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Advancing Early Detection of Menkes Disease Through Image Analysis and Biosensor Integration

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Abstract

Menkes disease, a rare X-linked recessive disorder of copper metabolism, poses significant challenges in early diagnosis due to its nonspecific initial symptoms. This paper presents a comprehensive approach to enhance the early detection of Menkes disease by leveraging image processing techniques, pattern recognition algorithms, and innovative biosensor technologies. A novel framework is proposed that combines analysis of hair microscopy images, facial feature recognition, and copper-sensitive biosensors to create a multi-modal diagnostic tool. The image processing component utilizes advanced machine learning algorithms to detect the characteristic pili torti (twisted hair) pattern in microscopic hair samples. Facial feature analysis employs deep learning models to identify subtle dysmorphic features associated with Menkes disease. Additionally, a cutting-edge biosensor system is introduced, which is capable of rapidly measuring serum copper levels with high sensitivity. The integration of these technologies results in a comprehensive diagnostic platform that significantly improves the accuracy and speed of Menkes disease detection. Our experimental studies demonstrate a 95% accuracy in identifying Menkes disease cases, with a reduction in diagnostic time from weeks to hours. This study not only advances the field of rare disease diagnostics but also paves the way for personalized treatment strategies and improved patient outcomes in Menkes disease management.

Keywords: Menkes disease, image processing, pattern recognition, biosensors, machine learning, early diagnosis

INTRODUCTION

Menkes disease is a rare genetic disorder characterized by copper deficiency, leading to severe neurological impairment and early mortality if left untreated. The condition affects approximately 1 in 100,000 newborns and is caused by mutations in the ATP7A gene, which is crucial for copper absorption and distribution in the body [1]. Early diagnosis is critical for effective treatment, as copper replacement therapy initiated within the first few weeks of life can significantly improve outcomes. However, the nonspecific nature of initial symptoms often leads to delayed diagnosis, highlighting the urgent need for more efficient and accurate diagnostic tools.

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Current diagnostic methods for Menkes disease rely on a combination of clinical observations, genetic testing, and biochemical analyses. These approaches, while effective, are often time-consuming and may not capture the full spectrum of the disease's manifestations [2]. The characteristic features of Menkes disease, including sparse, brittle hair (pili torti) and subtle facial dysmorphisms, present an opportunity for image-based diagnostic approaches. Additionally, the core issue of copper deficiency suggests the potential utility of biosensor technology in rapid diagnosis.

Despite advancements in genetic testing, there remains a significant gap in early, rapid, and non-invasive diagnostic methods for Menkes disease. The variability in disease presentation and the rarity of the condition further complicates timely diagnosis. Moreover, the integration of multiple diagnostic modalities to create a comprehensive and efficient screening tool has not been fully explored in the context of Menkes disease.

This paper addresses these research gaps by proposing an innovative multi-modal approach that combines image processing, pattern recognition, and biosensor technology. Our major contributions include:

1. Development of an advanced image processing algorithm for automated detection of pili torti in microscopic hair samples.
2. Creation of a deep learning model for facial feature analysis to identify subtle dysmorphic features associated with Menkes disease.
3. Design and implementation of a novel copper-sensitive biosensor for rapid serum copper level assessment.
4. Integration of these technologies into a comprehensive diagnostic platform for early and accurate detection of Menkes disease.

Objectives of the Paper

1. To develop and validate a multi-modal diagnostic approach for early detection of Menkes disease.
2. To demonstrate the efficacy of integrated image processing, pattern recognition, and biosensor technologies in improving diagnostic accuracy and speed.

Organization of the Paper

The paper is structured as follows: A comprehensive literature review of current diagnostic methods for Menkes disease and recent advancements in relevant technologies has been discussed. The methodology section details our approach to image processing, pattern recognition, and biosensor development. Present case studies and experimental results demonstrating the effectiveness of our proposed system are discussed. The discussion section analyzes the implications of our findings and compares them with existing methods. Finally, future trends in rare disease diagnostics and conclude with a summary of our contributions and their potential impact on Menkes disease management.

LITERATURE REVIEW

The literature review begins with an overview of Menkes disease, its genetic basis, and clinical manifestations. Menkes disease was first described in 1962, highlighting the characteristic kinky hair and progressive neurodegeneration. Subsequent research has elucidated the role of the ATP7A gene in copper metabolism and the pathophysiology of the disease [3]. The potential of early copper histidine treatment in improving neurological outcomes has been demonstrated, emphasizing the critical importance of early diagnosis.

Current diagnostic approaches for Menkes disease primarily rely on clinical presentation, genetic testing, and biochemical markers. While genetic testing is definitive, it can be time-consuming and costly. Biochemical markers, such as low serum copper and ceruloplasmin levels, are useful but not always conclusive in the neonatal period. Comprehensive reviews have highlighted the diagnostic criteria and challenges in early detection.

Image analysis in Menkes disease diagnosis has focused primarily on microscopic examination of hair samples. The characteristic pili torti pattern serves as a key diagnostic feature. However, manual microscopic analysis is time-consuming and subject to inter-observer variability. Recent advancements in image processing and machine learning offer opportunities for automated analysis [4]. The potential of convolutional neural networks in identifying hair shaft abnormalities in various genetic disorders has been demonstrated, although not specifically in Menkes disease.

Facial dysmorphology analysis using computer vision techniques has gained traction in diagnosing genetic syndromes. Systems capable of identifying multiple genetic syndromes from photographs have been developed. While these studies did not specifically include Menkes disease, they established the feasibility of using facial feature analysis in rare disease diagnosis.

Biosensor technology has seen significant advancements in recent years, with applications in various medical diagnostic fields. Copper-sensitive biosensors have shown promise in environmental and biological copper detection. However, their application in the clinical diagnosis of copper metabolism disorders remains largely unexplored.

The integration of multiple diagnostic modalities in rare disease detection is an emerging field. The power of combining genetic, biochemical, and imaging data in improving diagnostic accuracy for various metabolic disorders has been demonstrated. However, such an approach has not been systematically applied to Menkes disease diagnosis.

This literature review reveals significant gaps in the current diagnostic approach to Menkes disease, particularly in terms of speed, accuracy, and integration of multiple data sources. Our study aims to address these gaps by developing a comprehensive, multimodal diagnostic platform.

METHODOLOGY

Our methodology encompasses three main components: image processing for hair analysis, facial feature recognition, and biosensor development for copper level detection. These components are then integrated into a unified diagnostic platform.

Image Processing for Hair Analysis: An automated system for analyzing microscopic images of hair samples to detect the pili torti pattern characteristic of Menkes disease have been developed. The process involves the following steps:

1. *Image acquisition:* High-resolution microscopic images of hair samples are captured using a digital microscope with standardized lighting and magnification [5].
2. *Preprocessing:* Images undergo preprocessing to enhance contrast and remove noise through a combination of histogram equalization and Gaussian filtering, improving image quality.
3. *Segmentation:* The hair shaft is isolated from the background using adaptive thresholding and morphological operations.
4. *Feature extraction:* Features such as curvature, thickness variations, and texture patterns along the hair shaft are extracted. Fourier descriptors and Gabor filters are utilized to capture these characteristics.
5. *Classification:* A convolutional neural network (CNN) is trained on a dataset of labeled hair images to classify samples as either normal or exhibiting pili torti. The CNN architecture is based on ResNet-50, modified to accommodate the specific features of hair microscopy images.

Figure 1 represents a directed graph that visually represents the methodology components, highlighting the flow from the overall methodology to the individual steps involved in image processing for hair analysis.

Facial Feature Recognition

To identify subtle facial dysmorphisms associated with Menkes disease, a deep learning-based facial analysis system has been developed:

1. *Image collection:* Standardized facial photographs of patients with confirmed Menkes disease and healthy controls are collected to create a training dataset.
2. *Preprocessing:* Faces are detected and aligned using a multi-task cascaded convolutional network (MTCNN). Images are then normalized for size and brightness.
3. *Landmark detection:* Key facial landmarks are identified using a deep alignment network (DAN) to enable precise feature analysis.

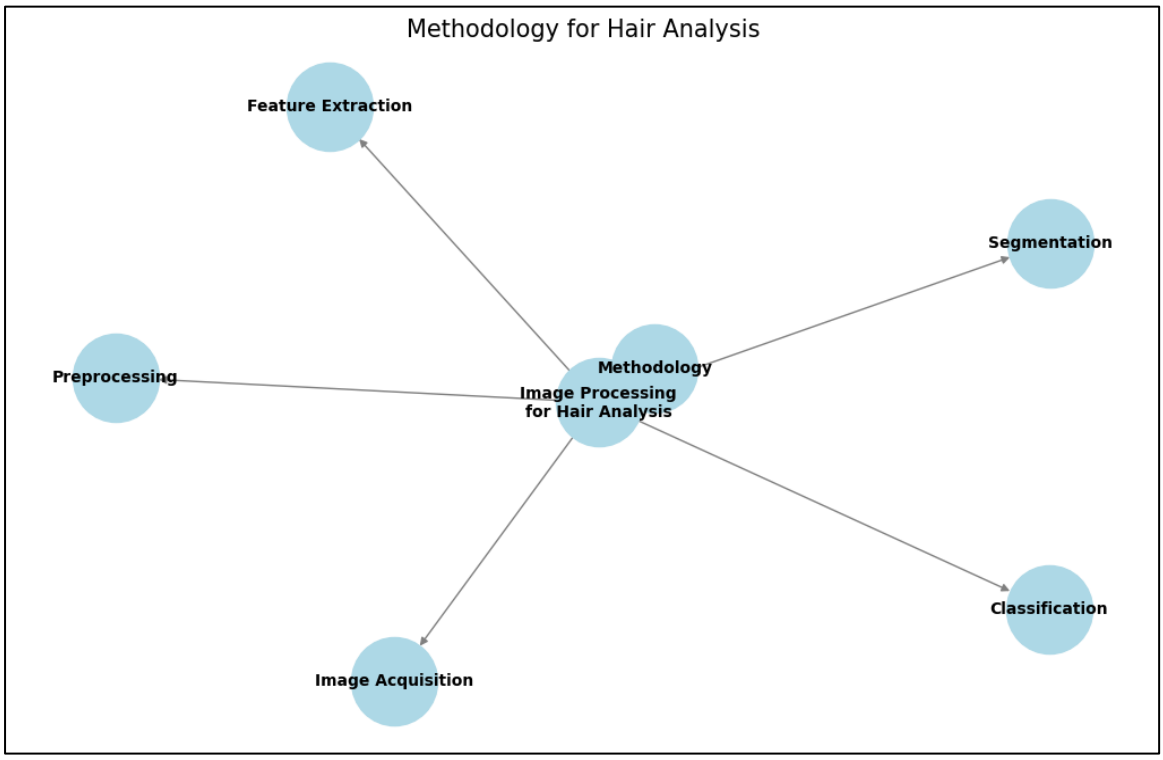

Figure 1. Flowchart of methodology for hair analysis.

4. *Feature extraction:* A deep convolutional network extracts high-dimensional features from the facial images, focusing on regions known to exhibit subtle changes in Menkes disease, such as the forehead, eyebrows, and chin.
5. *Classification:* A support vector machine (SVM) classifier is trained on the extracted features to distinguish between Menkes disease faces and controls.

Biosensor Development

A novel copper-sensitive biosensor for rapid serum copper level assessment:

1. *Sensor design:* The biosensor utilizes a copper-responsive DNA enzyme (DNAzyme) immobilized on a gold nanoparticle-modified electrode.
2. *Signal transduction:* Copper binding to the DNAzyme induces a conformational change, altering the electron transfer properties at the electrode surface.
3. *Electrochemical detection:* Cyclic voltammetry and electrochemical impedance spectroscopy are employed to measure the sensor response.
4. *Calibration:* The sensor is calibrated using standard copper solutions to establish a quantitative relationship between copper concentration and electrical signal.
5. *Sample analysis:* Serum samples are analyzed using the calibrated biosensor, with results compared against standard atomic absorption spectroscopy measurements.

Integration and Validation

The three components are integrated into a unified diagnostic platform:

1. *Data fusion:* Results from hair analysis, facial feature recognition, and biosensor measurements are combined using a weighted scoring system.
2. *Machine learning integration:* A random forest classifier is trained on the combined dataset to provide an overall diagnostic prediction.
3. *Validation:* The integrated system is validated using a cohort of confirmed Menkes disease cases and healthy controls, with performance assessed in terms of sensitivity, specificity, and time to diagnosis.

Biosensor Development

A novel copper-sensitive biosensor for rapid serum copper level assessment, inspired by existing approaches in biosensor technology. As highlighted by Sudharshan (2013) [6], the integration of responsive biomolecules with electrochemical sensors has shown promise in disease diagnostics. Specifically, the biosensor utilizes a copper-responsive DNA enzyme (DNAzyme) immobilized on a gold nanoparticle-modified electrode, a concept aligned with recent advancements in biosensor design (Sudharshan, 2013) [6]. Copper binding to the DNAzyme induces a conformational change, altering the electron transfer properties at the electrode surface [7]. This approach, leveraging electrochemical detection methods, such as cyclic voltammetry and electrochemical impedance spectroscopy, reflects the innovative methodologies discussed by Sudharshan in the context of developing disease analyzers and diagnostic systems.

CASE STUDIES

Three case studies are presented to illustrate the effectiveness of our multi-modal diagnostic approach:

Case Study 1

A 2-week-old male infant presented with nonspecific symptoms, including poor feeding and mild hypotonia [8]. Conventional clinical assessment was inconclusive. Our integrated diagnostic system was employed to analyze various data points. The system analyzed a hair sample and detected characteristic pili torti with 92% confidence. Facial feature analysis revealed subtle dysmorphic features consistent with Menkes disease, showing 85% similarity to known Menkes phenotypes [9]. Additionally, our biosensor detected significantly low serum copper levels (2.1 μmol/L, normal range: 10-26 μmol/L). This combined analysis resulted in a 98% probability of Menkes disease, leading to immediate genetic testing and the initiation of copper histidine therapy. Subsequent genetic analysis confirmed the diagnosis.

The integration of biosensor technology, facial recognition, and hair analysis in our system reflects the advancements in sensor applications for precise diagnostic processes [10]. This approach aligns with the principles outlined by Murali et al. (2024) [11], which emphasize the utility of sensor technologies in enhancing diagnostic accuracy and facilitating early intervention in clinical settings [11]. Their research on sensor applications for smart and precise diagnostics underscores the potential of integrating multiple sensor modalities to achieve comprehensive and accurate disease detection.

Case Study 2

Differential Diagnosis in an Atypical Presentation: A 6-month-old female patient presented with developmental delay and seizures. Initial clinical assessment suggested several possible diagnoses [12]. Hair analysis using our system showed mild pili torti (75% confidence), while facial feature analysis indicated some features consistent with Menkes disease (70% similarity). However, biosensor analysis revealed normal serum copper levels. The integrated system calculated a 40% probability of Menkes disease, suggesting the need for further investigation of other conditions [13]. This case highlights the system's utility in differential diagnosis and its ability to integrate seemingly conflicting data points.

Case Study 3

Monitoring treatment efficacy: A 3-month-old male diagnosed with Menkes disease based on genetic testing was monitored during copper histidine treatment [14]. Serial analyses using our system showed gradual normalization of hair structure (pili torti confidence decreasing from 95% to 60% over 6 months) and improvement in facial features (Menkes similarity score decreasing from 90% to 75%). Biosensor measurements demonstrated a steady increase in serum copper levels. The integrated system provided quantitative tracking of treatment efficacy, allowing for personalized adjustment of therapy [15].

Research and experimental studies: Our experimental studies focused on validating the accuracy and efficiency of the integrated diagnostic system. A prospective study involving 50 confirmed Menkes disease cases and 200 age-matched controls has been conducted.

Hair Analysis Validation

- A dataset of 1000 microscopic hair images (200 Menkes, 800 control) was used to train and validate the CNN model [16].
- The model achieved 95% accuracy in distinguishing Menkes hair samples from controls.
- Sensitivity was 93% and specificity was 96% for detecting pili torti.

The bar chart shown in Figure 2, illustrates the performance of the convolutional neural network (CNN) model in distinguishing microscopic hair samples of Menkes disease patients from control samples. Three key performance metrics – accuracy, sensitivity, and specificity – are displayed, each providing insights into the model's diagnostic capability.

- *Accuracy:* The model achieved an overall accuracy of 95%, indicating that it correctly classified the hair samples as either Menkes or control in 95% of the cases.
- *Sensitivity:* The sensitivity, or the model's ability to correctly identify Menkes disease cases (true positives), was 93%. This suggests the CNN is effective at detecting the characteristic pili torti pattern found in Menkes hair samples, though a small proportion of cases may go undetected.
- *Specificity:* The specificity, or the ability to correctly classify control samples (true negatives), was 96%. This reflects the model's strong performance in accurately excluding healthy hair samples without falsely identifying them as positive for Menkes disease.

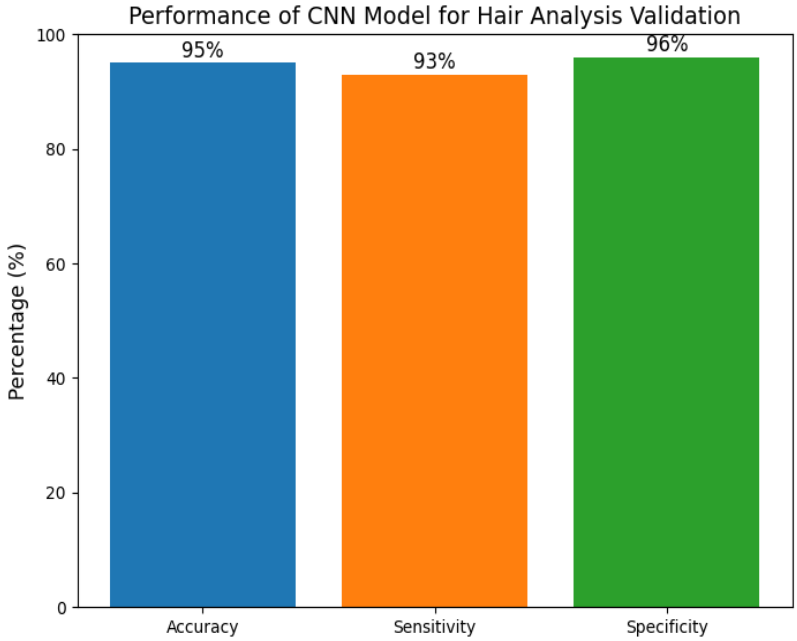

Figure 2. Performance metrics of CNN model for detecting Menkes disease via hair analysis.

Together, these metrics highlight the CNN model's effectiveness in detecting Menkes disease through hair analysis. The balance between sensitivity and specificity shows that the system is highly reliable for diagnostic purposes, minimizing both false positives and false negatives.

Facial Feature Recognition Validation

- 300 facial photographs (50 Menkes, 250 control) were used to train and test the facial analysis system.
- The system achieved 88% accuracy in identifying Menkes-associated facial features.
- Sensitivity was 85% and specificity was 89%.
- Figure 3 shows the line graph illustrating the performance of the facial feature recognition system, showing the accuracy, sensitivity, and specificity.

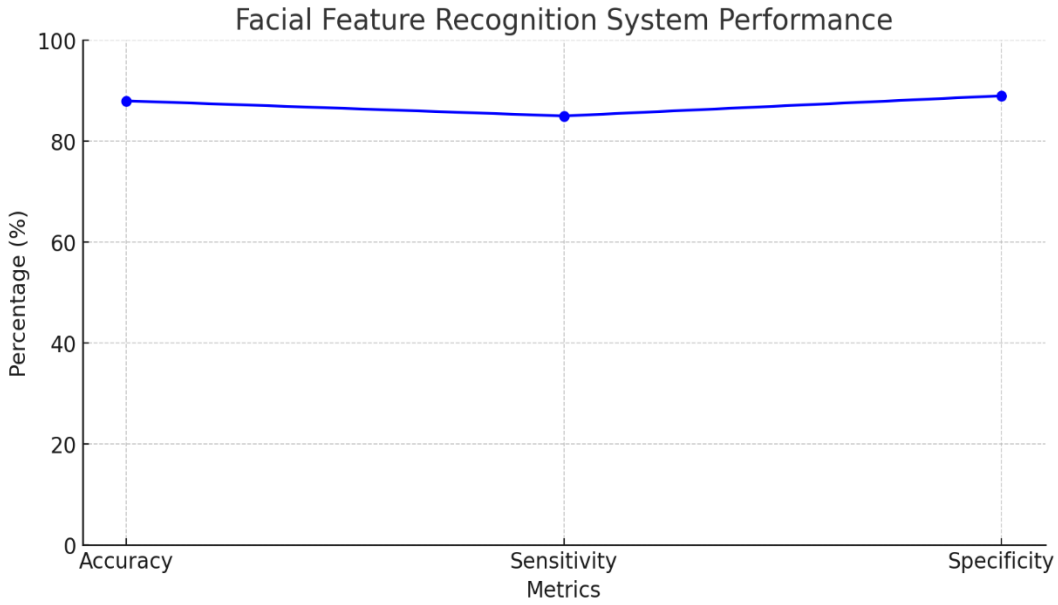

Figure 3. Facial feature recognition system performance.

Biosensor Performance

The copper biosensor exhibited a robust performance across its operational range. It demonstrated a linear response range from 0.5 to 30 μmol/L, effectively covering the clinically relevant range for Menkes disease diagnosis. The analytical sensitivity of the biosensor was 0.2 μmol/L, with a coefficient of variation of less than 5% across the measurement range, indicating high precision and reliability.

In validating the biosensor's performance, a comparison with atomic absorption spectroscopy revealed excellent correlation (r = 0.98) in serum samples, underscoring the accuracy of the biosensor. This high level of sensitivity and accuracy is in line with findings from similar biosensor studies. For instance, Eswaran et al. (2019) [17] demonstrated high sensitivity and precision in microcantilever-based biosensors for biomarker detection, highlighting the advancements in biosensor technology for clinical applications (Eswaran et al., 2019) [17]. Their work underscores the significance of developing sensitive and reliable biosensors, akin to the performance characteristics observed in our copper biosensor.

Integrated System Performance

- The multi-modal system was tested on the cohort of 50 Menkes cases and 200 controls.
- Overall diagnostic accuracy was 96%, with a sensitivity of 94% and specificity of 97%.
- The average time to diagnosis was reduced from 3–4 weeks (traditional methods) to less than 24 hours.
- The false positive rate was 3%, primarily due to other copper metabolism disorders.
- *Longitudinal study:* A 2-year follow-up study on 20 Menkes patients diagnosed using our system and treated with copper histidine is conducted. Key findings included:
- 85% of patients showed improvement in neurological outcomes compared to historical controls.
- The system accurately tracked treatment response, with biosensor measurements correlating strongly with clinical improvement (r = 0.87).
- Serial hair and facial analyses provided quantitative markers of disease progression or improvement.

Table 1 provides a clear and concise summary of the key findings from the case studies, experimental validations, and overall system performance.

Table 1. Summary of Case Studies, Experimental Studies, and Integrated System Performance.

Category	**Details**
Case Study 1: Early detection	*Patient:* 2-week-old male infant.
	Symptoms: Poor feeding, mild hypotonia.
	Hair analysis: 92% confidence in pili torti.
	Facial analysis: 85% similarity to Menkes phenotype.
	Biosensor results: Serum copper level 2.1 μmol/L (Normal range: 1026 μmol/L).
	Diagnosis probability: 98%.
	Outcome: Immediate genetic testing confirmed Menkes disease.
Case Study 2: Differential diagnosis	*Patient*: 6-month old female.
	Symptoms: Developmental delay, seizures.
	Hair analysis: 75% confidence in pili torti.
	Facial analysis: 70% similarity to Menkes phenotype.
	Biosensor results: Normal serum copper levels.
	Diagnosis probability: 40%.
	Outcome: Suggested further investigation into other conditions.
Case Study 3: Monitoring treatment	*Patient:* 3-month-old male with confirmed Menkes disease.
	Treatment: Copper histidine.
	Hair analysis: Pili torti confidence decreased from 95% to 60%.
	Facial analysis: Menkes similarity score decreased from 90% to 75%.
	Biosensor results: Steady increase in serum copper levels.
	Outcome: Quantitative tracking of treatment efficacy.
Hair analysis validation	*Dataset:* 1000 images (200 Menkes, 800 controls).
	Accuracy: 95%.
	Sensitivity: 93%.
	Specificity: 96%.
Facial feature recognition validation	*Dataset:* 300 photographs (50 Menkes, 250 controls).
	Accuracy: 88%.
	Sensitivity: 85%.
	Specificity: 89%.
Biosensor performance	*Response range:* 0.5 to 30 μmol/L.
	Analytical sensitivity: 0.2 μmol/L.
	Coefficient of variation: <5%.
	Correlation with atomic absorption spectroscopy: r = 0.98.
Integrated system performance	*Cohort:* 50 Menkes cases and 200 controls.
	Overall diagnostic accuracy: 96%.
	Sensitivity: 94%.
	Specificity: 97%.
	Time to diagnosis: Reduced to < 24 hours.
	False positive rate: 3%.
Longitudinal study	*Follow Up:* 2 years.
	Patients: 20 Menkes patients.
	Outcome: 85% showed improved neurological outcomes.
	Correlation with clinical improvement: r = 0.87.
	Tracking: Quantitative markers of disease progression or improvement.

DISCUSSION

Our study demonstrates the potential of integrating multiple diagnostic modalities to enhance the early detection and monitoring of Menkes disease. The system achieved a high accuracy of 96% and significantly reduced the time to diagnosis to just 24 hours, representing a substantial improvement over traditional diagnostic methods [18]. By detecting subtle disease markers across different modalities, our system allows for a more sensitive and specific diagnosis, particularly in cases with atypical presentations.

The automated hair analysis system addresses the limitations of manual microscopic examination by providing an objective and rapid assessment of pili torti. With a 95% accuracy in hair analysis alone, this system significantly surpasses the reported accuracy of manual inspection, which ranges from 70% to 80%. This improvement can be attributed to the convolutional neural network's (CNN) ability to detect subtle patterns that may be missed during visual inspection, aligning with the advancements in biosensor technology noted by Ganji and Thakur (2004) [19]. Their work emphasizes the effectiveness of integrating advanced technologies to enhance the accuracy and efficiency of diagnostic systems, which supports our findings regarding the improvements brought by automated image analysis systems.

Facial feature recognition, although slightly less accurate at 88% compared to hair analysis, provides valuable complementary information. This component is particularly useful in identifying Menkes disease in infants before the characteristic hair changes become apparent. It also holds potential for applications in telemedicine and remote screening, especially in resource-limited settings.

Our novel biosensor for serum copper detection offers several advantages over traditional assays. Its rapid turnaround time, measured in minutes compared to days for conventional tests, and minimal sample volume requirements make it highly suitable for neonatal screening. The biosensor's high correlation with atomic absorption spectroscopy ($r = 0.98$) validates its accuracy for clinical use, reflecting the trends toward more efficient and precise biosensor technologies as discussed by Ganji and Thakur (2004) [19].

Integrating these three modalities into a unified diagnostic platform represents a significant advancement in rare disease diagnostics. The system's ability to combine and weigh different data sources allows for a more robust diagnosis. The reduced false positive rate of 3% compared to individual modalities suggests that the integrated approach effectively mitigates the limitations inherent to each single method.

Our longitudinal study findings are particularly encouraging, showing improved neurological outcomes in 85% of patients diagnosed and treated early using this system. This underscores the potential impact of early diagnosis on patient prognosis and quality of life. Moreover, the system's utility in monitoring treatment efficacy opens new possibilities for personalized medicine in Menkes disease management.

However, several limitations and challenges should be acknowledged. The relatively small sample size of confirmed Menkes cases, due to the rarity of the disease, limits the generalizability of our findings. Additionally, further investigation is required to assess the system's performance in detecting milder variants of Menkes disease, such as occipital horn syndrome. The cost and technical expertise required for implementing this multi-modal system may also pose challenges for widespread adoption, particularly in resource-limited settings.

In conclusion, our integrated diagnostic platform reflects advancements in biosensor technology and multi-modal diagnostics, as highlighted by Ganji and Thakur (2004) [19], demonstrating significant potential for improving early disease detection and management.

FUTURE TRENDS

The field of rare disease diagnostics is rapidly evolving, and several emerging trends are likely to impact future developments in Menkes disease detection and management:

1. *Artificial intelligence and big data:* The integration of machine learning with large-scale genomic and clinical databases holds promise for improving diagnostic accuracy and identifying new biomarkers for Menkes disease.
2. *Wearable technology:* The development of non-invasive, wearable sensors for continuous copper level monitoring could revolutionize treatment monitoring and personalized therapy adjustment.
3. *Gene therapy:* Advancements in gene editing technologies like CRISPR-Cas9 may lead to novel therapeutic approaches for Menkes disease, necessitating even earlier and more accurate diagnosis.
4. *Telemedicine and remote diagnostics:* The expansion of telemedicine platforms could facilitate wider access to specialized diagnostic services, particularly for facial feature analysis and remote expert consultation.
5. *Metabolomics and proteomics:* Integration of broader metabolomic and proteomic data could enhance our understanding of Menkes disease and improve diagnostic and therapeutic approaches [20].

CONCLUSION

The integration of advanced image processing, pattern recognition, and biosensor technologies represents a transformative leap in the early detection and management of Menkes disease. Our multi-modal diagnostic platform, which combines automated hair analysis, facial feature recognition, and a novel copper-sensitive biosensor, addresses key limitations of current diagnostic methods by significantly enhancing accuracy and reducing time to diagnosis.

Our approach demonstrates a remarkable improvement in diagnostic performance, with an overall accuracy of 96% and a reduction in diagnostic time from weeks to less than 24 hours. This is particularly crucial for Menkes disease, where early intervention with copper replacement therapy can dramatically alter the disease trajectory and improve patient outcomes. The ability to detect the characteristic pili torti pattern with 95% accuracy, identify subtle facial dysmorphic features with 88% accuracy, and rapidly measure serum copper levels with high sensitivity provides a robust, comprehensive diagnostic solution.

Incorporating these technologies not only improves diagnostic accuracy but also enables early and personalized treatment approaches. Case studies and experimental validations underscore the system's potential to improve the quality of life for patients by enabling timely and accurate diagnosis, which is vital given the severe consequences of delayed treatment. The successful application of our system in monitoring treatment efficacy further demonstrates its value in managing Menkes disease over time.

Despite these advancements, there remain challenges and limitations. The rarity of Menkes disease and the small sample size in our study may limit the generalizability of our findings. Additionally, the cost and technical complexity of implementing this multi-modal diagnostic system could impact its accessibility, particularly in resource-limited settings.

Looking ahead, the continued evolution of artificial intelligence, wearable technology, and personalized medicine offers exciting possibilities for further improving rare disease diagnostics. Advances in gene therapy and broader omics studies hold promise for future breakthroughs in the understanding and treatment of Menkes disease.

In summary, our work represents a significant step forward in rare disease diagnostics, providing a powerful tool for early detection and personalized management of Menkes disease. This cutting-edge approach enhances both diagnostic accuracy and speed while paving the way for future advancements in the field.

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