Journal of Pharmaceutical Research and Integrated Medical Sciences (JPRIMS)
ISSN: 3049-1681 | Vol. 03, Issue-08, August-2026 | pp.-43-57

ORIGINALARTICLE https://jprims.in/

ML in Rare Facial Disorders: Hemifacial Microsomia, Parry–Romberg Syndrome, Moebius Syndrome, Treacher Collins Syndrome, Apert Syndrome, and Crouzon Syndrome-From Etiological Mapping and Pathology to AI-Driven Bio-Computational Gene Therapy

Yash Srivastav[1*], Stuti Verma[2], Kamini Prajapati[1], Sandeep Prakash[1], Rajeev Kumar[2], Anubha Dhuriya[2], Anup Kumar Sirbaiya[3], Shivani Singh[1]

[1]D.K.R.R Pharmacy College, Amberpur, Sitapur (Uttar Pradesh), India. 261303
[2]Aryakul College of Pharmacy and Research, Sitapur, Uttar Pradesh, India. 261303
[3]K.P. Singh Memorial Institute of Pharmacy, Sitapur, U.P, India

***Corresponding Email: yashsrv.108@gmail.com**

Abstract:

These rare facial diseases, which include hemifacial microsomia, Parry–Romberg syndrome, Moebius syndrome, Treacher Collins syndrome, Apert syndrome, and Crouzon syndrome, among others, pose considerable difficulties in diagnosis and treatment due to their clinical variability, rare occurrence, and complex genetic etiology. This review highlights the increasing potential of artificial intelligence (AI) and machine learning (ML) technologies in the better diagnosis, phenotyping, genotyping, and clinical management of these rare disorders. In this review, the applications of AI to facial phenotyping, three-dimensional (3D) imaging, radiomics, multimodal learning, and explainable AI have been highlighted. It also points out some latest developments in the field of bioinformatics, genome editing, RNA therapies, patient-derived models, and digital twin technology for precision medicine and translational research. Presently, there is sufficient evidence indicating the benefits of AI in increasing the accuracy in diagnosis, objective craniofacial evaluation, and customized treatment plans, whereas computational therapy is still experimental. However, various barriers such as data limitations, variability in phenotype, bias in the algorithms, external validation, ethical issues, and regulation prevent its widespread adoption in clinical practice. Future studies need to concentrate on multicenter data sharing, multimodal explainable AI, precision genomics, and translational framework to speed up the adoption of AI in rare craniofacial medicine.

Keywords: Artificial intelligence (AI); Machine learning (ML); Rare facial disorders; Craniofacial anomalies; Facial phenotyping; Precision medicine; Genomics.

Received: May 11, 2026 **Revised: June 12, 2026** **Accepted: July 19, 2026** **Published: August 13, 2026**

DOI: https://doi.org/10.64063/3049-1681.vol3.issue8.000294

1. INTRODUCTION

Rare disorders of the face include a diverse set of congenital, developmental, neurologic, and genetic diseases that impact the development and function of the craniofacial region[1]. Conditions like hemifacial microsomia, Parry-Romberg syndrome, Moebius syndrome, Treacher Collins syndrome, Apert syndrome, and Crouzon syndrome generally have presentations like facial asymmetry, craniosynostosis, jaw deformities, cranial nerve deficits, hearing loss, and airway anomalies[2]. Due to their rarity, overlapping symptoms, and variable presentations, diagnosing and treating them can be challenging.

Rarity occurs in many diseases of the face, which includes various congenital, developmental, neurological, and genetic disorders affecting the craniofacial complex. Hemifacial microsomia, Parry-Romberg syndrome, Moebius syndrome, Treacher Collins syndrome, Apert syndrome, and Crouzon syndrome, among others, usually present as facial asymmetry, craniosynostosis, jaw deformity, cranial nerve abnormalities, hearing problems, and abnormalities of the airway tract[3]. The difficulties in their diagnosis and treatment usually arise because of their rare occurrence and similarities in clinical presentations[4].

1.1 Background and Context

The diagnosis of rare craniofacial syndromes is conventionally done using clinical examinations, radiographic images, and molecular genetic testing, but all these methods face limitations due to their subjectivity and overlapping characteristics of diseases[5]. ML offers an opportunity to automate the analyses of facial pictures, 3D imaging, computed tomography (CT) scans, magnetic resonance imaging (MRI), and genomics for the purposes of improving diagnosis and genotype-phenotype relationships. New advances in the field of deep learning (DL), radiomics, multimodal learning, and explainable AI have increased the applications of computational techniques from diagnosis to surgery planning and outcomes prediction[6].

1.2 Objectives of the Review

Aims of this review are:

- To provide an overview of the etiology, pathogenesis, and clinical features of hemifacial microsomia, Parry-Romberg syndrome, Moebius syndrome, Treacher Collins syndrome, Apert syndrome, and Crouzon syndrome.
- To understand how ML is being applied to facial phenotyping, medical imaging, disease classification, and genomic analysis.
- To explore how AI is contributing to surgical planning, precision medicine, and patient-specific treatment.
- To investigate AI-driven genome editing, RNA therapies, and digital twin systems.
- To discover current knowledge gaps, translational barriers, ethical concerns, and areas for future research.

1.3 Importance of the Topic

These disorders not only have a considerable impact on the appearance of the face, but also on breathing, hearing, sight, speaking, and other aspects that have an impact on one's overall quality of life. AI provides excellent ways of bringing together all this data to provide correct diagnosis and individualized treatment[7]. While currently most AI-based therapies are still in the investigational phase, the potential of intelligent decision-making systems becomes ever more apparent with the help of computational genomics.

2. MACHINE LEARNING–BASED DIAGNOSIS AND PHENOTYPIC ANALYSIS

ML has made great strides in the diagnosis of uncommon craniofacial syndromes due to its ability to perform quantitative analysis of facial form, imaging, medical history, and genomics. In contrast to traditional methods, which depend heavily on clinical knowledge, ML systems can detect small morphological features that cannot be readily detected through a simple physical examination[8]. Through DL, computer vision, radiomics, and multimodal learning, facial images, 3D scanning, CT, MRI, and genomic data are analyzed for early diagnosis and treatment.

2.1 Facial Imaging, Preprocessing, and Phenotypic Classification

Facial imaging serves as the foundation of the use of ML in rare craniofacial disorders. Information regarding facial shape, skeletal morphology, symmetry, and soft tissue features can be obtained from standardized facial images, 3D stereophotogrammetry, CT, cone-beam CT, MRI, and facial videos. Prior to image analysis, pre-processing techniques including face detection, landmark identification, normalization of the pose, illumination adjustment, image segmentation, and noise removal are performed[9].

DL systems, especially CNNs and vision transformers, help identify the complex traits related to a particular syndrome. AI -based facial phenotyping systems like DeepGestalt and GestaltMatcher have the capability to rank several rare genetic diseases by analyzing the traits of a patient against a database. These systems work as decision support systems for clinicians, providing ranked differential diagnosis rather than being used as an alternative to specialist consultation and genetic testing.

ML algorithms also enhance the distinction between diseases that share similar craniofacial features. ML helps distinguish between unilateral mandibular hypoplasia in hemifacial microsomia, progressive facial atrophy in Parry-Romberg syndrome, congenital facial paralysis in Moebius syndrome, bilateral mandibular hypoplasia in Treacher Collins syndrome, and craniosynostosis syndromes of Apert and Crouzon syndromes[10].

2.2 Three-Dimensional Imaging and Multimodal Diagnosis

3D imaging allows for proper analysis of facial asymmetries, skeletal features, airway anatomy, and cranial development. Methods such as stereophotogrammetry, CT scans, CBCT scans, and MRI scans allow for accurate measurements of mandibular measurements, orbital positioning, cranial sutures, and facial soft tissues. ML methods can accurately segment anatomical structures, measure volumetric discrepancies, and track changes in craniofacial development and postoperative outcomes.

Moreover, Radiomics further facilitates the diagnostic process through the extraction of quantitative imaging markers based on texture, shape, and intensity from CT and MRI images. The use of supervised ML models can then help in the identification of imaging biomarkers specific to a disease condition[11]. AI helps in diagnosing craniosynostosis syndromes through the detection of fused sutures, estimation of intracranial volumes, and assessment of airway compromise; while longitudinal imaging facilitates the objective assessment of facial growth in conditions like Parry-Romberg syndrome and hemifacial microsomia.

The performance of diagnostics can be further improved through multimodal learning techniques that integrate imaging results with clinical examinations, photographs, electronic medical records, familial history, and genomics[12]. Such combined learning models can be much more effective in disease categorization, severity assessment, surgical planning, and longitudinal follow-up than purely imaging-based analyses.

2.3 Genomic Interpretation and Explainable Clinical Decision Support

Genomic sequencing is a critical aspect in the detection of congenital craniofacial disorders; however, interpreting the large number of genetic variations poses some difficulties. The use of ML can be useful by filtering out the potentially pathogenic variations through the integration of facial phenotypes, clinical traits, Human Phenotype Ontology terms, modes of inheritance, and genomics.

The application of AI technology to genetics also enhances the genotype-phenotype association through the identification of particular gene mutations responsible for specific facial dysmorphism. For instance, the AI-based algorithm correlates mutations of FGFR2 with Apert syndrome and Crouzon syndrome and TCOF1, POLR1C, and POLR1D mutations with Treacher Collins syndrome[13].

For the safe implementation of AI in the clinical setting, there needs to be transparency and explainability of the algorithms used. Saliency maps, feature attributions, Grad-CAM visualization, and uncertainty quantification are some of the methods used to make AI explainable to clinicians, hence making them understand how the algorithm arrives at its predictions. It is not about the clinicians being replaced but assisting them in their work[14].

Table 1. ML Applications in the Diagnosis of Rare Craniofacial Disorders

AI Technique	Primary Data Source	Clinical Application	Major Clinical Benefit
Facial Phenotyping	2D facial photographs	Syndrome recognition and disease classification	Early diagnosis and differential diagnosis
3D Morphometric	3D facial scans, stereophotogrammetry	Facial asymmetry and craniofacial	Objective severity assessment

Analysis		measurements	
Radiomics	CT and MRI images	Detection of skeletal and soft-tissue abnormalities	Improved diagnostic accuracy
Multimodal Learning	Imaging, clinical records, genomic data	Disease classification and treatment planning	Comprehensive clinical decision support
Genomic Interpretation	Whole-exome/genome sequencing	Variant prioritization and genotype–phenotype correlation	Precision diagnosis and genetic counselling
Explainable AI (XAI)	Integrated clinical and imaging data	Interpretation of AI predictions	Increased transparency and clinician confidence

3. DISEASE-SPECIFIC ETIOLOGY, PATHOLOGY, AND AI APPLICATIONS

Rare craniofacial disorders have a wide range of etiologies and pathogenic presentations that include congenital abnormalities of the face and rare diseases like neurocutaneous and craniosynostosis syndromes[15]. Even though all these rare disorders have similar features on their faces, they differ in their underlying genotypes, progression, severity, and treatment. AI is proving helpful in disease-specific diagnosis and can be combined with phenotyping and 3D imaging along with radiologic assessment and genomics. Besides aiding in early diagnosis, AI helps in assessing the severity of the condition, surgical intervention, monitoring treatment, and genotypic-phenotypic correlation.

3.1 Hemifacial Microsomia and Parry–Romberg Syndrome

Hemifacial microsomia is an anomaly that affects development of facial features on one side of the face arising from the first and second pharyngeal arches, which include the mandible, external ear, facial muscles, and soft tissue components of the face. Its causes are diverse and include problems in neural crest cell migration, vascular disruption, environmental factors, and genetic mutations like SF3B2 in some patients. On the other hand, Parry-Romberg syndrome is an acquired disorder that involves progressive degeneration of facial structures such as skin, subcutaneous tissue, muscle, and sometimes even bone. The precise causes of this condition are unknown, but there are several theories.

ML plays an important role in distinguishing among such diseases through quantitative assessment of facial asymmetry, mandible shape, soft tissue volume, and progression in structure based on two-dimensional images, 3D facial imaging, CT, and MRI. Automatic image segmentation and morphometrics provide an objective means of evaluating the disease severity and monitoring the growth of facial structures or loss of tissue. This is particularly important in longitudinal AI models where stable versus progressive abnormalities have to be distinguished[16].

In addition to diagnostic purposes, the use of AI enables clinicians to make decisions on the basis of a combination of data from medical imaging and genetics, along with the patient's clinical history. 3D surgery simulation might be helpful in mandibular reconstruction in patients with hemifacial microsomia, whereas volumetric imaging is useful in choosing the right time for surgical reconstruction in Parry-Romberg syndrome. Despite the limited possibilities of molecular treatments owing to etiological diversity, computation continues to advance our knowledge of pathogenetic mechanisms.

3.2 Moebius Syndrome and Treacher Collins Syndrome

Introduction Moebius syndrome is an extremely rare congenital neurological condition associated with facial palsy and restricted eye movements because of defects in the development of the facial and abducens cranial nerves[17]. The condition has a genetic and environmental heterogeneity of causes, although there have been described some gene mutations like PLXND1 and REV3L that affect this condition in a limited number of patients. On the other hand, Treacher Collins syndrome is a craniofacial syndrome associated mainly with mutations in TCOF1, POLR1C, and POLR1D that cause bilateral mandibular and zygomatic hypoplasia.

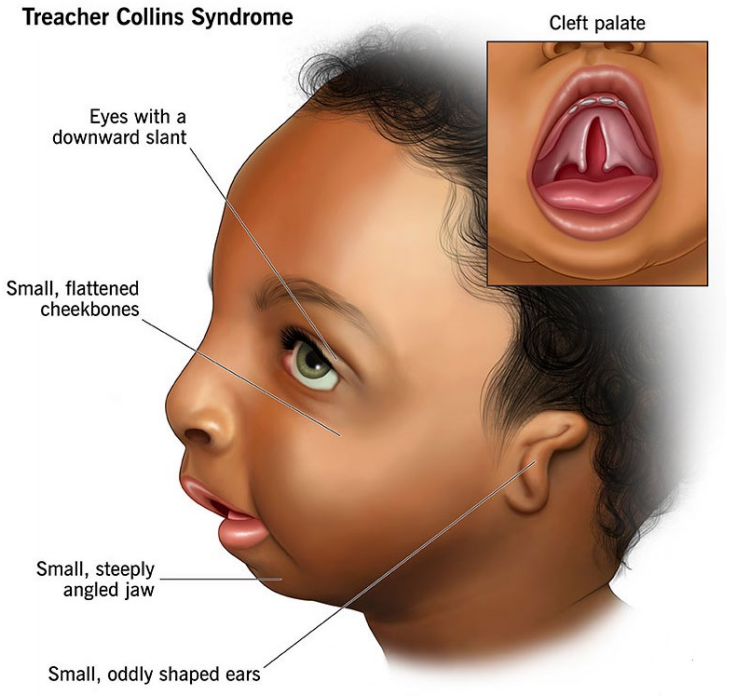

Figure 1. Clinical features of Treacher Collins syndrome

These conditions can be accurately diagnosed using AI with the help of sophisticated techniques of facial phenotyping, medical imaging, and movement analysis. DL techniques detect facial characteristics related to Treacher Collins syndrome, while video analysis of ML assesses movement of the face, blink rate, lip movement, and eye movements in Moebius syndrome[18]. Facial images combined with CT, MRI, and clinical data contribute to accurate diagnosis of patients with unusual symptoms.

Additionally, AI helps in personalized treatment planning through airway evaluation, craniofacial reconstruction, facial reanimation, and postoperative prediction of outcomes. The genomics analysis also facilitates genotype-phenotype correlation, making it possible to conduct molecular diagnosis and genetic counseling for families affected with the condition. While there have not been any successful gene-based treatment approaches, AI and genomics analysis provide an excellent base for future treatments.

3.3 Apert Syndrome and Crouzon Syndrome

Apert syndrome and Crouzon syndrome are two autosomal dominant craniosynostosis syndromes, which are mainly caused due to activating mutations in the FGFR2 gene. Both syndromes show the same symptoms like early closure of cranial sutures, aberrant skull development, midface hypoplasia, exophthalmos, and airway problems. Apert syndrome also shows complex syndactyly in the hands and feet, while Crouzon syndrome does not show any limb problems.

The field of ML has gained immense value with regard to automated analysis of craniosynostosis utilizing CT, MRI, and 3D craniofacial imaging. ML algorithms can correctly detect fused sutures, analyze the cranial shape, determine intracranial volume, analyze airway compromise, and detect any orbital abnormalities[19]. They can even help predict surgical results and conduct cranial vault expansion and midface reconstruction surgery.

Similarly, the distinct molecular nature of Apert syndrome and Crouzon syndrome is what makes them ideal candidates for precision medicine aided by AI. This is because ML can help incorporate genomic variations, protein structures, developmental biology pathways, and clinical phenotypes to enhance the genotype–phenotype correlation, and find treatment targets. Moreover, the use of AI facilitates computational prediction of gene-editing mechanisms, RNA therapies, and drugs targeting specific pathways[20]. Though still experimental, ongoing developments in bioinformatics and precision genomics may facilitate rapid advances in personalized treatment of FGFR2-related craniofacial diseases.

Table 2. Comparative Etiology, Pathology, and AI Applications in Rare Facial Disorders

Disorder	Etiology/Genetics	Key Pathology	Major AI Application	Clinical Benefit
Hemifacial Microsomia	Multifactorial; SF3B2 (subset)	Unilateral facial underdevelopment	3D facial analysis, CT segmentation	Early diagnosis and surgical planning
Parry–Romberg Syndrome	Autoimmune/neurovascular (uncertain)	Progressive unilateral facial atrophy	Volumetric analysis, MRI monitoring	Disease monitoring and reconstruction planning

Moebius Syndrome	PLXND1, REV3L (rare); heterogeneous	Congenital facial paralysis	Facial movement analysis	Functional assessment and rehabilitation
Treacher Collins Syndrome	TCOF1, POLR1C, POLR1D	Mandibular hypoplasia, microtia	Facial phenotyping, airway analysis	Precision diagnosis and treatment planning
Apert Syndrome	FGFR2 mutation	Craniosynostosis, syndactyly	Cranial imaging and surgical simulation	Personalized craniofacial management
Crouzon Syndrome	FGFR2 mutation	Craniosynostosis, midface retrusion	CT/MRI-based craniofacial analysis	Surgical planning and outcome prediction

4. AI-DRIVEN THERAPEUTICS AND CLINICAL TRANSLATION

With the incorporation of AI technology in genomics, bioinformatics, regenerative medicine, and precision therapy, the treatment of rare facial disorders has opened up new avenues. At present, treatment in clinics revolves around early diagnosis, reconstruction and rehabilitation, but with the use of AI, treatment is becoming more inclined towards target identification, optimizing treatment plans, and predicting outcomes of the procedure[21]. Gene editing therapies and RNA-based treatments are still experimental in case of craniofacial disorders; nevertheless, computation has aided in the process of translating technology into medicine in such cases. It should be noted that the application of technology in clinical practice involves rigorous validation and ethics.

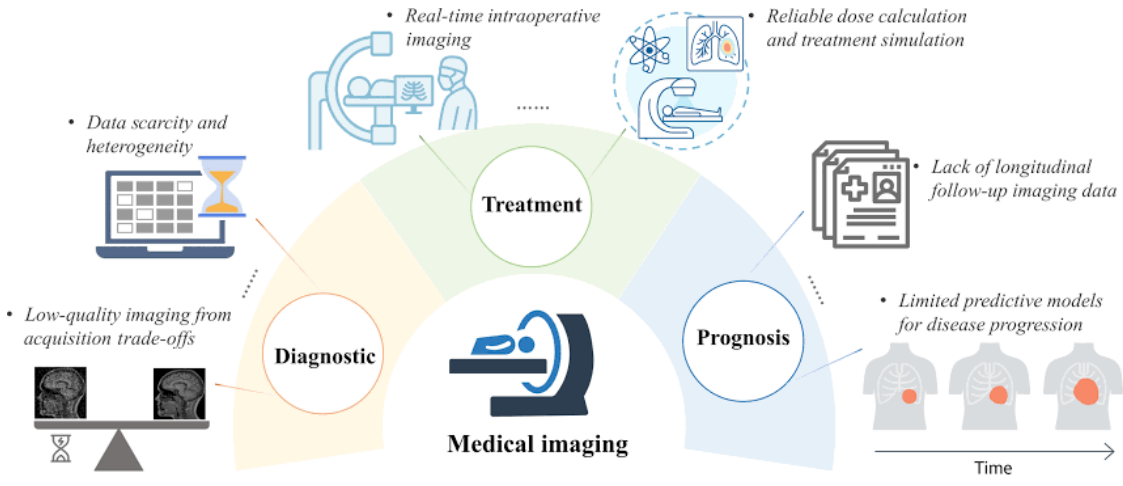

Figure 2. AI-enabled medical imaging framework supporting diagnosis, treatment planning, and prognosis in rare craniofacial disorders

4.1 Genotype–Phenotype Mapping, Genome Editing, and RNA-Based Therapies

Establishing the link between genetic variations and clinical presentations is vital to the development of precision medicine for rare craniofacial diseases. ML combines genomic sequence information and facial phenotypes, radiological data, and clinical features to predict disease-associated variations and determine genotype-phenotype associations[22]. The utility of this approach is especially notable in syndromes like Treacher Collins, Apert, and Crouzon, where disease-causing variations in genes such as TCOF1, POLR1C, POLR1D, and FGFR2 are well documented. ML also helps in diagnosing diseases molecularly and classifying the disease and its prognosis.

AI is playing an important role in the development of new methods such as genome editing and RNA-based therapeutics. ML techniques can assist in optimizing CRISPR guide RNA sequences, predicting off-target editing, prioritizing therapeutic targets, and modeling molecular pathways that lead to disease[23]. Moreover, computational techniques are used to develop RNA-based therapy, which includes antisense oligonucleotides, messenger RNA replacement, and small interfering RNA to control the abnormal expression of genes. Though these techniques are not being considered as clinical treatments of the disorders mentioned in this review, AI greatly speeds up the process of drug development.

4.2 Delivery Systems, Patient-Derived Models, and Digital Twins

Delivery of genetics and molecular therapeutics efficiently is one of the biggest hurdles that needs to be overcome in translational craniofacial medicine. AI helps in designing more effective methods for delivery by predicting the tissue penetration, dosing, delivery kinetics, and biological distribution of viral vectors, lipid nanoparticles, hydrogels, and biomaterial-based delivery systems[24]. Such predictive analysis helps in improving the efficacy of the treatments while reducing the chances of any harmful effects of the delivery method.

Models derived from patient-induced pluripotent stem cells, cranial neural crest cells, organoids, and tissue-engineered 3D systems offer clinically relevant systems that can be used to understand mechanisms and treatments for diseases. ML offers the ability to analyze high-dimensional biological data obtained from these systems quickly, thus identifying pathways, treatments, and biomarkers. The human-derived models serve as an essential link between computer predictions and clinical applications in the future.

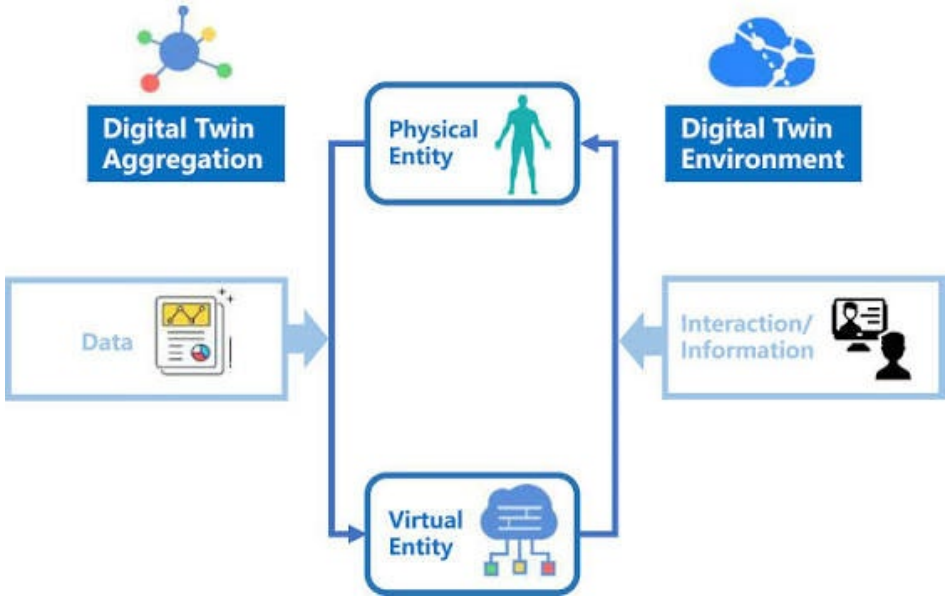

Figure 3. Digital twin architecture supporting AI-driven personalized diagnosis, treatment planning, and longitudinal monitoring in rare craniofacial disorders

AI-based digital twins provide another innovative use of AI in precision craniofacial medicine. The digital twin integrates facial structure, 3D imaging, genomics, medical history, and treatment history into a patient-specific digital model[25]. Digital models are capable of simulating craniofacial development, predicting disease development, assessing different surgery options, and projecting treatment outcomes. While the technology is still in its infancy, digital twins show significant promise in terms of personalized treatment planning and lifetime monitoring of patients[26].

4.3 Clinical Validation, Ethical Challenges, and Surgical Implementation

The integration of AI into clinical practice necessitates extensive validation involving multi-center and externally validated databases. Algorithms employed for diagnostics and therapy should be tested not only for their validity but also for sensitivity, specificity, calibration, reproducibility, fairness, and practicality in clinical settings. Validation studies performed prospectively are vital for showing how AI increases the efficiency of diagnosis, treatment, surgery, and quality of life of patients.

Ethical issues continue to play a crucial role in AI-powered craniofacial medicine since the face pictures and genetic information are extremely private pieces of information[27]. The proper use of the technology involves giving informed consent, proper data management, securing privacy, explainability, and constant demographic bias checking. Explainable AI is especially important since medical professionals need to know the evidence behind the algorithmic decisions before implementing them.

From the currently available uses of AI, the most translational one lies in planning surgeries and assessing post-surgery status. 3D reconstruction, automated segmentation, virtual surgical simulation, and predictive modeling help medical professionals in the planning of craniofacial reconstruction, mandibular distraction, cranial vault expansion, midface advancement, and facial

reanimation surgeries[28]. However, by combining imaging data, genomics, and clinical data, AI provides better personalization of treatment plans and outcome prediction. Despite this, however, these technologies must be utilized as decision support systems supervised by specialists, thus ensuring the reliability and ethicality of AI-based treatments in the future.

Table 3. Comparison of Recent Literature on Rare Facial Disorders and AI-Based Clinical Applications

Author(s) & Year	Study Focus	Major Findings	Contribution to the Present Review
Pniak (2024)[29]	Pathogenesis and treatment of hemifacial microsomia	Reviewed current hypotheses of embryological, vascular, and genetic mechanisms and discussed available therapeutic approaches.	Supports the discussion on the heterogeneous etiology of hemifacial microsomia and highlights the need for AI-assisted diagnosis and personalized treatment planning.
Schmetz et al. (2021)[30]	Genetics of craniofacial malformations	Summarized the molecular basis and developmental mechanisms underlying major craniofacial anomalies.	Provides the genetic foundation for integrating ML with genotype–phenotype analysis in rare facial disorders.
Sharma et al. (2024)[31]	DL in genomics and personalized medicine	Demonstrated the growing role of DL in genomic interpretation, disease prediction, and precision medicine.	Supports the application of AI in genomic analysis, precision diagnosis, and future AI-assisted therapeutic strategies for craniofacial disorders.
Spineli-Silva et al. (2020)[32]	Genomic imbalances in craniofacial microsomia	Reported chromosomal abnormalities and genomic alterations associated with craniofacial microsomia, emphasizing genetic heterogeneity.	Reinforces the importance of AI-driven genomic analysis and variant prioritization for improving molecular diagnosis.
Taiwo (2020)[33]	Classification and clinical management of hemifacial microsomia	Reviewed classification systems, clinical manifestations, and reconstructive management strategies for hemifacial microsomia.	Highlights the potential of AI-based facial phenotyping, 3D imaging, and surgical planning to improve disease classification and patient management.

5. DISCUSSION

Results of this review show that ML and AI have proven to be useful in the management of rare facial disorders through their application in the diagnosis, characterization, and treatment of rare diseases. This is facilitated by the integration of 3D imaging, radiological studies, and genomic data into ML processes, which facilitate early diagnosis, objective assessment of the disease, and surgical planning[34]. Despite much having been done in computer diagnosis and precision medicine, the implementation of AI-based therapeutic interventions is still at an early stage[35].

5.1 Interpretation and Analysis of Findings

The paper shows that AI-driven facial phenotyping, multimodal imaging, and genomic analyses considerably enhance the detection of rare craniofacial conditions sharing similar clinical symptoms[36]. Disease-specific cases show that ML techniques help to assess the severity of the disease, make genotype-phenotype correlations, plan surgery, and monitor the course of the disease longitudinally, while new computational approaches like genome editing and digital twins hold great promise for the future of precision medicine[37].

5.2 Implications and Significance

Incorporation of AI technology into the field of craniofacial medicine has significant implications for all concerned professionals – from physicians, surgeons to patients – through improved diagnosis, customized treatment, and management by multiple specialists[38]. AI decision-support systems can enhance efficiency in clinical practice, conduct genetic counseling, perform reconstruction surgeries, and provide precision-based medicine[39].

5.3 Research Gaps and Limitations

Although there have been many encouraging developments, there are still some limitations, such as the lack of large-scale annotated databases, limited external validation, variable phenotype, demographic bias, and the inability to incorporate multi-modality clinical and genomics data[40]. Also, the use of AI for genome editing and RNA therapy is still very much at an experimental stage.

5.4 Future Research Directions

Areas for future research include the creation of international databases for craniofacial disorders, development of AI systems for multimodalities, ML explainability, federated learning, patient organoids, and digital twin technology. Integration of genomics, bioinformatics, and computational therapeutics with clinical practice will further enhance precision medicine efforts and expedite the deployment of AI-based advances in craniofacial health care.

6. CONCLUSION

AI and ML are changing the diagnosis and treatment of rare facial diseases by enhancing facial phenotyping, medical imaging, genomic analysis, and personalization of treatments. Although AI-guided diagnosis and surgical planning have shown significant clinical promise, therapeutic uses of genome editing and RNA therapy are still experimental. Future improvements in multimodal learning, precision genomics, explainable AI, and clinical research can be expected

to increase diagnostic accuracy, personalize patient treatment, and advance the translation of AI-guided precision medicine in rare craniofacial disorders.

REFERENCES

1. Abbas, S. R., Abbas, Z., Zahir, A., & Lee, S. W. (2025). Advancing genome-based precision medicine: A review on machine learning applications for rare genetic disorders. Briefings in Bioinformatics, 26(4), bbaf329.
2. Abdallah, S., Sharifa, M., Almadhoun, M. K. I. K., Khawar Sr, M. M., Shaikh, U., Balabel, K. M., ... & Kanwar Sr, M. (2023). The impact of artificial intelligence on optimizing diagnosis and treatment plans for rare genetic disorders. Cureus, 15(10).
3. Adenekan, T. K. (2024). Unveiling the Complexity of Craniofacial Anomalies: Integrative Approaches for Early Diagnosis and Effective Management.
4. Ahmed, M. K., Ye, X., & Taub, P. J. (2016). Review of the genetic basis of jaw malformations. Journal of Pediatric Genetics, 5(04), 209-219.
5. Almoammar, K. A. (2024). Harnessing the power of artificial intelligence in cleft lip and palate: an in-depth analysis from diagnosis to treatment, a comprehensive review. Children, 11(2), 140.
6. Amorim, A. M., Orzeł, U., Caniceiro, A. B., Rosário-Ferreira, N., & Moreira, I. S. (2025). Artificial intelligence in rare diseases: toward clinical impact. Trends in Pharmacological Sciences.
7. Areo, G. (2024). Rare Craniofacial Anomalies: Multidisciplinary Strategies for Timely Diagnosis and Intervention.
8. Atiba, P. M., Omotoso, B. R., Madaree, A., & Lazarus, L. (2024). Hemifacial microsomia: a scoping review on progressive facial asymmetry due to mandibular deformity. Oral and Maxillofacial Surgery, 28(4), 1441-1455.
9. Bhat, M. (2020). The human face: genes, embryological development and dysmorphology. International Journal of Developmental Biology, 64(4-5-6), 383-391.
10. Chen, Q., Zhao, Y., Shen, G., & Dai, J. (2018). Etiology and pathogenesis of hemifacial microsomia. Journal of dental research, 97(12), 1297-1305.
11. de Barros, F. R. D., da Silva, C. N. F., de Castro Michelassi, G., Brentani, H., Nunes, F. L., & Machado-Lima, A. (2023). Computer aided diagnosis of neurodevelopmental disorders and genetic syndromes based on facial images–A systematic literature review. Heliyon, 9(10).
12. Faria-Teixeira, M. C., Tordera, C., Salvado e Silva, F., Vaz-Carneiro, A., & Iglesias-Linares, A. (2024). Craniofacial syndromes and class III phenotype: common genotype fingerprints? A scoping review and meta-analysis. Pediatric Research, 95(6), 1455-1475.
13. Germain, D. P., Gruson, D., Malcles, M., & Garcelon, N. (2025). Applying artificial intelligence to rare diseases: a literature review highlighting lessons from Fabry disease. Orphanet Journal of Rare Diseases, 20(1), 186.
14. Guo, L., Park, J., Yi, E., Marchi, E., Hsieh, T. C., Kibalnyk, Y., ... & Lyon, G. J. (2022). KBG syndrome: videoconferencing and use of artificial intelligence driven facial phenotyping in 25 new patients. European Journal of Human Genetics, 30(11), 1244-1254.

15. Harrison, L. M., Edison, R. L., & Hallac, R. R. (2025). Artificial intelligence applications in pediatric craniofacial surgery. Diagnostics, 15(7), 829.

16. Heike, C. L., Wallace, E., Speltz, M. L., Siebold, B., Werler, M. M., Hing, A. V., ... & Luquetti, D. V. (2016). Characterizing facial features in individuals with craniofacial microsomia: a systematic approach for clinical research. Birth Defects Research Part A: Clinical and Molecular Teratology, 106(11), 915-926.

17. Hennocq, Q. (2023). AIDY: application of Artificial Intelligence to Dysmorphology (Doctoral dissertation, Université Paris Cité).

18. Huh, J., Park, J. S., Sodnom-Ish, B., & Yang, H. J. (2024). Growth characteristics and classification systems of hemifacial microsomia: a literature review. Maxillofacial Plastic and Reconstructive Surgery, 46(1), 18.

19. James, K. N., Phadke, S., Wong, T. C., & Chowdhury, S. (2020). Artificial intelligence in the genetic diagnosis of rare disease. Advances in Molecular Pathology, 3, 143-155.

20. Kadakia, S., Helman, S. N., Schwedhelm, T., Saman, M., & Azizzadeh, B. (2015). Examining the genetics of congenital facial paralysis—a closer look at Moebius syndrome. Oral and maxillofacial surgery, 19(2), 109-116.

21. Kruszka, P., & Tekendo-Ngongang, C. (2023, September). Application of facial analysis Technology in Clinical Genetics: Considerations for diverse populations. In American Journal of Medical Genetics Part C: Seminars in Medical Genetics (Vol. 193, No. 3, p. e32059). Hoboken, USA: John Wiley & Sons, Inc..

22. Leprevost, C. M. (2023). The use of artificial intelligence tools in the elucidation of cases of neurodevelopmental disorders. Arquivos de Neuro-Psiquiatria, 81(S 01), A052.

23. Liu, X., Zhang, Z., Han, W., Zhao, Z., Kim, B. S., Yan, Y., ... & Chai, G. (2024). Efficacy of navigation system-assisted distraction osteogenesis for hemifacial microsomia based on artificial intelligence for 3 to 18 years old: study protocol for a randomized controlled single-blind trial. Trials, 25(1), 42.

24. Luo, S., Sun, H., Bian, Q., Liu, Z., & Wang, X. (2023). The etiology, clinical features, and treatment options of hemifacial microsomia. Oral Diseases, 29(6), 2449-2462.

25. Ma, L., Zhao, S., Xu, X., Shu, K., Li, X., Liang, Y., ... & Zhang, Z. (2022). Bioinformatics analysis of Hub genes involved in alcohol-related hemifacial microsomia pathogenesis. Journal of Craniofacial Surgery, 33(6), e607-e612.

26. Marszałek-Kruk, B. A., Piotr, W., Krzysztof, D., & Śmigiel, R. (2021). Treacher Collins syndrome: genetics, clinical features and management. Genes, 12(9), 1392.

27. Matthews, H., de Jong, G., Maal, T., & Claes, P. (2022). Static and motion facial analysis for craniofacial assessment and diagnosing diseases. Annual Review of Biomedical Data Science, 5(1), 19-42.

28. Ozcelik, F., Dundar, M. S., Yildirim, A. B., Henehan, G., Vicente, O., Sánchez-Alcázar, J. A., ... & Dundar, M. (2024). The impact and future of artificial intelligence in medical genetics and molecular medicine: an ongoing revolution. Functional & integrative genomics, 24(4), 138.

29. Pniak, M. (2024). Hemifacial microsomia–a review of the literature of current hypotheses of pathogenesis, and possible therapeutic methods. Polski Przegląd Otorynolaryngologiczny, 13(3), 14-21.

30. Schmetz, A., Amiel, J., & Wieczorek, D. (2021, December). Genetics of craniofacial malformations. In Seminars in Fetal and Neonatal Medicine (Vol. 26, No. 6, p. 101290). WB Saunders.

31. Sharma, A., Kala, S., Kumar, A., Sharma, S., Gupta, G., & Jaiswal, V. (2024). Deep learning in genomics, personalized medicine, and neurodevelopmental disorders. Intelligent Data Analytics for Bioinformatics and Biomedical Systems, 235-264.

32. Spineli-Silva, S., Sgardioli, I. C., Dos Santos, A. P., Bergamini, L. L., Monlleó, I. L., Fontes, M. I., ... & Vieira, T. P. (2020, December). Genomic imbalances in craniofacial microsomia. In American Journal of Medical Genetics Part C: Seminars in Medical Genetics (Vol. 184, No. 4, pp. 970-985). Hoboken, USA: John Wiley & Sons, Inc..

33. Taiwo, A. O. (2020). Classification and management of hemifacial microsomia: a literature review. Annals of Ibadan postgraduate medicine, 18(1), S9.

34. Tiberio, F., Polito, L., Salvati, M., Di Pietro, L., Massimi, L., Parolini, O., ... & Lattanzi, W. (2025). Current understanding of crouzon syndrome pathophysiology and new therapeutic approaches. Journal of Craniofacial Surgery, 36(8), 2959-2970.

35. Wu, D., Yang, J., Liu, C., Hsieh, T. C., Marchi, E., Blair, J., ... & Wang, K. (2024). Gestaltmml: Enhancing rare genetic disease diagnosis through multimodal machine learning combining facial images and clinical texts. ArXiv, arXiv-2312.

36. Xu, M., Liu, B., Luo, Z., Sun, M., Wang, Y., Yin, N., ... & Song, T. (2023). Using a new deep learning method for 3D cephalometry in patients with hemifacial microsomia. Annals of Plastic Surgery, 91(3), 381-384.

37. Xu, X., Wang, B., Jiang, Z., Chen, Q., Mao, K., Shi, X., ... & Zhang, Y. B. (2021). Novel risk factors for craniofacial microsomia and assessment of their utility in clinic diagnosis. Human molecular genetics, 30(11), 1045-1056.

38. Xu, Z., Song, J., Bi, C., Zhang, Y., Zheng, X., Xiao, M., ... & Shen, B. (2025). Computer Vision for Rare Diseases: A Scoping Review.

39. Zebanaz, A., Kareem, A. M., Aher, A. A., & Thitame, S. N. (2025). Personalized medicine in treating rare genetic disorders: a review. Journal of Pharmacy and Bioallied Sciences, 17(Suppl 1), S59-S62.

40. Zhao, S., Sun, P., Li, X., Xu, X., Peng, Q., Shu, K., ... & Zhang, Z. (2022). Identification of hub genes in hemifacial microsomia: evidence from bioinformatic analysis. Journal of Craniofacial Surgery, 33(2), e145-e149.