, inborn errors of metabolism, mitochondrial disease, and congenital anomalies (Alkuraya 2014; Monies et al. 2019).

Taif is located on the eastern slopes of the Sarawat Mountains at approximately 1,800 m above sea level (Saudipedia 2026). That elevation is below the conventional 2,500 m threshold generally used for high altitude, so Taif should be described as a moderate-altitude setting rather than a classic high-altitude population. The distinction is not semantic: the magnitude of hypobaric hypoxia, developmental acclimatization, and evolutionary selection varies with elevation, ancestry, duration of residence, and individual physiology (Stobdan et al. 2008; Beall 2014).

Three scientific questions must therefore be kept separate. First, which hereditary disorders and molecular variants are relevant to Saudi and Arab populations? Second, which pathways mediate human adaptation to severe high-altitude hypoxia? Third, does long-term residence at moderate altitude modify penetrance or severity of hereditary disease in Taif? Evidence is substantial for the first two questions but limited for the third. This review critically synthesizes the applicable evidence, identifies the limits of inference, and proposes a community genomics agenda designed to generate direct Taif-specific data.

Review approach and scope

This article is a critical narrative review rather than a systematic review or meta-analysis. It was developed through targeted bibliographic verification and thematic synthesis rather than a prospectively registered, protocolized, exhaustive search. The evidence was organized around population structure, Saudi and Arab genomic medicine, hypoxia biology, diagnostic methods, and implementation. Bibliographic details and digital object identifiers were verified against PubMed, PubMed Central, and publisher records through July 2026. The review does not claim exhaustive coverage, quantitative completeness, or pooled prevalence estimates for the population of Taif.

Evidence was interpreted according to directness. Human studies conducted in Taif were considered most directly applicable; national Saudi and wider Arab genomic studies were used to characterize disease architecture and diagnostic practice; and research in Tibetan, Andean, and Ethiopian populations was used only to explain oxygen-sensing mechanisms. Candidate-gene associations were treated cautiously because small samples, population stratification, and limited replication can produce unstable findings. Large sequencing cohorts, deeply phenotyped families, and replicated functional observations were given greater interpretive weight.

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Taif as a community-genetics setting

Saudi and Arab populations are genetically heterogeneous, with regional, tribal, and family-level substructure. Consanguinity increases autozygosity and the probability that both parents carry the same rare pathogenic allele, while founder effects can create marked local differences in carrier frequency (Tadmouri et al. 2009; Hamamy et al. 2011; Tadmouri et al. 2014). These characteristics can increase recessive disease burden but also make family-based gene discovery unusually informative. National averages may obscure local clusters, so a Taif program should combine population-based surveillance with pedigree-centered recruitment.

Large Saudi sequencing initiatives have demonstrated the value of first-tier clinical exome sequencing in a highly consanguineous population. They have identified recurrent and novel disease alleles, improved diagnostic yield, and shown that population-specific frequency data are essential for distinguishing pathogenic variants from benign regional polymorphisms (Abouelhoda et al. 2016; Monies et al. 2019). The broader development of genomic medicine in Saudi Arabia supports integration of laboratory diagnosis with counseling, registries, and preventive services rather than treating sequencing as an isolated test (Alkuraya 2014).

Table 1 distinguishes the evidence domains relevant to Taif and the claims each can legitimately support. This framework prevents mechanistic findings from severe high-altitude populations from being presented as proof of Taif-specific adaptation.

Table 1 Evidence domains and limits of inference for a Taif community-genetics review

Evidence domain	Primary contribution	Legitimate inference for Taif	Major limitation
Taif human studies	Local clinical, environmental, and biomarker observations	Direct description of sampled Taif residents	Few genomic studies; representativeness may be limited
Saudi genomic cohorts	Disease spectrum, diagnostic yield, recurrent variants, population frequencies	National context and methods for family-based diagnosis	Cannot substitute for Taif-specific sampling
Arab population genetics	Consanguinity, founder effects, population substructure	Rationale for local carrier and founder-variant studies	Substantial heterogeneity within and between populations
Classic high-altitude populations	HIF biology, selection signals, adaptive phenotypes	Mechanistic hypotheses for oxygen-sensitive traits	No direct proof of Taif-specific adaptation
Diagnostic-method literature	Test selection, variant classification, clinical validation	Standards for a Taif genomic service	Does not estimate local disease frequency

Molecular evidence relevant to hereditary disorders

Neurodevelopmental disorders are a major indication for genomic testing in consanguineous families. Intellectual disability, developmental delay, epilepsy, microcephaly, spasticity, and syndromic congenital anomalies may arise from hundreds of recessive, dominant, X-linked, or de novo mechanisms. Clinical utility depends on detailed phenotyping, segregation, copy-number analysis, and periodic reinterpretation. The Human Phenotype Ontology provides a standardized vocabulary that can improve computational matching and reproducibility across clinics (Kohler et al. 2021).

Inherited retinal disorders are similarly heterogeneous and may follow recessive, dominant, or X-linked inheritance. Autozygome-guided exome sequencing has been effective in consanguineous retinal-dystrophy families and has identified both established pathogenic variants and candidate genes (Abu-Safieh et al. 2013). A Taif registry should pair genomic findings with ophthalmic imaging, electroretinography, age at onset, and longitudinal visual outcomes because molecular diagnosis informs prognosis, family testing, and eligibility for gene-specific interventions.

Hemoglobinopathies are a priority because they are prevalent in Saudi Arabia, molecularly tractable, and biologically linked to oxygen transport. Premarital screening data demonstrate a continuing national burden of sickle-cell and thalassemia traits, while molecular studies show regional heterogeneity in alpha-thalassemia genotypes (Alsaeed et al. 2018; Alhuthali et al. 2023). Recent private-

sector laboratory data also document the distribution of abnormal hemoglobins across Saudi Arabia (Raslan et al. 2026). Taif studies should distinguish carrier frequency from disease prevalence and integrate complete blood counts, high-performance liquid chromatography or electrophoresis, molecular confirmation, transfusion history, oxygen saturation, iron status, and clinical severity.

Inborn errors of metabolism and mitochondrial disorders are disproportionately represented among recessive diseases and may present across the life course. Genomic testing is most informative when paired with biochemical measurements such as amino acids, acylcarnitines, organic acids, lactate, and disease-specific metabolites. Mitochondrial diagnosis requires attention to heteroplasmy, tissue selection, maternal inheritance, and nuclear-mitochondrial interactions (Larsson and Clayton 1995). Moderate hypoxia could plausibly aggravate disorders of oxidative metabolism, but this hypothesis remains untested in Taif.

Congenital anomalies may result from chromosomal abnormalities, copy-number variants, single-gene disorders, teratogenic exposures, or multifactorial mechanisms. A comprehensive pathway should therefore retain chromosomal microarray and cytogenetic testing where indicated, rather than relying on exome sequencing alone. Prenatal, neonatal, pediatric, and dysmorphology services are key entry points for surveillance and genomic referral. Table 2 summarizes the priority disease groups, preferred diagnostic approaches, and Taif-specific data needs.

Table 2 Priority hereditary-disorder groups and Taif-specific diagnostic needs

Priority group	Typical architecture	Preferred assessment	Taif-specific research need
Neurodevelopmental disorders	Recessive, de novo, X-linked, copy-number, structural	Trio/family exome or genome; chromosomal microarray when indicated	Standardized developmental phenotype, segregation, periodic reinterpretation
Inherited retinal disease	Recessive, dominant, X-linked; high locus heterogeneity	Panel, exome, or genome with copy-number analysis	Imaging, electroretinography, longitudinal outcome registry
Hemoglobinopathies	HBB, HBA1/HBA2, structural hemoglobins, modifier loci	CBC, HPLC/electrophoresis, targeted molecular confirmation	Carrier frequency, molecular spectrum, oxygen-sensitive severity modifiers
Metabolic disorders	Enzyme and transporter defects; mainly recessive	Biochemical screening plus exome/genome and functional confirmation	Rapid diagnostic pathway for acute and neonatal presentations
Mitochondrial disease	mtDNA and nuclear mitochondrial genes	mtDNA sequencing plus nuclear analysis; tissue-aware testing	Heteroplasmy, tissue selection, altitude-related phenotype study
Congenital anomalies	Chromosomal, copy-number, monogenic, multifactorial	Karyotype, microarray, exome/genome according to phenotype	Integrated prenatal-neonatal surveillance and dysmorphology assessment

Hypoxia biology and the limits of extrapolation

The hypoxia-inducible factor (HIF) pathway is the principal transcriptional system for cellular oxygen sensing. Under normoxia, prolyl hydroxylase domain proteins hydroxylate HIF- α subunits, enabling recognition by the von Hippel-Lindau complex and proteasomal degradation. Under hypoxia, hydroxylation decreases, HIF- α accumulates, dimerizes with HIF- β , and activates genes involved in erythropoiesis, angiogenesis, metabolism, iron handling, and vascular regulation (Bigham and Lee 2014).

Human high-altitude adaptation is population-specific. Tibetan populations maintain relatively low hemoglobin concentrations despite hypoxia and show strong selection signals at EPAS1 and EGLN1. Andean populations more often exhibit increased hemoglobin concentration, whereas Ethiopian groups display different combinations of hematologic and physiologic traits (Beall 2014; Bigham 2016). These contrasts demonstrate that similar environmental pressure can produce different evolutionary solutions and that no single high-altitude genotype can be assumed.

For Taif, HIF-pathway genes are rational candidates for investigation but not grounds for presuming adaptation. A candidate-gene-only study would be inadequate. Exome or genome sequencing should be combined with ancestry-aware population analysis, standardized oxygen-sensitive phenotypes, environmental exposure data, and replication. The appropriate hypothesis is that common or rare variants in oxygen-sensing, erythropoietic, nitric-oxide, and

mitochondrial pathways may modify measurable traits in some residents.

Direct evidence remains limited. A study labeled as investigating high-altitude living in Taif evaluated oxidative stress and histologic changes in rats housed at approximately 2,600 m; it did not sequence human residents or establish a population-genetic adaptation (Soliman et al. 2022). The study is useful as an experimental indication that altitude-related exposure can influence oxidative biology, but it cannot support claims about allele frequencies, selection, or hereditary-disease modification in Taif.

Hematologic traits are the most practical initial phenotype for a modifier study. Hemoglobin concentration, hematocrit, reticulocyte count, erythropoietin, iron indices, oxygen saturation, and markers of hemolysis should be analyzed together because each can alter the interpretation of the others. In hemoglobinopathy carriers and affected patients, genotype, transfusion exposure, hydroxyurea use, renal function, and cardiopulmonary disease are important covariates. Cross-sectional comparisons alone would not establish causation; longitudinal measurements and lower-altitude comparisons would be stronger.

Cardiopulmonary phenotypes also warrant careful study. Pulmonary function, echocardiographic estimates, sleep-disordered breathing, exercise tolerance, smoking, obesity, and chronic lung or heart disease may influence oxygen-sensitive outcomes more strongly than modest altitude exposure. Associations with nitric-oxide or HIF-pathway variants should therefore be pre-specified, adjusted

for ancestry and clinical covariates, and replicated rather than reported as isolated candidate-gene findings.

Pregnancy and early life provide another clinically relevant setting because placental function, fetal growth, congenital anomalies, and neonatal adaptation are sensitive to oxygen delivery. A future birth cohort could integrate maternal hemoglobinopathy status, anemia, placental and fetal-growth measures, neonatal oxygenation, and genetic diagnosis. Such a design should avoid ecological comparisons and should separate inherited disease from obstetric, nutritional, and socioeconomic determinants.

Diagnostic and translational framework

The diagnostic yield of sequencing depends on the quality of pre-analytic characterization. Each participant should have a three-generation pedigree, documentation of consanguinity, structured clinical examination, Human Phenotype Ontology terms, and relevant laboratory and

imaging data. The suspected inheritance model should guide but not unduly restrict analysis, because de novo, compound-heterozygous, X-linked, mitochondrial, and structural mechanisms can coexist in consanguineous families.

Test selection should be phenotype-driven. Targeted testing is efficient for a known familial or validated founder variant. Disease-focused panels offer high coverage for coherent phenotypes but may become outdated. Exome sequencing is effective for heterogeneous Mendelian disease, and genome sequencing improves structural-variant, copy-number, repeat-expansion, and noncoding assessment, although cost and interpretation remain constraints. Chromosomal microarray remains useful when genome sequencing is unavailable, especially for developmental delay and congenital anomalies (Abu-Amro and Kondkar 2013). Table 3 compares the principal modalities.

Table 3 Molecular diagnostic modalities applicable to hereditary disorders in Taif

Modality	Best use	Strengths	Key limitations
Targeted variant testing	Known familial or validated founder variant	Rapid, inexpensive, straightforward counseling	Misses other diagnoses and phenocopies
Disease-focused gene panel	Clinically coherent disorder	High depth; manageable interpretation	Panel obsolescence; limited discovery
Whole-exome sequencing	Heterogeneous Mendelian disease	Broad coding assessment; useful in consanguineous families	Incomplete noncoding and structural-variant detection
Whole-genome sequencing	Undiagnosed disease or research cohort	Most comprehensive; improved structural and copy-number detection	Higher cost, data burden, and interpretation complexity
Chromosomal microarray	Developmental delay and congenital anomalies	Established copy-number detection	Misses most sequence variants
Mitochondrial DNA analysis	Suspected mitochondrial disease	Detects mtDNA variants and heteroplasmy	Tissue dependence; nuclear genes require separate analysis

Runs of homozygosity can prioritize candidate regions, but homozygosity alone is not evidence of pathogenicity. Variant interpretation should integrate allele frequency, molecular consequence, gene-disease validity, segregation, phenotype concordance, and functional evidence. Classification should follow professional standards, with explicit evidence documentation and scheduled reinterpretation as databases evolve (Richards et al. 2015). Population-specific frequency resources are essential because variants that appear rare globally may be common benign alleles in Saudi families.

Clinically actionable findings should be confirmed by an accredited laboratory when required. Return of results

must include pre-test and post-test counseling, explanation of uncertainty, family implications, and a plan for reanalysis. A curated regional variant registry linked to national resources would reduce false-positive interpretation, identify recurrent founder variants, and support cascade testing and locally validated carrier screening.

Bioinformatic and analytical considerations

Quality control should be designed for the characteristics of the recruited population. Sample identity, sex concordance, contamination, coverage, variant-call quality, and batch effects require routine monitoring. In

families with parental relatedness, kinship estimates and runs of homozygosity should be compared with the reported pedigree. Ancestry principal components and relatedness-aware models are necessary because standard case-control analyses can produce biased associations when participants are closely related or when geographic substructure is ignored.

For Mendelian diagnosis, evidence from segregation and phenotype concordance is generally more informative than single-variant association statistics. Rare-variant analyses in larger cohorts may use gene-based burden or kernel tests, but variant grouping, allele-frequency thresholds, functional annotations, and primary outcomes should be specified before analysis. Modifier studies require formal power calculations based on allele frequency, expected effect size, phenotype variance, relatedness, and the multiple-testing burden. Exploratory findings should be clearly labeled and independently replicated.

Reproducibility requires version-controlled pipelines, documented software and database versions, stable phenotype dictionaries, and retention of quality-control metrics and interpretation decisions. A regional multidisciplinary review board should record the evidence used for each classification and the reason for any subsequent reclassification. De-identified aggregate results and analysis code should be shared when consent, privacy safeguards, and national governance permit. This infrastructure is necessary for reliable longitudinal reinterpretation rather than one-time reporting.

Clinical and public-health translation

The most immediate clinical benefit of a Taif program would be earlier diagnosis for families with unresolved hereditary disease. A coordinated referral network should connect primary care, pediatrics, neurology, ophthalmology, hematology, metabolic medicine, cardiology, obstetrics, neonatology, and clinical genetics. Multidisciplinary case conferences can reduce fragmented testing and align phenotype review, laboratory interpretation, counseling, and follow-up. Turnaround-time, diagnostic-yield, and management-change indicators should be monitored as service-quality measures.

Locally validated recurrent variants may support cost-effective cascade testing and focused carrier screening, but the design of a screening panel requires more than a list of frequent alleles. Each target should represent a serious and well-defined condition, have an analytically reliable test, and be linked to confirmatory diagnosis and counseling. Residual risk must be communicated because a negative targeted panel does not exclude all pathogenic variants. Panel content should be re-evaluated periodically as the Taif and national Saudi variant resources expand.

Precision prevention includes reproductive options but is not limited to them. Molecular diagnosis can trigger disease-specific surveillance, avoidance of metabolic or pharmacologic triggers, anticipatory management, and testing of at-risk relatives. Public-health evaluation should measure equitable access, uptake, psychological effects, time to diagnosis, changes in management, and health outcomes. Programs should avoid coercive messaging and should distinguish voluntary informed choice from administrative screening requirements.

Proposed community genomics program for Taif

A credible Taif program should proceed from governance and registry development to discovery, validation, and implementation. The first phase should establish a community advisory mechanism, ethics-approved protocols, consent language for familial findings and data sharing, a standardized phenotype dictionary, and interoperable laboratory procedures. Recruitment should prioritize families with unresolved neurodevelopmental disease, inherited retinal disease, hemoglobinopathies, metabolic or mitochondrial phenotypes, and congenital anomalies.

The discovery phase should use family-centered exome or genome sequencing with copy-number, structural-variant, and mitochondrial analysis where indicated. Segregation and orthogonal confirmation should be built into the workflow. For recurrent variants, haplotype and autozygosity analyses can test founder effects. Diagnostic yield should be reported by phenotype, family structure, degree of consanguinity, and test modality rather than as a single undifferentiated percentage.

Testing altitude-related modifiers requires a separate design. Taif participants should be compared with harmonized lower-altitude Saudi groups using consistent recruitment, ancestry assessment, and phenotype measurement. Core variables should include resting and exertional oxygen saturation, complete blood count, erythropoietin, iron status, pulmonary function, sleep-disordered breathing, smoking, obesity, cardiopulmonary disease, and relevant medications. Pre-specified interaction models and independent replication are essential because small candidate-gene analyses are especially vulnerable to false-positive results.

Translation should begin only after analytical and clinical validation. Recurrent severe variants may support targeted cascade testing, premarital or preconception counseling, prenatal or preimplantation options where ethically and legally available, newborn testing, or condition-specific surveillance. Screening panels must be reviewed periodically as the regional database grows. Table 4 presents a staged implementation roadmap with measurable outputs.

Table 4 Proposed staged community genomics program for Taif

Phase	Core activities	Primary outputs	Indicative timing
1. Governance and protocol	Community advisory input, ethics, consent, SOPs, phenotype dictionary, data governance	Approved protocol, trained sites, audit-ready workflow	0-6 months
2. Pilot clinical genomics	Recruit 100-200 families; deep phenotyping; exome/genome; segregation	Feasibility, diagnostic yield, workflow refinement	6-18 months
3. Expanded cohort	Multi-site recruitment; local variant registry; founder analyses	Recurrent variants, disease-group estimates, validated registry entries	18-42 months
4. Modifier study	Lower-altitude comparison group; oxygen-sensitive phenotypes; ancestry-aware analysis	Replicated gene-environment estimates	24-54 months
5. Clinical validation	Orthogonal confirmation, functional follow-up, multidisciplinary review	Clinically reportable variant set	30-60 months
6. Implementation	Cascade testing, counseling pathways, validated carrier screening, outcome monitoring	Screening performance, service uptake, health outcomes	48-72 months

Ethical, legal, and social considerations

Genomic research in extended families raises privacy risks because a result in one participant may reveal information about relatives, lineages, or geographically clustered groups. Consent should address familial implications, secondary findings, recontact, data sharing, cross-border transfer, and future reinterpretation. Community engagement should precede recruitment and continue through dissemination. Reporting must avoid stigmatizing tribes, families, or regions, and population labels should be used only when scientifically justified.

Carrier screening should be voluntary, clinically validated, and accompanied by equitable access to confirmatory testing and nondirective counseling. Pediatric testing should prioritize disorders with childhood relevance or clear clinical benefit. Data governance should define access, retention, linkage, and audit procedures. Aggregate findings should be returned to participating communities in accessible formats to support trust and accountability.

Limitations

This review is narrative and cannot provide the completeness or reproducibility of a prospectively registered systematic review. The literature is heterogeneous and contains limited direct human genomic evidence from Taif. National Saudi data may not capture local founder effects, while classic high-altitude studies are mechanistically relevant but geographically indirect. No pooled prevalence or effect estimates are presented. The proposed research agenda is therefore a framework for generating evidence,

not proof that altitude currently explains hereditary-disease patterns in Taif.

Conclusion

The hereditary-disorder landscape relevant to Taif is most plausibly shaped by consanguinity, family-specific founder effects, and regionally distributed pathogenic variants. Moderate-altitude residence may modify selected hematologic, cardiopulmonary, or metabolic phenotypes, but direct evidence of Taif-specific genetic adaptation is insufficient. The scientifically defensible position is to treat altitude as a testable modifier rather than a demonstrated cause.

A community genomics program integrating deep phenotyping, family-based exome or genome sequencing, homozygosity mapping, segregation, population-specific variant interpretation, and a governed regional registry could deliver immediate diagnostic benefits while testing longer-term gene-environment hypotheses. Such evidence would support locally validated carrier screening, counseling, cascade testing, and precision prevention for families in Taif and comparable Saudi communities.

The proposed agenda also has value beyond a single city. A reproducible Taif model could clarify how genomic services should be adapted for Saudi regions that differ in elevation, ancestry, settlement history, and access to specialist care. Its success should be judged not only by the number of variants identified, but also by shorter diagnostic journeys, appropriate changes in management, informed

family decisions, and equitable delivery of counseling and confirmatory testing.

Statements and Declarations

Author contributions

Yahya Hamed Alzahrani conceived and coordinated the review and drafted the manuscript. Faten A. S. Alsulaimany, Mohd Rehan, Maged Mostafa Mahmoud, Mohamed Morsi M. Ahmed, Tagreed S. AlGhamdi, and Waleed Altaweli contributed to literature evaluation, clinical and molecular interpretation, and critical revision. All authors reviewed and approved the final manuscript.

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Competing interests

Yahya Hamed Alzahrani, Faten A. S. Alsulaimany, Mohd Rehan, Maged Mostafa Mahmoud, Mohamed Morsi M. Ahmed, Tagreed S. AlGhamdi, and Waleed Altaweli declare that they have no conflict of interest.

Ethics approval

This article does not contain any studies with human or animal subjects performed by any of the authors.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

No datasets were generated or analyzed during the current study.

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