ANNALS OF CHILD NEUROLOGY

Brief communication

pISSN 2635-909X • eISSN 2635-9103
Ann Child Neurol 2023;31(4):271-275
https://doi.org/10.26815/acn.2023.00227

Lessons Learned from the Point-of-Care Use of a Facial Analysis Technology

Jon Soo Kim, MD[1], Hansol Ko, BSN[1], Hyewon Woo, MD[1], Won Seop Kim, MD[1,2]

[1]Department of Pediatrics, Chungbuk National University Hospital, Cheongju, Korea
[2]Department of Pediatrics, Chungbuk National University College of Medicine, Cheongju, Korea

Received: July 13, 2023
Revised: August 9, 2023
Accepted: August 16, 2023

Corresponding author:
Won Seop Kim, MD
Department of Pediatrics, Chungbuk National University Hospital, Chungbuk National University College of Medicine, 776 1sunhwan-ro, Seowon-gu, Cheongju 28644, Korea
Tel: +82-43-269-7342
Fax: +82-43-269-6064
E-mail: wskim@chungbuk.ac.kr

Purpose: We aimed to evaluate the utility of facial analysis technology for genetic diagnoses in a typical pediatric genetic clinic.
Methods: A retrospective review identified children (aged <18 years) who had not previously received a definitive genetic diagnosis and underwent a comprehensive genetic evaluation. Their photographs and relevant clinical non-facial features were uploaded to the CLINIC application of the Face2Gene web interface, and the resulting analysis was accessed and correlated to the molecular diagnosis.
Results: Of the 23 children included, the overall diagnostic yield in this study was 60.9% (14/23). In total, 64.3% of patients had the correct condition suggested in the top 10 differential diagnoses. The gestalt similarity was only 55.6%, but the phenotypic features added by the clinician showed a similarity of more than the medium level in all patients.
Conclusion: Our data underscore the usefulness of facial analysis technology as an auxiliary point-of-care tool in pediatric genetic clinics, and we also present some considerations to increase accuracy.

Keywords: Face; Genetic techniques; Machine learning

Findings

With recent remarkable advances in diagnostic and treatment technologies for genetic syndromes, a timely diagnosis has become crucial [1]. However, establishing an accurate diagnosis remains a lengthy, expensive, and expert-dependent process, especially considering the increasing number of possible rare syndromes [2]. Facial dysmorphology often offers valuable diagnostic clues, but interpreting these facial features and identifying specific genetic syndromes can pose a challenge, even for genetic experts [3,4]. Recent studies have demonstrated the considerable potential of deep learning-based facial analysis technologies as diagnostic tools for genetic syndromes [1-6]. The aim of this study was to contribute additional data on the utility of facial analysis technology for genetic diagnosis in a typical pediatric genetic clinic.

A retrospective review was carried out from September 2020 to August 2022 of patients treated at the clinic for rare genetic diseases at Chungbuk National University Hospital. We identified children under 18 years of age who had not previously received a definitive genetic diagnosis and underwent a comprehensive genetic evaluation. These patients sought consultation at the clinic for rare genetic diseases for various reasons, including unexplained developmental delay, intellectual disability, and craniofacial dysmorphism. The clinician's discretion guided the conventional diagnos-

tic investigations. Chromosomal microarray (CMA) and/or targeted panel sequencing were employed as first-line tests, while whole-genome sequencing (WGS) was utilized as a second-line test when the genetic cause remained unidentified. Additional confirmatory tests, such as G-banded karyotyping and methylation polymerase chain reaction assay, were conducted as needed. All parents or legal guardians provided written informed consent for image publication. Furthermore, at least one full frontal face image was collected beforehand to validate the facial recognition software for patients who later received a confirmed genetic diag-

Table 1. Summary of 14 patients receiving genetic diagnosis

Case	Sex	Age (yr)	HPO phenotype[a]	Genetic finding	Diagnosis (OMIM)	Similarity		Top 10 lists
						Gestalt	Feature	
F01	F	3	Global DD, feeding difficulties in infancy, FTT, hypotonia	PV_KLHL40 c.1582G>A(p.Glu528Lys) Hom	Nemaline myopathy (#615340)	None	Med	Included
F02	F	1.1	Global DD, ID, feeding difficulty in infancy, FTT, hypotonia, strabismus, seizure	LPV_YY1 c.1130A>G(p.His377Arg) Het, *de novo*	Gabriele-de Vries syndrome (#617557)	-	-	-
F05	M	16.6	Global DD, ID, autistic behavior, seizure	PV_SZT2 c.2507del(p.Ser836Metfs*95) Het LPV_SZT2 c.6553C>T(p.Arg2185Trp) Het	Developmental epileptic encephalopathy (#615476)	-	-	-
F06	M	0.4	Nystagmus, albinism	LPV_OCA2 c.1160C>T(p.Thr387Met) Het Exon 20-24 deletion of OCA Het	Oculocutaneous albinism (#203200)	None	High	Included
F07	F	16.6	Global DD, ID, autistic behavior, stereotypical body rocking	P_arr 7q11.23 (72,589,903-74,392,574)×1	Williams syndrome (#194050)	Med	Med	Included
F08	F	8.5	Myopathy, feeding difficulty in infancy, lumbar hyperlordosis, waddling gait	PV_RYR1 c.5653G>T(p.Glu1885*) VUS_RYR1 c.7487C>T(p.Pro2496Leu) Het (compound)	Central core disease (#255320)	None	Med	Included
F09	F	9.9	Myopathy, feeding difficulty in infancy, lumbar hyperlordosis, waddling gait	PV_RYR1 c.5653G>T(p.Glu1885*) VUS_RYR1 c.7487C>T(p.Pro2496Leu) Het (compound)	Central core disease (#255320)	None	Med	Included
F11	F	0.1	Premature birth, hemivertebrae	LP_arr 16q11.2 (29,580,020-30,177,240)×1	16p11.2 deletion syndrome (#611913)	-	-	-
F16	F	7.2	Global DD, ID, autistic behavior, stereotypical hand wringing, seizure	PV_FOXG1 c.256del(p.Gln86Argfs*106) Het, *de novo*	Rett syndrome (#613454)	Med	Med	Included
F19	F	0.1	Hearing impairment, umbilical hernia	P_arr 7q11.23 (72,718,277-74,141,603)×1	Williams syndrome (#194050)	Med	Med	Included
F20	M	6.6	Global DD, ID, autistic behavior	LP_arr 16p12.2 (21581028_21946045)×1	16p12.2 deletion syndrome (#136570)	-	-	-
F21	F	5.5	Global DD, ID, ectopic kidney, short stature	LP_arr 16p12.2 (21,405,327-21,816,543)×1	16p12.2 deletion syndrome (#136570)	-	-	-
F22	M	6	Hypotonia, feeding difficulty in infancy, cryptorchidism	LP_arr15q11.2 (22,817,870-102,397,317)×2 hmz Uniparental disomy	Prader-Willi syndrome[b] (#176270)	Low	Med	Included
F23	F	11	Global DD, ID, autistic behavior, stereotypical hand wringing, seizure	PV_MECP2 c.880C>T(p.Arg294*) Het	Rett syndrome (#312750)	Med	Med	Included

HPO, human phenotype; OMIM, online Mendelian inheritance in Man; DD, developmental delay; FTT, failure to thrive; PV, pathogenic variant; Hom, homozygous; Med, medium; ID, intellectual disability; LPV, likely pathogenic variant; SZT2, seizure threshold 2; P, pathogenic; VUS, variant of uncertain significance; LP, likely pathogenic; hmz, hemizygous.

[a]Exclusive of craniofacial dysmorphism; [b]Confirmed by an additional methylation-specific test.

https://doi.org/10.26815/acn.2023.00227

nosis. These photos, along with pertinent clinical non-facial features, were uploaded to the CLINIC application of the Face2Gene (F2G) web interface (https://www.face2gene.com/). The resulting analysis was then correlated with the molecular diagnosis. The app presents the degree of similarity as a bar plot, indicating "high," "medium," or "low" levels. The study adhered to the Declaration of Helsinki and received approval from the Institutional Review Board of Chungbuk National University Hospital (2020-04-005). Written informed consent was obtained from all patients' parents for research purposes and publication, including photographs with recognizable faces.

Frontal facial photographs of 23 children, suspected of having a genetic syndrome with craniofacial dysmorphism, were available for review (14 females; median age, 5.5 years; range, 0.1 to 16.6). Genetic testing was conducted based on the clinical diagnosis made by the clinician. Of these children, 12 received a genetic diagnosis through the first-tier test. The remaining 11 underwent second-tier testing, with two of them receiving a final genetic diagnosis. The overall diagnostic yield of this study was 60.9% (14/23). Table 1 presents the clinical characteristics and genetic findings of the 14 patients who received a final genetic diagnosis. The cases that made it to the top 10 lists are also indicated, along with the level of similarity in gestalt and feature. Nine out of the fourteen (64.3%) patients had conditions that were correctly included in the top 10 differential diagnoses by the F2G system. Among the patients who matched the top 10 lists, the most common disease was congenital myopathies (three cases), followed by Williams syndrome (two cases), Rett syndrome (two cases), Prader-Willi syndrome (one case), and oculocutaneous albinism (one case). The majority of the syndromes (88.9%) were diagnosed with the first-line genetic test, based on the clinician's clinical diagnosis. Interestingly, for the diseases included in the top 10 lists, the gestalt similarity was only 55.6%. However, the non-facial phenotypic features added by the clinician showed a similarity of more than a medium level in all patients. Four children were diagnosed with syndromes that did not make it to the top 10 differential diagnoses. These included 16p11.2 deletion syndrome (two cases), seizure threshold 2 (SZT2)-related early onset epileptic encephalopathy (one case), and Gabriele-de Vries syndrome (one case).

This study illustrates the integration of facial analysis technology into the practical clinical workflow for Korean children who are strongly suspected of having a genetic syndrome. A definitive genetic diagnosis was reached in 60.9% of children exhibiting distinct facial features, following a systematic genetic work-up. Of these children, 64.3% had conditions that were included in the top 10 syndromes suggested by F2G.

Since the first publication by Boehringer et al. [7] in 2011, several studies have assessed facial phenotyping software. This software uses patient photographs and automated computer tools to identify genetic syndromes [2,7-9]. F2G CLINIC, a deep learning-based system, is a freely available online application for facial phenotyping in patients with genetic syndromes. It is widely used by geneticists [2,5,10]. This software has been successfully validated for various genetic syndromes, including Cornelia de Lange syndrome, Williams-Beuren syndrome, Noonan syndrome, and Down syndrome [11-14]. Following the report of Gurovich et al. [2] that F2G successfully suggested the correct syndrome in 90.5% of cases, several clinical studies have been conducted on various ethnic groups. A German study involving 323 patients diagnosed with 17 different genetic syndromes demonstrated DeepGestalt's high top 10 sensitivity at 91% [5]. In a smaller Turkish study, 48% (12/25 patients) were correctly matched within a suggested list of 30 diseases [3]. A Canadian research group achieved a slightly lower diagnostic yield of 57% in its top 10 [4]. A recent Japanese study reported a top 10 sensitivity rate of 86.6% (52/60 patients) in a routine clinical setting [6]. In the study by Porras et al. [15], the dataset included 1,400 children with 128 genetic conditions, and the average detection rate was 88%. However, the accuracy of these tools has been found to be lower in Asian populations (82%) compared to White (90%) and Hispanic populations (91%).

Our data demonstrated a relatively low sensitivity (64.3%), a finding that is consistent with previous studies that reported inconsistent results in real clinical settings. This fluctuation in detection rate can be attributed to several factors. First, facial dysmorphology presents a significant challenge due to its variations according to age, race, and ethnicity [11-14]. Porras et al. [15] suggested that the lower-than-average accuracy in non-White populations could be due to the limited number of corresponding patients in their dataset. The development of race-specific facial phenotype models could enhance the accuracy of this technology. Second, the effectiveness of deep learning varies depending on the rarity of the genetic syndrome itself. This makes it challenging to detect newly identified rare genetic diseases, except for those that have been extensively studied previously. Indeed, certain syndromes consistently appear in the top suggested syndromes [4]. Our study underscores the limited utility of this technology in diagnosing various rare diseases using advanced diagnostic tools such as CMA and WGS. Third, the additional input of clinical features by clinicians is extremely valuable. In our study, cases that matched the top 10 list showed only a partial similarity of gestalt, but a 100% similarity above the medium level in annotated phenotypic features. In instances where a syndrome is suggested with a medium-high probability, clinicians should critically evaluate whether the suggestion aligns with the patient's phenotype [16]. This underscores that the

utility of this software is enhanced when clinicians supplement the physical examination and patient history, rather than relying solely on facial photography.

The small number of subjects included in our study is a limitation. Thus, in cases where direct comparison of similarity is necessary, it may be essential to directly compare the similarity bars. Another limitation is that we expressed the similarity of gestalts and features in three broad levels, rather than using specific scores. This approach means that even within the same level of similarity, there can be significant differences in scores. Therefore, it may be necessary to directly compare similarity bars when required.

In conclusion, our data underscore the utility of facial analysis technology as an auxiliary tool in pediatric genetic clinics at the point-of-care. We also underscore several considerations for enhancing the accuracy of this machine learning-based screening tool for genetic diseases. By augmenting the quality and volume of training datasets, computer-assisted pattern recognition platforms can function as invaluable decision support tools, bolstering clinicians' confidence in genetic diagnostics.

Conflicts of interest

Jon Soo Kim is an editorial board member of the journal, but he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts.

ORCID

Jon Soo Kim, https://orcid.org/0000-0003-2586-1942
Hyewon Woo, https://orcid.org/0000-0002-1407-3441
Won Seop Kim, https://orcid.org/0000-0003-4541-7902

Author contribution

Conceptualization: JSK and WSK. Data curation: JSK, HK, and WSK. Formal analysis: JSK, HW, and WSK. Funding acquisition: JSK and WSK. Methodology: JSK, HW, and WSK. Project administration: JSK and WSK. Visualization: JSK and WSK. Writing-original draft: JSK and WSK. Writing-review & editing: JSK and WSK.

Acknowledgements

Whole-genome sequencing was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Ministry of Health and Welfare, Ministry of Science and ICT, Ministry of Trade Industry and Energy, Korea Disease Control and Prevention Agency (No. 2020M3E5D7086780, The National Project of Bio Big Data).

This work was supported by a research grant from Chungbuk National University Hospital in 2020.

References

1. Mishima H, Suzuki H, Doi M, Miyazaki M, Watanabe S, Matsumoto T, et al. Evaluation of Face2Gene using facial images of patients with congenital dysmorphic syndromes recruited in Japan. J Hum Genet 2019;64:789-94.
2. Gurovich Y, Hanani Y, Bar O, Nadav G, Fleischer N, Gelbman D, et al. Identifying facial phenotypes of genetic disorders using deep learning. Nat Med 2019;25:60-4.
3. Elmas M, Gogus B. Success of face analysis technology in rare genetic diseases diagnosed by whole-exome sequencing: a single-center experience. Mol Syndromol 2020;11:4-14.
4. Marwaha A, Chitayat D, Meyn MS, Mendoza-Londono R, Chad L. The point-of-care use of a facial phenotyping tool in the genetics clinic: enhancing diagnosis and education with machine learning. Am J Med Genet A 2021;185:1151-8.
5. Pantel JT, Hajjir N, Danyel M, Elsner J, Abad-Perez AT, Hansen P, et al. Efficiency of computer-aided facial phenotyping (DeepGestalt) in individuals with and without a genetic syndrome: diagnostic accuracy study. J Med Internet Res 2020;22:e19263.
6. Zarate YA, Bosanko KA, Gripp KW. Using facial analysis technology in a typical genetic clinic: experience from 30 individuals from a single institution. J Hum Genet 2019;64:1243-5.
7. Boehringer S, Guenther M, Sinigerova S, Wurtz RP, Horsthemke B, Wieczorek D. Automated syndrome detection in a set of clinical facial photographs. Am J Med Genet A 2011;155A:2161-9.
8. Ferry Q, Steinberg J, Webber C, FitzPatrick DR, Ponting CP, Zisserman A, et al. Diagnostically relevant facial gestalt information from ordinary photos. Elife 2014;3:e02020.
9. Dudding-Byth T, Baxter A, Holliday EG, Hackett A, O'Donnell S, White SM, et al. Computer face-matching technology using two-dimensional photographs accurately matches the facial gestalt of unrelated individuals with the same syndromic form of intellectual disability. BMC Biotechnol 2017;17:90.
10. Hurst AC. Facial recognition software in clinical dysmorphology. Curr Opin Pediatr 2018;30:701-6.
11. Kruszka P, Porras AR, Sobering AK, Ikolo FA, La Qua S, Shotelersuk V, et al. Down syndrome in diverse populations. Am J Med Genet A 2017;173:42-53.
12. Kruszka P, Porras AR, Addissie YA, Moresco A, Medrano S, Mok GT, et al. Noonan syndrome in diverse populations. Am J

https://doi.org/10.26815/acn.2023.00227

Med Genet A 2017;173:2323-34.
13. Kruszka P, Porras AR, de Souza DH, Moresco A, Huckstadt V, Gill AD, et al. Williams-Beuren syndrome in diverse populations. Am J Med Genet A 2018;176:1128-36.
14. Dowsett L, Porras AR, Kruszka P, Davis B, Hu T, Honey E, et al. Cornelia de Lange syndrome in diverse populations. Am J Med Genet A 2019;179:150-8.
15. Porras AR, Rosenbaum K, Tor-Diez C, Summar M, Linguraru MG. Development and evaluation of a machine learning-based point-of-care screening tool for genetic syndromes in children: a multinational retrospective study. Lancet Digit Health 2021;3:e635-43.
16. Ciancia S, Goedegebuure WJ, Grootjen LN, Hokken-Koelega AC, Kerkhof GF, van der Kaay DC. Computer-aided facial analysis as a tool to identify patients with Silver-Russell syndrome and Prader-Willi syndrome. Eur J Pediatr 2023;182:2607-14.