RESEARCH PAPER

Computer-aided Facial Analysis in Diagnosing Dysmorphic Syndromes in Indian Children

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Objective: To assess the utility of computer-aided facial analysis in identifying dysmorphic syndromes in Indian children. **Methods**: Fifty-one patients with a definite molecular or cytogenetic diagnosis and recognizable facial dysmorphism were enrolled in the study and their facial photographs were uploaded in the Face2Gene software. The results provided by the software were compared with the molecular diagnosis. **Results**: Of the 51 patients, the software predicted the correct diagnosis in 37 patients (72.5%); predicted as the first in the top ten suggestions in 26 (70.2%). In 14 patients, the software did not suggest a correct diagnosis. **Conclusions**: Computer-aided facial analysis is a method that can aid in diagnosis of genetic syndromes in Indian children. As more clinicians start to use this software, its accuracy is expected to improve.

Keywords: *Facies, Gestalt theory, Photographs*.

Many of the genetic syndromes have distinct facial features and recognizing a syndrome from facial gestalt is the first step in diagnosis. Based on facial features, many a times, a geneticist or a pediatrician is able to reach a possible diagnosis and order appropriate tests for confirmation of the same. In many instances, failure to identify a particular genetic syndrome results in a delay in diagnosis and unwarranted investigations for the patients and families. Memorizing facial gestalt of common syndromes is a cumbersome task and is challenging for geneticists and pediatricians. With recent advances in artificial intelligence, tools like Face2Gene (FDNA, Inc., Boston, MA) have been developed, which aid clinicians recognize genetic syndromes based on facial gestalt. Face2Gene utilizes deep convolutional neural networks (DCNN) and compares a patient's gestalt to its database for syndrome suggestion [1]. Previous studies have shown superiority of this computer-aided facial recognition in identifying genetic syndromes in different populations groups [2-4]. Since the original software was trained with photographs from Caucasian population and since the results of the software can change based on ethnicity, it becomes important to assess its utility in other populations. Our aim was to assess the use of Face2Gene in accurately identifying proven genetic syndromes in Indian children.

Accompanying Editorial: Pages 1007-08.

Methods

After obtaining informed consent from parents or guardians, patients with recognizable facial dysmorphism and a proven genetic diagnosis were included in this study from the records available in the Genetics outpatient departments from two different centers in India between January to June 2018. Institutional Ethics Committees approved the study. Age, sex, anthropometry and other clinical details were noted from the records. A minimum of two facial photographs (a frontal and lateral, wherever available) were collected and uploaded to the Face2Gene CLINIC app. No clinical details were added in the first go. If the software provided the correct clinical diagnosis as one among the first ten differential diagnoses, we considered it as a positive result. If the correct diagnosis was not available in the first ten diagnoses, then we added additional clinical information required and modified the phenotype and assessed whether the software gave a correct diagnosis. If the software was unable to provide the correct diagnosis even after providing additional information, it was taken as a negative result.

RESULTS

Fifty-one patients (28 males, age 11 d-18 y) with a facial phenotype and a proven genetic diagnosis were included in the study. Fifteen (29.4%) children had chromosomal abnormalities or micro deletion/ duplication syndromes, and rest had single gene disorders. A positive result (correct diagnosis in the first ten differential diagnoses) was obtained in 37 patients (72.5%); in 26 patients (26/37; 70.2%), the correct diagnosis was the first in the list. In 15 patients, the correct diagnosis was not listed in the first ten diagnoses. Out of these 15, for one patient when additional details were provided, the software predicted the correct diagnosis as one among the predicted ten diagnoses and hence that was considered as a positive result. Of the 14 patients for whom the software did not provide the correct diagnosis, no suggestions were obtained for 8 patients. ***Web Table* 1** summarizes the details of the patients and the prediction by the software. We herein describe two representative cases to explain the use of the software.

Patient 1: A 13-year-old female, who was the only offspring of non-consanguineous parents, was brought for evaluation of mental subnormality and primary amenorrhea. On evaluation, she had facial dysmorphism with prominent metopic ridge, microcephaly and borderline mental sub normality (***Fig.* 1a, 1b**). MRI pelvis showed hypoplastic uterus and ovaries. Her karyotype was 46,XX. Chromosomal microarray was normal. Since she had facial dysmorphism, her photograph was uploaded to Face2Gene, which predicted the diagnosis of fetal valproate syndrome with high accuracy (***Fig.* 1c**). On revisit, details about maternal drug intake during pregnancy were enquired to the grandparents who accompanied the patient. The mother was on 1000 mg of sodium valproate during the entire course of pregnancy. This suggests that the child most probably had fetal valproate syndrome, though this could not be conclusively proven; hence, she was not included in this cohort.

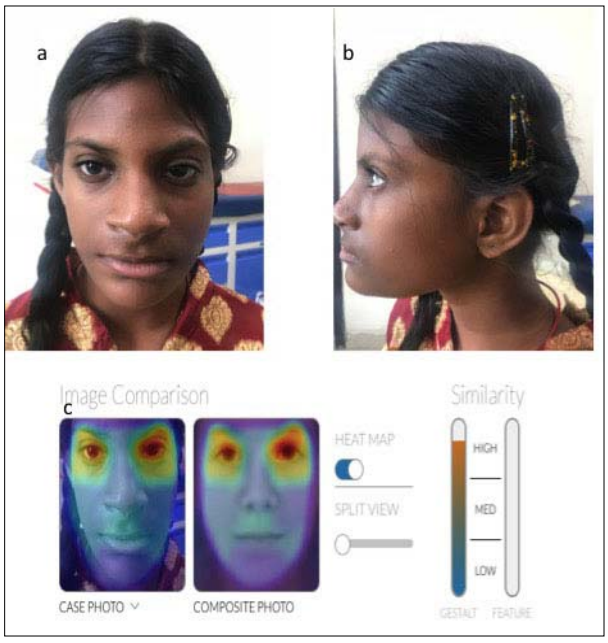

FIG. 1 *(a) Frontal view of patient with probable fetal alcohol syndrome showing high forehead, prominent metopic suture, long thin upper lips, (b) Low set ears; and (c) Heatmap showing high similarity of patient photograph with that of Fetal Valproate syndrome.*

Patient 2: A four-year-old female was evaluated for developmental delay. She did not cry soon after birth. She had facial dysmorphism and swelling in nape of neck at birth. She never had any seizures. She had arched eyebrows, short neck, epicanthal folds and bilateral iris coloboma (***Fig*. 2a, b, c**). We suspected chromosomal abnormality. But the software predicted it to be Baraitser-Winter syndrome. Baraitser-Winter syndrome can be caused due to heterozygous variations in *ACTB* or *ACTG1* genes. Exome sequencing in the proband identified a previously unreported heterozygous variant in exon 4 of the *ACTB* gene (c.575T>G p.Ile192Ser), located in a highly conserved nucleotide and amino acid position, confirming the diagnosis of Baraitser-Winter Syndrome. The same variant was absent in her parents indicating that the variant was *de novo*.

DISCUSSION

In our study, the software was able to provide an accurate clinical suggestion as the first option in 50% of patients.

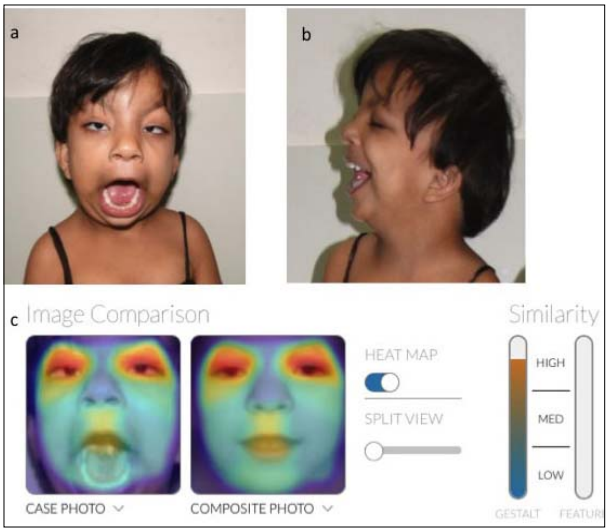

FIG. 2 *(a,b): facial dysmorphism in a child with Winter Baraitser syndrome; and (c) Heatmap showing high similarity of patient photograph with that of fetal valproate syndrome.*

WHAT THIS STUDY ADDS?

- This study demonstrates the use of computer-aided facial analysis in diagnosing syndromes in Indian patients.

But in some easily recognizable conditions like Turner syndrome, Waardenburg syndrome and Wolfe Hirschhorn syndrome, the software was unable to provide a diagnosis. Even though our study is descriptive and limited in terms of the number of patients, results show that computer-aided facial recognition for syndrome identification can be used for diagnosing genetic syndromes.

Advances in computer vision and machine learning have now aided in the development of softwares like Face2Gene, which enable face recognition and thus syndrome diagnosis. Face2Gene is able to compare 2D facial images to more than 300 syndromic phenotype models [6]. Vanagaite, *et al*. [2] concluded that Face2Gene detection rate was comparable to that of dysmorphologists in a study done on facial recognition of Cornelia De Lange phenotype. A study on computer-aided facial recognition of fetal alcohol spectrum disorders concluded that software enabled better detection of individuals with fetal alcohol spectrum disorders [3]. Though geometric morphometrics was used to characterize Rubinstein Taybi syndrome [7], studies using computer-aided facial recognition for syndrome diagnosis were lacking in India. To the best of our knowledge our study is the first such attempt from India. Deep phenotyping is also important in the next generation sequencing era because it helps in classification of variants and ascertains their clinical significance.

As more and more clinicians use the software, the system can be trained to make more accurate diagnosis. Computer-aided facial recognition has an important role in diagnosing genetic syndromes and can be used as a tool by both pediatricians and geneticists.

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Consent for publication of photographs has been obtained from parents of included children.

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WEB TABLE I INDIVIDUAL PATIENT DETAILS AND SOFTWARE PREDICTIONS

No.	*Age/Sex*	*Clinical gestalt diagnosis*	*Molecular/Cytogenetic diagnosis*	*Predicted as first diagnosis*	*Correct diagnosis in first ten diagnoses*	*Correct diagnosis after additional information*
1.	4 y/M	Mucopolysaccharidosis	MPS II	Yes	Yes	-
2.	4 mo/F	Mowat Wilson syndrome	Mowat WilsonSyndrome	Yes	Yes	-
3.	4 y/M	Waardenburg syndrome	Waardenburg syndrome	No	No	No
4.	2 y/M	William syndrome	William syndrome	Yes	Yes	-
5.	5 y/F	Prader Willi syndrome	Angelman syndrome	Yes	Yes	-
6.	9 y/M	?Chromosomal	5p duplication	No	No	No
7.	12 y/F	Turner syndrome	Turner syndrome	No	No	No
8.	11 d/F	Down syndrome	Down syndrome	Yes	Yes	-
9.	4 y/M	?Chromosomal	MED12 related intellectual disability	No	No	No
10.	11 y/M	Cockayne syndrome	Cockayne syndrome	No	Yes	-
11.	1 y/M	Trisomy 18	Trisomy 18	No	Yes	-
12.	4 y/F	William syndrome	William syndrome	Yes	Yes	-
13.	12 y/M	Fragile X syndrome	Fragile X syndrome	Yes	Yes	-
14.	12 y/F	William syndrome	William Syndrome	Yes	Yes	-
15.	7 y/M	Fragile X syndrome	Fragile X syndrome	Yes	Yes	-
16.	1 y/M	Cockayne syndrome	Cockayne syndrome	Yes	Yes	-
17.	8 y/M	Cockayne syndrome	Cockayne syndrome	No	Yes	-
18.	6 y/M	Cockayne syndrome	Cockayne syndrome	No	No	Yes
19.	9 y/M	William syndrome	William syndrome	Yes	Yes	-
20.	8 y/F	Mucopolysaccharidoses	MPS III	No	No	No
21.	9 y/M	Smith Magenis syndrome	Smith Magenis syndrome	Yes	Yes	-
22.	5.5y/F	Mucopolysaccharidoses	MPS III	No	Yes	-
23.	2 y/F	Mucopolysacharidoses	I cell disease	No	Yes	-
24.	2 y/F	Wolf–Hirschhorn syndrome	Wolf- Hirschhorn syndrome	No	No	No
25.	1 y/F	I cell disease	I cell disease	Yes	Yes	-
26.	13 y/F	William syndrome	William syndrome	No	No	No
27.	8 y/M	Lipodystrophy	Berardinelli Seip syndrome	No	No	No
28.	5 y/M	Syndromic intellectual disability	Cohen syndrome	No	Yes	-
29.	3 mo/F	Di George syndrome	Di George syndrome	No	Yes	-
30.	10 mo/M	I cell disease	I cell disease	No	No	No
31.	16 y/M	Noonan syndrome	Noonan syndrome	Yes	Yes	-
32.	7 mo/M	Geleophysic dysplasia	Geleophysic dysplasia	No	No	No
33.	1 y/M	MPS	Hurler syndrome	No	Yes	-
34.	7 y/M	MPSII	Hunter syndrome	No	Yes	-
35.	5 y/M	Achondroplasia	Achondroplasia	Yes	Yes	-
36.	3 y/M	Fragile X syndrome	Fragile X syndrome	Yes	Yes	-
37.	1 y/M	I cell disease	I cell disease	No	No	No
38.	5 y/F	Apert syndrome	Apert syndrome	No	No	No
39.	4 y/F	?Chromosomal	Winter Baraitser syndrome	Yes	Yes	-
40.	2 y/F	Cornelia De Lange syndrome	Cornelia De Lange syndrome	Yes	Yes	-

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No.	*Age/Sex*	*Clinical gestalt diagnosis*	*Molecular/Cytogenetic diagnosis*	*Predicted as first diagnosis*	*Correct diagnosis in first ten diagnoses*	*Correct diagnosis after additional information*
41.	13 y/F	Noonan syndrome	Noonan syndrome	Yes	Yes	-
42.	5 y/F	Mandibulo acral dysostosis	Mandubular Hypoplasia, Deafness, Progeroid features and Lipodystrophy syndrome	No	Yes (Progeria)	-
43.	12 Y/F	Noonan syndrome	Noonan syndrome	Yes	Yes	-
44.	9 y/M	Apert syndrome	Apert syndrome	Yes	Yes	-
45.	18 y/M	Noonan syndrome	Noonan syndrome	Yes	Yes	-
46.	1 y/F	Jacobson syndrome	Jacobson syndrome	No	No	No
47.	9 y/F	Noonan syndrome	Noonan syndrome	Yes	Yes	-
48.	15 y/M	Prader Willi syndrome	Prader Willi syndrome	No	No	No
49.	18 mo/F	Noonan syndrome	Noonan syndrome	Yes	Yes	-
50.	10mo/M	Down syndrome	Down syndrome	Yes	Yes	-
51.	9 mo/M	Achondroplasia	Achondroplasia	Yes	Yes	-