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Advancing Trisomy 21 Diagnosis in Mali through Fluorescence *In Situ* Hybridization

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Abstract

Down syndrome, caused by an extra copy of chromosome 21, is the most common constitutional chromosomal disorder and a leading cause of intellectual disability worldwide. In low-resource settings such as Mali, limited access to cytogenetic testing often results in diagnoses based primarily on clinical features. The need to implement a rapid cytogenetic method such as fluorescence *in situ* hybridization (FISH) to diagnose trisomy 21 in Mali is imperative. We prospectively enrolled twelve individuals presenting clinical features of Down syndrome and carried out FISH on their samples using a chromosome 21–specific RUNX1 probe. In parallel, we performed conventional cytogenetic analysis using DAPI banding to assess chromosomal structural characterization. Interphase FISH analysis was successful in all 12 samples (100%) and consistently showed three RUNX1 signals per nucleus, confirming trisomy 21 in all patients, with no evidence of mosaicism above the assay detection threshold. Among the 11 cases with analyzable metaphases, combined DAPI banding and FISH identified nine cases of free trisomy 21 and two cases of Robertsonian translocation rob (21; 21). This study shows, for the first time in Mali, the successful use of FISH as a rapid and reliable diagnostic tool for trisomy 21. Its integration with conventional cytogenetics improves diagnostic precision, allows detection of structural rearrangements, and compensates for the limitations of metaphase-dependent analyses, providing a scalable model for genetic diagnostics in resource-limited settings.

Keywords

Down Syndrome, Trisomy 21, Cytogenetic, FISH, Mali

1. Introduction

Down syndrome is the most common chromosomal disorder associated with intellectual disability, with an estimated prevalence of approximately 1 in 643 live births in the United States [1]. Worldwide prevalence varies considerably, reflecting differences in genetic background, maternal age distribution, access to prenatal screening, and diagnostic reporting systems [2]. In Mali, the true prevalence of Down syndrome remains unknown due to the absence of systematic surveillance and limited access to cytogenetic diagnostic services, although the condition is frequently encountered in clinical practice.

Cytogenetically, Down syndrome results from the presence of an additional copy of chromosome 21 and occurs in three major cytogenetic forms. Free trisomy 21, caused by meiotic nondisjunction, accounts for the majority of cases. Translocation trisomy 21, most commonly involving Robertsonian translocations, represents a smaller but clinically important proportion, while mosaic trisomy 21 is characterized by the presence of both normal and trisomic cell lines. These cytogenetic subtypes have distinct implications for recurrence risk, clinical presentation, and genetic counseling, underscoring the importance of precise chromosomal characterization [2]-[5].

Clinically, individuals with trisomy 21 typically present with intellectual disability, developmental delay, and characteristic craniofacial features. The condition is frequently associated with a wide spectrum of congenital and acquired medical complications. Congenital heart defects affect approximately 40% - 50% of individuals, gastrointestinal anomalies such as duodenal atresia occur in 5% - 10% of cases, and endocrine disorders, particularly congenital hypothyroidism, are also common [2] [6] [7]. Although the underlying chromosomal abnormality is irreversible, early diagnosis enables timely multidisciplinary interventions, including physical, speech, and cognitive therapies, which can significantly improve developmental and functional outcomes [7].

Definitive diagnosis of trisomy 21 relies on cytogenetic or molecular techniques, most commonly conventional karyotyping and fluorescence *in situ* hybridization (FISH). These methods not only confirm the presence of an extra chromosome 21 but also allow precise identification of the underlying chromosomal mechanism, which is essential for clinical management and genetic counseling [2] [4]. However, in many low-resource settings, including Mali, access to such diagnostic technologies remains limited, resulting in delayed or incomplete diagnosis and suboptimal patient care [8] [9].

The present study aimed to establish and evaluate the use of FISH for the diagnosis of trisomy 21 in Mali. Implementing this cytogenetic approach represents a critical step toward strengthening national diagnostic capacity, enabling earlier detection, improving genetic counseling, and supporting more targeted clinical management.

2. Materials and Methods

2.1. Participants and Samples

Twelve individuals presenting clinical features suggestive of Down syndrome were

consecutively enrolled between January and March 2022 in the study through referrals from the Malian Association of Trisomy 21. Written informed consent was obtained from the parents or legal guardians of all participants. Inclusion criteria included characteristic craniofacial dysmorphism (e.g., upslanting palpebral fissures, epicanthic folds, flat nasal bridge), developmental delay, and/or intellectual disability. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine and Odonto-Stomatology and the Faculty of Pharmacy, University of Bamako (Approval number: 2020/129/CE/FMOS/FAPH).

For each participant, demographic information including age, sex, and place of residence was recorded. Peripheral venous blood samples (4 mL) were collected in sodium heparin-coated Vacutainer® tubes and stored at room temperature (20–25˚C) prior to cell culture on the same day.

2.2. Cell Culture and Chromosome Harvesting

For each participant, 750 µL of peripheral blood was added to 10 mL of RPMI 1640 medium supplemented with 10% fetal bovine serum, 1% Penicillin/Streptomycin, and 1% phytohemagglutinin (Thermo Fisher Scientific, Canada). Cultures were incubated at 37˚C in a humidified atmosphere containing 5% CO_2 for 72 hours. Cells were arrested at the metaphases by adding colchicine (Thermo Fisher Scientific, Canada) at a final concentration of 0.05 µg/mL for 30 minutes. Subsequently, cells were subjected to hypotonic treatment with 0.075 M of potassium chloride at 37˚C for 25 minutes. Fixation was performed using a freshly prepared of methanol: acetic acid (3v:1v) solution, applied in three sequential rounds. Fixed cells were then dropped onto clean glass microscope slides and allowed to air dry. The slides were aged at 37˚C for 24 hours prior to FISH analysis.

2.3. Fluorescence *In Situ* Hybridization

Slides were pretreated with 1 × Tris-buffered saline (1 × TBS: 20 mM Tris, 150 mM NaCl) and dehydrated through an ethanol series (80%, 90%, and 100%). After air-drying, a 10 µL hybridization mixture was applied to each slide, consisting of 1 µL of the RUNX1 probe (Agilent Technologies, Canada), targeting the *RUNX*1 gene at 21q22.12, and 9 µL of hybridization buffer. Denaturation was performed at 76˚C for 10 minutes, followed by hybridization at 37˚C for 24 hours in a humidified chamber. Post-hybridization washes were carried out in 1 × TBS with 0.05% Tween 20 at 55˚C for 5 minutes, followed by a rinse in 1 × TBS at room temperature (20˚C - 25˚C) for 2 minutes. Nuclei and chromosomes were counterstained with 4′,6-diamidino-2-phenylindole (DAPI), and slides were stored at −20˚C until microscopic analysis.

2.4. Image Acquisition and Analysis

FISH signals were visualized using an Axio Imager 2 epifluorescence microscope (Zeiss, USA) equipped with the ISIS imaging system (MetaSystems, USA). For

each sample, approximately 400 interphase nuclei and 30 metaphase spreads were analyzed. The RUNX1 probe, labeled with a green fluorochrome, was used to detect chromosome 21 copies: normal diploid cells showed two distinct green signals, while trisomic cells displayed three signals, indicating the presence of an additional copy of chromosome 21. The fluorescent signals were systematically searched for and localized within both interphase nuclei and metaphase chromosomes. An analyzable nucleus was defined as a nucleus with intact morphology, uniform DAPI staining, and clearly distinguishable fluorescent signals. All samples were independently scored by two experienced cytogeneticists in a double-blind manner. Split signals separated by less than one signal diameter were counted as a single signal. Overlapping signals were evaluated using focal plane adjustment. Signal enumeration was reviewed by a second observer when necessary. Chromosomes were identified based on DAPI banding patterns.

3. Results

The study included twelve participants (seven males and five females) with a median age of 9.5 years (range: 0.3 - 14 years) (Table 1). All individuals were referred by the Malian Association of Trisomy 21 based on clinical suspicion of Down syndrome, characterized by key phenotypic features including intellectual disability, global developmental delay, and characteristic craniofacial dysmorphisms such as upslanting palpebral fissures, a flat nasal bridge, and epicanthic folds.

Table 1. The median age of the individuals was 9.5 years, ranging from 0.3 to 14 years. Patients P11 and P12 were those carrying the Robertsonian translocation rob (21; 21) (q10; q10) associated with trisomy 21.

Individuals	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12
Sex	M	M	M	F	M	M	F	F	M	F	F	M
Age (years)	13	10	1.8	14	9	10	0.3	8	11	0.58	6	10

Trisomy 21 was confirmed in all twelve cases either by chromosomal structural analysis using DAPI banding or by RUNX1 copy number assessment with FISH. Metaphase chromosome preparations were successfully obtained in eleven of the twelve cases (91.7%). In one case (Patient P2), microcoagulation during blood collection precluded metaphase harvest. In all eleven analyzable samples, karyotypic analysis identified nine cases of free trisomy 21 (47, XX, +21 or 47, XY, +21) and two cases of Robertsonian translocations: 46, XX, rob (21; 21) (q10; q10), +21 and 46, XY, rob (21; 21) (q10; q10), +21 (Table 1). In the two cases of Robertsonian translocations, parental karyotyping revealed normal chromosomal complements in both families, suggesting that the rearrangements occurred de novo. Given the relative rarity of Robertsonian translocations, the two cases were investigated and described in greater detail in [10].

FISH analysis was first performed by testing the probe on a normal diploid control sample. Control experiments showed the expected two distinct RUNX1 signals in all 400 interphase nuclei analyzed, with no background fluorescence de-

tected. In metaphase spreads from the control sample, two signals were consistently observed at the expected 21q22.12 loci, confirming both the specificity and sensitivity of the probe (Figure 1(A)). Subsequently, FISH interphase analysis was successfully performed on the twelve patient samples, achieving a 100% success rate, including in patient P2, whose karyotype analysis was inconclusive due to the absence of metaphase spreads. All 400 interphase nuclei analyzed per patient displayed three distinct green fluorescent signals, indicating the presence of three copies of chromosome 21. No nuclei showed fewer than three signals, excluding mosaicism above the detection threshold (≥1/400 cells). These findings are consistent with non-mosaic trisomy 21 within the limits of detection of the assay. In metaphase spreads, three signals were precisely localized to 21q22.12, confirming the presence of an extra copy of chromosome 21 (Figures 1(B)-(D)).

Results from both cytogenetic approaches were fully concordant in the eleven cases for which both FISH and karyotyping results were available, consistently showing three copies of chromosome 21. In the single case lacking metaphase data, FISH alone provided definitive diagnostic confirmation.

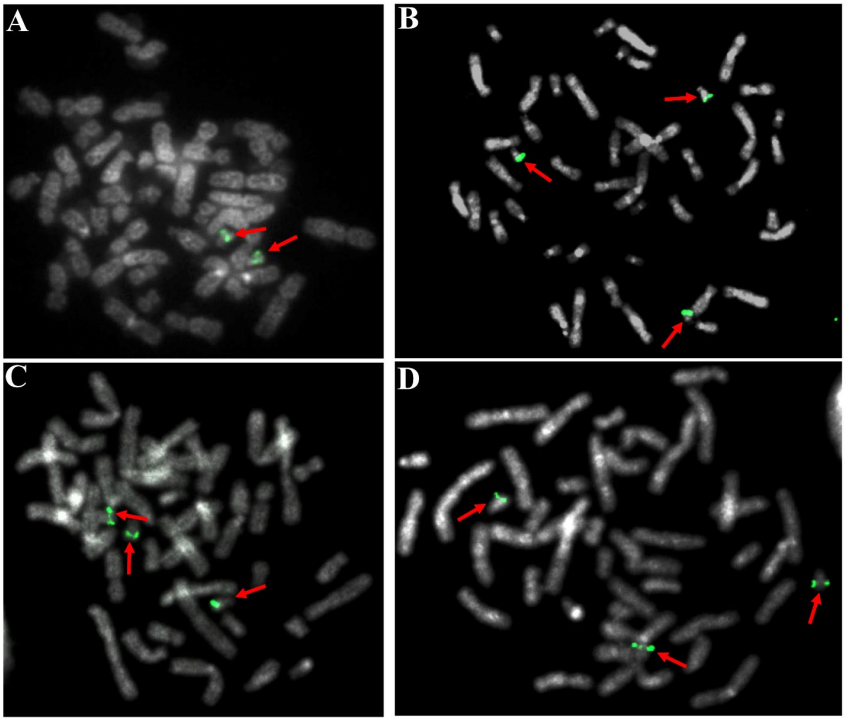

Figure 1. Representative images of fluorescence *in situ* hybridization analysis. (A) Metaphase spread from a healthy individual showing two distinct hybridization signals (indicated by red arrows) corresponding to chromosome 21. (B)-(D) Metaphase spreads from three different affected individuals showing three distinct signals on chromosome 21. In each case, the presence of three discrete hybridization signals (red arrows) confirms an additional copy of chromosome 21.

4. Discussion

This study is the first to combine conventional karyotyping and FISH for the diag-

nosis of trisomy 21 in Mali, confirming the complementarity of these methods in a cohort of twelve clinically suspected cases. Karyotyping can reveal structural and numerical chromosomal abnormalities while FISH provided high-resolution quantitation of copy number and allowed detection or exclusion of low-level mosaicism [2].

Metaphase spreads were achieved in eleven of twelve samples (91.7% success). The lone failure was due to microcoagulation during blood collection, a known pre-analytical factor compromising lymphocyte culture, particularly in pediatric patients [11]. This underscores the necessity of stringent sample collection protocols, especially in low-resource settings where repeat sampling and experiment are resource demanding.

Among the eleven patients with analyzable metaphases, nine presented three distinct copies of chromosome 21, consistent with free trisomy 21 (47, XX, +21 or 47, XY, +21). The remaining two patients had trisomy 21 associated with a Robertsonian translocation, resulting in a total of 46 chromosomes due to fusion of two chromosome 21 homologs. These cases, including evidence supporting their de novo occurrence, are described in greater detail in [10]. Although rob (21; 21) accounts for only 1% - 1.5% of Down syndrome cases worldwide [12] [13], its detection in 2 of 11 cytogenetically confirmed cases (18.18%) in this cohort likely reflects the small sample size, referral bias, and potential underdiagnosis of free trisomy 21. These findings underscore the importance of systematic cytogenetic screening in the Malian population.

FISH succeeded in all samples, reinforcing its utility when karyotyping is impeded by culture failure or poor sample quality. This reflects the growing technical expertise in our laboratory in applying FISH for both constitutional and acquired chromosomal disorders [14] [15]. A major advantage of FISH is its ability to provide rapid, targeted analysis directly on interphase nuclei, eliminating the need for cell culture and making it valuable in urgent or technically challenging cases [16]. Using a chromosome 21-specific probe allowed precise enumeration of chromosomal copies across numerous nuclei, confirming trisomy 21 diagnoses and sensitively excluded mosaicism. This shows that FISH serves as both a practical alternative and a complementary tool to standard cytogenetics. Its ability to detect low-level mosaicism enhances diagnostic confidence, particularly in ambiguous or borderline cases [16]-[18].

Although FISH has been used routinely for the detection of common chromosomal abnormalities such as trisomy for more than three decades in high-income countries, its clinical implementation in resource-limited settings, including Mali, remains limited. This study shows the feasibility of a robust FISH-based diagnostic workflow for trisomy 21 in resource-constrained environments. FISH is particularly well suited to such settings, as it enables reliable analysis even when sample quality or cell culture viability is suboptimal. Importantly, this work provides a practical proof of concept for integrating cytogenetic testing into both postnatal and prenatal diagnostic pathways in settings where advanced genomic technologies such as chromosomal microarray analysis or cell-free fetal DNA testing are not yet availa-

ble, despite their routine use in developed countries [19] [20]. In settings where chromosomal abnormalities remain prevalent, partly due to the absence of pregnancy termination for fetal aneuploidies, this successful implementation shows feasibility, reproducibility, and scalability, and establishes a foundation for expanding cytogenetic diagnostics and strengthening national clinical genetics services.

This study has several limitations. First, the referral-based recruitment may have introduced selection bias. Second, the absence of systematic early postnatal enrollment likely limited accurate estimation of the relative frequencies of cytogenetic subtypes of trisomy 21 and may have introduced survival bias due to early mortality. Third, the exclusively clinically selected, all-positive cohort limits its generalizability and precludes assessment of diagnostic sensitivity and specificity.

To ensure long-term sustainability, continued efforts are required to address the challenges that limited earlier initiatives aimed at implementing cytogenetic diagnostic services for trisomy 21 in Mali more than two decades ago. Despite its pioneering contribution, that effort faced substantial barriers to continuity, including insufficient funding, inadequate infrastructure, and a shortage of qualified personnel, resulting in a prolonged absence of routine cytogenetic services in Mali [9]. Building on lessons learned from that experience, the present study serves as both a foundation and a catalyst for establishing durable, accessible, and sustainable cytogenetic diagnostics for trisomy 21 in the country. As genomic diagnostics continue to expand globally, particularly with the routine use of non-invasive prenatal testing in developed countries [19] [21], the development of context-appropriate and affordable workflows remains essential to ensure equitable access to accurate diagnosis, recurrence risk assessment, and effective genetic counseling. Our findings show how conventional and molecular cytogenetic methods can be successfully integrated into resource-limited settings to deliver reliable, high-quality diagnostic care.

5. Conclusion

This study shows the practical feasibility of implementing cytogenetic diagnosis of trisomy 21 in Mali using a combined approach of karyotyping and FISH. The integration of these complementary techniques enhances diagnostic accuracy, informs patient management, and strengthens genetic counseling within clinical settings. Beyond the immediate diagnostic benefit, these results provide a critical foundation for the development of national cytogenetic diagnostic capacity and the broader integration of genetic medicine into Mali's healthcare system.

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Author Contributions

OS: Conceptualization, formal analysis, funding acquisition, investigation, methodology, resources, validation, writing - original draft, writing - review & editing.

CO: Formal analysis, methodology, writing - original draft, writing - review & editing.

COS: Investigation, methodology.

OT: Investigation, writing - review & editing.

DS: Investigation, methodology.

MKG: Methodology, writing - review & editing.

AT: Investigation.

GL: Funding acquisition, resources, writing - review & editing.

MK: Methodology, writing - review & editing.

MT: Methodology, writing - review & editing.

Data Availability Statement

All data generated or analyzed during this study are available upon reasonable requested from the corresponding author. included in this published article.

Institutional Review Board Statement

This study was conducted in full compliance of the declaration of Helsinki and the study protocol has been approved by the institutional Ethics Committee of Faculty of Medicine and Dentistry of the University of Sciences, Techniques and Technologies of Bamako, Mali, under approval number 2020/129/CE/FMOS/FAPH. Written consent and assent forms were obtained from all participants before enrollment and share of data.

Informed Consent Statement

Informed consent was obtained from all the legal guardian of participants involved in the study.

Sample Availability

Samples used in this study are available upon reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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