British Journal of Healthcare and Medical Research - Vol. 9, No. 5
Publication Date: October, 25, 2022
DOI:10.14738/jbemi.95.13309.
Mahwish, N., Saherawala, B. A., & Jhancy, M. (2022). Clinical Decision Making in Dysmorphology- Emerging Role of Artificial Intelligence. British Journal of Healthcare and Medical Research, 9(5). 366-374.

Clinical Decision Making in Dysmorphology- Emerging Role of Artificial Intelligence

Nayesha Mahwish
Department of Pediatrics, Ras Al Khaimah College of Medical Sciences (RAKCOMS), RAK Medical and Health Sciences University (RAKMHSU), Ras Al Khaimah, United Arab Emirates

Batul Abdeali Saherawala
Department of Pediatrics, Ras Al Khaimah College of Medical Sciences (RAKCOMS), RAK Medical and Health Sciences University (RAKMHSU), Ras Al Khaimah, United Arab Emirates

Malay Jhancy
Department of Pediatrics, Ras Al Khaimah College of Medical Sciences (RAKCOMS), RAK Medical and Health Sciences University (RAKMHSU), Ras Al Khaimah, United Arab Emirates

ABSTRACT

The human genome codes for more than 22,000 genes, many of which have been implicated in human diseases. These genetic diseases are often associated with dysmorphic facial features. Dysmorphic features occur due to premature closure of cranial sutures resulting in changes in skull shape and facial characteristics. Assessment of dysmorphic features is a crucial component of genetic consultations. This requires a great deal of clinical experience and expertise and tends to be subjective. Artificial intelligence-based analysis can come in handy for quick and accurate identification of dysmorphic features. This review explores the role played by artificial intelligence in identifying dysmorphic facies and diagnosing various genetic diseases in children.

Keywords: artificial intelligence, dysmorphism, facial recognition technology, genetic disorders

INTRODUCTION

Genetic disorders affect a large proportion of the human population. Individuals affected by these diseases suffer from multiple comorbidities such as congenital heart diseases, respiratory problems, and developmental delays. Early diagnosis can help prevent these comorbidities thus, improving the quality of life of these patients [1].

Dysmorphic facial features occur in over 1500 different human genetic syndromes. These dysmorphic features are quite distinct to each disorder [2]. Downs syndrome, for example, is distinguished by a flattened facial profile, upward slanting palpebral fissures, small ears, a protruding tongue, and extremity variations [3]. Another genetic disorder, Noonan syndrome,

displays characteristics such as hypertelorism, down slanted palpebral fissures, ptosis, a depressed and wide nasal bridge, and low set ears [4].

Identifying dysmorphic facial features aids in the early identification and diagnosis of genetic disorders. It forms an essential component of genetic consultations. However, it requires a great deal of clinical experience and expertise. There may be subjective variations in assessment of dysmorphic facies by different clinicians [5]. Hence, recognizing dysmorphic features is a daunting task.

With recent advances in the field of artificial intelligence, facial recognition systems have been developed that assist in the screening and diagnosis of genetic disorders [6]. Deep learning systems can identify and distinguish genetic conditions based solely on facial phenotyping. They have been shown to be more accurate than human experts in phenotype recognition of genetic diseases [7].

In this review, we summarize the role played by artificial intelligence (AI) in identification of dysmorphic facial features in children with various genetic disorders.

METHODOLOGY & DATA ANALYSIS

Journal articles published from January 2010 to October 2021 about application of artificial intelligence in identification of dysmorphism were collected from the databases ProQuest, PubMed, Scopus and Medline using the key words Artificial intelligence OR AI AND identification OR diagnosis AND dysmorphology OR dysmorphism AND children AND genetic disorders. The articles were reviewed. The method is represented below in figure I.

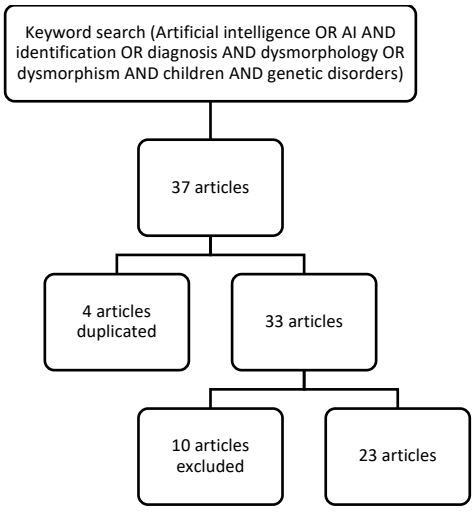

Fig.I Methodology

RESULTS

Facial recognition technology

Artificial intelligence (AI) allows computers to solve complex problems and turn raw data into meaningful data to be used to classify syndrome types. It uses convolutional neural networks (CNNs) that have massive neurons, layers, and connectivity [8]. Systems such as DeepFace use

URL: http://dx.doi.org/10.14738/jbemi.95.13309

CNNs while being trained on large amounts of training data to reach performance at the level of humans.

The most widely used facial recognition application by geneticists is Face2Gene [created by Facial Dysmorphology Novel Analysis (FDNA Inc., Boston, Massachusetts, USA)] [9]. The Face2Gene application is readily available to download onto a mobile device and can be used worldwide wherever there is access to the internet. Face2Gene has a large and an ever-growing of database of digital images of syndromic patients acting as a reference for the system. Real life images are taken and processed by a landmark detection algorithm to geometrically standardize the patient's face for face verification and reduce pose variation. Ratios between the points are calculated and compared to a holistic patient ratio. The system is then trained on these images from a large data set with the help of clinicians identifying patients. The system then can give a diagnosis on what a patient's gestalt is best matched to a syndrome [10].

Genetic disorders identified by facial recognition technology

Artificial intelligence-based systems have been tried and tested for the identification of various genetic disorders ranging from common disorders such as Turners syndrome to rare disorders such as Phosphomannomutase-2 deficiency (**Table I**).The clinical trials have been discussed below.

Noonan syndrome

Noonan syndrome is an autosomal dominant/recessive disorder. Some of its features include short stature, craniofacial dysmorphism, cardiac abnormalities, short and/or webbed neck, and cryptorchidism in male patients. This syndrome occurs due to mutations in genes encoding proteins of the RAS-MAPK signaling pathway, resulting in pathway dysregulation. 15 such genes have been identified so far: PTPN11, SOS1, RAF1, BRAF, HRAS, KRAS, NRAS, SHOC2, MAP2K1, MAP2K2, CBL, RIT1, RASA2, A2ML1, and LZTR1.

In one study, facial images of 60 molecularly confirmed Chinese NS were evaluated with the Face2Gene Research Application (FDNA Inc., Boston, Massachusetts). The images comprised six pathogenic variants (PTPN11, SOS1, SHOC2, KRAS, RAF1, and RIT1) of the disorder. Results showed that the mean accuracy that was achieved by Face2Gene on the original sample set was 28%. Moreover, each gene was accompanied with different facial features, all of which were distinguished by the application. Patients with SHOC2 pathogenic variants were characterized by significant macrocephaly and thin sparse hair, while patients with RAF1 pathogenic variants had prominent foreheads [11].

Angelman syndrome

Angelman syndrome is a neurogenetic disorder characterized by developmental delay, excessive laughter, absent or severely limited speech, seizures with a characteristic electroencephalogram (EEG) and microcephaly. Characteristic facial features include wide mouth, protruding tongue, midface recession and prognathism. AS occurs due to deficient expression of gene UBE3A on chromosome 15. Different molecular subtypes of AS are characterized by minor differences in facial features. Identification of these subtle facial features could guide genetic testing for AS patients and their families.

A study demonstrated that the Face2Gene application was able to recognize subtle differences in facial phenotypes and thus distinguish different cohorts of AS patients based on the molecular mechanisms [7].

Cornelia de Lange syndrome

CdLS is a genetic disorder characterized facial dysmorphism, intellectual disability, limb reduction and growth retardation. 65% of the cases are caused by mutations in one of five known cohesin-related genes: NIPBL, SMC1A, SMC3, HDAC8, and RAD21.It exhibits a wide phenotypic spectrum depending on the gene involved. Individuals suffering from the classic form CdLS caused by the NIPBL gene mutations commonly present with dysmorphic features that can be quite easily identified. However, recognition of patients with CdLS caused by SMC1A (also called SMC1L1) and SMC3 gene mutations is a challenge.

Automated facial dysmorphology novel analysis (FDNA) technology was able to detect CdLS (NIPBL or SMC1A gene mutation) facial features from 2D facial images with an average detection rate of 87% compared 77% detection rate by dysmorphologists. In another study, when a different set of photos from NIPBL, SMC1A and non-CdLS patient was evaluated, the detection rate rose to 94%. The results from both studies revealed that the system's detection rate was comparable to that of dysmorphology experts [9].

Another study tested the accuracy of Face2Gene application in identifying CdLS in 49 individuals suffering from clinically and molecularly confirmed as CdLS. The app showed CdLS within the top five differential diagnoses for 97.9% of the cases and listed it as first prediction for 83.7% [12].

XLHED

X-linked hypohidrotic ectodermal dysplasia (XLHED) is a genetic disorder that affects ectodermal structures and characterized by a triad of hypotrichosis, hypodontia or anodontia and reduced or absent sweating ability. Patients exhibit typical facial features including narrow, short face, long, prominent chin, narrow nose with a pinched tip, high zygomatic arches, short philtrum, midface retrusion, thick lower lip vermillion, prognathism, and narrow mouth. This typical facial phenotype is less apparent in XLHED females.

Facial Dysmorphology Novel Analysis software (FDNA) system identified XLHED phenotype in all genetically confirmed affected male patients of all ages, and in 55% of heterozygous females. It showed a high sensitivity and specificity, especially in males [13].

PMM2-CDG

Phosphomannomutase-2 deficiency (PMM2-CDG) also known as Jaeken syndrome, is a genetic disorder caused by pathogenic variants in the PMM2 gene. Clinically, PMM2-CDG presents as a multi-system disorder (manifesting as development disability, cerebellar atrophy, failure to thrive, enteropathy, coagulopathy and liver dysfunction), fat pads and inverted nipples. Dysmorphic features include strabismus, prominent forehead, large ears, thin upper lip, prominent jaw, and long and slender fingers and toes. The distinct features of PMM2-CDG are an abnormal fat distribution and inverted nipples.

URL: http://dx.doi.org/10.14738/jbemi.95.13309

The automated facial analysis software Face2Gene correctly identified 41 photographs of patients with a confirmed diagnosis of PMM2-CDG. In all cases, PMM2-CDG appeared as one of the top 10 syndrome matches given by the tool [14].

Turner syndrome

Turner syndrome is a chromosomal disorder that occurs due to total or partial absence or structural abnormality of one copy of the X chromosome. Clinical features include short stature, ovarian failure, lymphedema, cardiovascular diseases, and renal diseases. Affected individuals also exhibit dysmorphic features including epicanthal fold, ptosis, ocular hypertelorism, low-set ears, multiple facial nevi, low hairline, micrognathia, and webbed neck.

An automatic facial classification system was able to diagnose TS with 68.8% sensitivity and 87.5% specificity when used on 32 patients with TS. The system was able to identify the condition more accurately than clinicians [15].

Fetal Alcohol Spectrum Disorders

Fetal Alcohol Spectrum Disorders are a group of structural anomalies and neurocognitive disabilities caused sue to prenatal alcohol exposure. It comprised the following diagnostic categories: (1) fetal alcohol syndrome (FAS), (2) partial fetal alcohol syndrome (PFAS), (3) alcohol-related birth defects (ARBDs), and (4) alcohol-related neurodevelopmental disorders (ARNDs). It is characterised by dysmorphic features including short palpebral fissures, smooth philtrum and thin vermilion border of the upper lip.

The facial recognition and analysis software Face2Gene was found to be almost as accurate as expert dysmorphologists in the diagnosis of cases of FAS and PFAS. Moreover, it showed higher accuracy than dysmorphologists for diagnosis of ARND [16].

DDCRs

The developmental disorders of chromatin remodeling (DDCRs) are a group of disorders caused by impairment in chromatin remodeling. Characteristic features include cognitive impairment and dysmorphic facial features such as abnormal orbital region, nose and mouth conformation.

In a study using the Face2Gene application (FDNA Inc., Boston, MA, USA) on 120 individuals harboring variants in genes codifying for the histone enzymes, the app showed a remarkable capacity to identify and differentiate the syndromes. Moreover, it was also able to recognize unique facial details of the syndromes based on their phenotypes [17].

NDDs

Neurodevelopmental disorders (NDDs) comprise a range of conditions that manifest as development impairments in cognitive, social, academic, or occupational functioning. Intellectual disability (ID), communication disorders, autism spectrum disorder (ASD), attention–deficit/hyperactivity disorder (ADHD), specific learning disorders, and motor disorders fall under NDDs. Presence of genetic alterations may produce more morphological variants in individuals with NDDs, particularly ASD.

When Face2Gene Application was used on a cohort of 290 twins, a percentage agreement of 78.3 to 100% was found between facial morphological variants identified through clinical reexamination compared those identified through the application. In the twin sample, individuals with and without NDDs had comparable number of facial morphological variants, even after controlling for shared genetic and environmental factors within twin pairs. Common facial morphological variants in those with and without NDDs included thick upper lip vermilion, abnormality of the nasal tip, long face, and up slanted palpebral fissure. Thus, facial morphological variants can be evaluated reliably in NDDs with automated tools like Face2Gene. However, clinical utility is inadequate when just exploring the facial region [18].

Table I Clinical trials of facial recognition applications

Disorder	Application used	Type of study	Sample size	Accuracy	Reference
Noonan syndrome	Face2Gene Research Application (FDNA Inc., Boston, Massachusetts)	Cohort study	103	28%	11
Angelman syndrome	Face2Gene Research Application (FDNA Inc., Boston, Massachusetts)	Cohort	261	0.49 to 0.61 represent the comparisons with highest phenotypic similarities, which correspond to highly similar mechanisms. 0.67 to 0.77 primarily represent comparisons of UBE3A pathogenic variants versus other mechanisms. 0.81 or greater represent comparisons y involves binary comparisons between molecular subtypes derived from dissimilar molecular mechanisms (deletions vs. imprinting defects and deletions vs. UPD)	7
Cornelia de Lange syndrome	Face2Gene Research Application (FDNA Inc., Boston, Massachusetts)	Cohort	17	94%	9
Cornelia de Lange syndrome	Face2Gene Research Application (FDNA	cohort	49	The study shows that Face2Gene was able to diagnose CdLS patients with classic phenotype	12

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	Inc., Boston, Massachusetts)			(clinical score >11) with a top-one sensitivity of 88.8%. However only 66.6% top-one sensitivity was achieved in non-classic phenotypes (clinical score < 11).	
XLHED	Facial Dysmorphology Novel Analysis software (FDNA) system	cohort	1–10 years: 64 >11 years: 42 >1 month: 30 Total: 136	specificities of 99–100% and sensitivities of 75% in all age groups.	13
PMM2-CDG	Face2Gene Research Application (FDNA Inc., Boston, Massachusetts)	cohort	31	sensitivity of 96.8% and a specificity of 92.3%	14
Turner syndrome	An automatic facial classification system	cohort	54	68.8% sensitivity and 87.5% specifcity (and a 67.6% average sensitivity and 87.9% average specifcity after resampling)	15
Fetal Alcohol Spectrum Disorders	Face2Gene Research Application (FDNA Inc., Boston, Massachusetts)	cohort	FASD: 89 Control: 50 Total: 139	86 ± 3%	16
DDCRs	Face2Gene Research Application (FDNA Inc., Boston, Massachusetts)	Cohort	120 affected subjects 60 unaffected control 60 subjects affected by other ID syndromes with distinctive dysmorphic features Total: 240	In the comparison experiment 1, mean accuracy of 54.8%, standard deviation of 12.25% In the comparison experiment 2, mean accuracy of 73.11, standard deviation of 6.62%	17
NDDs	Face2Gene Research Application (FDNA Inc., Boston, Massachusetts)	cohort	290 twins enriched for NDDs (n = 135 with NDD diagnoses)	Agreement between automated and clinical assessments were satisfactory to complete (78.3–100%).	18

DISCUSSION

Facial recognition systems such as Face2Gene Research Application (FDNA Inc., Boston, Massachusetts) are more accurate than human experts in phenotype recognition of genetic disorders including Noonan syndrome, Angelman syndrome, Cornelia de Lange syndrome, Fetal Alcohol Spectrum Disorders, XLHED, PMM2-CDG, DDCRs as well as neurodevelopmental disorders. Moreover, the application is also able to distinguish amongst different molecular /pathogenic variants of Noonan syndrome and Angelman syndrome based on minor differences in facial features. Other newer facial recognition systems were also able to detect XLHED and Turner syndrome with high degree of accuracy. Use of facial recognition apps results in early diagnosis of children, lessening the time and money otherwise spent on lengthy and expensive genetic tests. In areas where facilities for molecular testing are limited, AI based analysis can assist in prioritizing a diagnosis so that limited resources are spent wisely. It can help to individualize genetic testing, resulting in cost savings. Facial recognition systems are especially useful in the diagnosis of rare genetic disorders, which may be easily missed out by less experienced clinicians.

However, there are some limitations to the use of artificial intelligence systems. Firstly, only sparse number of researches have been carried out that test the accuracy of facial recognition applications in recognizing dysmorphism. Of the studies done, most have been carried out on certain ethnic populations, undermining the accuracy of the applications in other ethnicities. Moreover, only one application which is the Face2Gene application has been fully developed to detect dysmorphic facial features, other applications are still in their infancy.

CONCLUSION

Artificial intelligence may have an upcoming role in the screening and diagnosis of genetic disorders in the future. However, newer applications need to be developed and more studies need to be carried out to fully explore the potential of artificial intelligence in the field of dysmorphology.

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