Artificial Intelligence in Medicine 62 (2014) 105–118

Contents lists available at ScienceDirect

Artificial Intelligence in Medicine

journal homepage: www.elsevier.com/locate/aiim

Biomedical visual data analysis to build an intelligent diagnostic decision support system in medical genetics

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ARTICLE INFO

Article history:
Received 12 May 2013
Received in revised form 15 August 2014
Accepted 16 August 2014

Keywords:
Decision support system
Machine learning
Visual data analysis
Principal components analysis
Medical genetics
Dysmorphology
Facial genotype–phenotype

ABSTRACT

Background: In general, medical geneticists aim to pre-diagnose underlying syndromes based on facial features before performing cytological or molecular analyses where a genotype–phenotype interrelation is possible. However, determining correct genotype–phenotype interrelationships among many syndromes is tedious and labor-intensive, especially for extremely rare syndromes. Thus, a computer-aided system for pre-diagnosis can facilitate effective and efficient decision support, particularly when few similar cases are available, or in remote rural districts where diagnostic knowledge of syndromes is not readily available.
Methods: The proposed methodology, *visual diagnostic decision support system (visual diagnostic DSS)*, employs machine learning (ML) algorithms and digital image processing techniques in a hybrid approach for automated diagnosis in medical genetics. This approach uses facial features in reference images of disorders to identify visual genotype–phenotype interrelationships. Our statistical method describes facial image data as principal component features and diagnoses syndromes using these features.
Results: The proposed system was trained using a real dataset of previously published face images of subjects with syndromes, which provided accurate diagnostic information. The method was tested using a leave-one-out cross-validation scheme with 15 different syndromes, each of comprised 5–9 cases, i.e., 92 cases in total. An accuracy rate of 83% was achieved using this automated diagnosis technique, which was statistically significant ($p < 0.01$). Furthermore, the sensitivity and specificity values were 0.857 and 0.870, respectively.
Conclusion: Our results show that the accurate classification of syndromes is feasible using ML techniques. Thus, a large number of syndromes with characteristic facial anomaly patterns could be diagnosed with similar diagnostic DSSs to that described in the present study, i.e., *visual diagnostic DSS*, thereby demonstrating the benefits of using hybrid image processing and ML-based computer-aided diagnostics for identifying facial phenotypes.

1. Introduction

Dysmorphology is an area of clinical genetics that is concerned with abnormal patterns of human development and syndrome diagnosis in patients who possess congenital malformations and unusual facial features, often with delayed motor and cognitive development [1]. A high degree of experience and expertise is required to diagnose a dysmorphic patient correctly [2] because most of these syndromes are very rare. However, in some parts of the world, the diagnosis of syndromes is generally performed by medical professionals who are not well trained in dysmorphology, such as general practitioners, pediatricians, or dermatologists, rather than medical geneticists, because the latter are scarce. In general, the diagnosis of dysmorphology is conducted based on databases that contain limited numbers of images, which use standard terminology. Medical professionals might not be highly familiar with this terminology, especially in areas where expert knowledge is not readily accessible, which may make it difficult to obtain correct diagnoses. These challenges may lead to diagnostic inaccuracy, thereby compromising the appropriate treatment for patients to suit their specific needs as well as the provision of adequate guidance to the parents of patients. Delays in diagnosis may

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http://dx.doi.org/10.1016/j.artmed.2014.08.003
0933-3657/

also hinder access to critical services, such as clinical trials, and a patient's referral to supportive services, including early intervention, physical therapy, and occupational therapy. Correct diagnoses and appropriate treatments, particularly during the early stages, can influence the course of dysmorphic diseases. For example, bone marrow transplantation or enzyme replacement therapy can now be offered for some innate metabolic disorders (e.g., Fabry disease) [1], in addition to many other specific treatments for other syndromes.

The face is acknowledged to be the attribute that best distinguishes a person from others, even at the first glance. Facial features provide many clues about the identity, age, gender, and even ethnicity of a person. The face may be influenced by many genes, particularly the genes related to syndromes, and the face provides significant information related to dysmorphology in many cases. Thus, the facial appearance is a significant cue during the early diagnosis of syndromes that are generally associated with cognitive impairments. Therefore, many decision support systems (DSSs) for dysmorphic diagnosis have been developed based on anthropometry, particularly craniofacial anthropometry, as well as stereophotogrammetry. Anthropometry is used to measure the weight, size, and proportions of the human body [3], while craniofacial anthropometry measures the distances between landmarks on the surface anatomy of the head [4]. Stereophotogrammetry employs multiple views in two-dimensional (2D) images to generate three-dimensional (3D) images [5]. Previous studies have shown that many syndromes can be diagnosed correctly using computer-aided face analysis DSSs [2,3,6–8]. In particular, Farkas [3] was the first to study facial morphology based on anthropometry using several methods. These techniques include the use of rulers, protractors, calipers, and tape measures, and they have been applied widely in the analysis of facial dysmorphology [8]. Similar craniofacial analyses that compare a patient's phenotype to the standardized norms in a control population are employed by many clinicians [8].

A possible approach for diagnosing dysmorphic patients is to define rule sets and to apply them manually based on standardized norms. This approach may be feasible in some cases, but it has many drawbacks and is prone to errors. In practice, it is very difficult for health care professionals to keep track of all the relevant up-to-date knowledge regarding syndromes and to deal effectively with large volumes of information in many dimensions [9]. Indeed, humans might not be able to develop a systematic response to any problem that involves more than seven variables [10]. Moreover, constructing and employing rule sets is also a labor-intensive process.

Assigning faces to classes based on appearance is unlikely to be accepted by medical professionals unless the mathematical features determined and identified by feature selection algorithms for discrimination can be related to facial patterns [11]. Several methods have been applied previously to the detection and analysis of facial patterns, such as principal components analysis (PCA), kernel PCA, independent components analysis, probability density estimation, local feature analysis, elastic graph matching (EGM), multi-linear analysis, kernel discriminant analysis, Gabor wavelet (GW), Fisher's linear discriminant analysis (LDA), and support vector machines. In particular, EGM, Fisher's LDA, GW, and PCA using eigenfaces have been employed widely to extract features from a face region. The high accuracy of these methods for extracting features and subsequently discerning patterns in faces has been demonstrated in many studies. Among these popular techniques, it is not easy to choose the best to implement a diagnostic DSS for dysmorphology. Thus, we suggest the use of ensembles of some of these methods to reduce error rates in future research. However, excellent results can be achieved using PCA based on feature extraction and the subsequent discernment of people from others, with accuracy rates of up to 96% [12]. Using PCA, good success rates can be obtained by detecting patterns in faces from images captured in ideal environments, particularly with good illumination, or by employing several image processing techniques to enhance images before feature extraction. PCA is an optimal transition scheme that minimizes the mean squared error between an image and its reconstruction [13]. PCA using eigenfaces is computationally efficient compared with other similar methods [14] because reducing the dimension from 2D to one-dimensional can be performed easily to accelerate the calculations. Thus, we employ the PCA-based eigenface method to extract features from faces in our *visual diagnostic DSS*. Furthermore, this machine learning (ML) method was selected because of its extensive and successful applications to many datasets.

In addition, Bayesian decision theory, multiple similarity, city block distance, subspace, Mahalanobis distance, and Euclidean distance are well-known methods for measuring the distance between two points in a features dataset [13]. The Mahalanobis distance and Euclidean distance are the most widely used of these methods [13]. However, Kapoor [13] showed that the Mahalanobis distance is more effective than the Euclidean distance. It differs from the Euclidean distance because it considers the correlations in the dataset and it is scale-invariant, i.e., it is not dependent on the scale of measurements [13,15].[1] In the present study, we tested these two methods using our features dataset to determine the best for use in our method, and we found that the Euclidean distance outperformed the Mahalanobis method for measuring distances. Thus, this matching technique was selected for our study.

Hammond [8] claimed that the analysis of 2D or 3D facial morphology images using computer-aided DSSs based on genotype–phenotype correlations could potentially benefit syndrome diagnosis, and our study supports this claim. The method established in the present study is called *visual diagnostic DSS*. This method aims to provide the required on-site expertise, but it also attempts to eliminate the time-consuming search of catalogs by practitioners and geneticists to diagnose syndromes, because there are approximately 4700 known syndromes.[2]

In the proposed methodology, ML algorithms and digital image processing techniques are employed in a hybrid approach to detect meaningful facial features in reference images of disorders by indicating visual genotype–phenotype interrelationships. The proposed system was trained using a real dataset constructed from previously published images of dysmorphic faces, which included accurate diagnostic information about the syndromes considered in the present study. After training, during the diagnosis phase, the system compares the patient's facial features to all the trained features in the database to obtain a ranked list of possible matches based on confidence values above the threshold value specified by the user. The ranking list with similarity values explains how similar a disease is to those classified in the database relative to a particular threshold value. The application can be implemented easily at any site. New syndromes can be trained and the dataset can be extended by the end user to improve the implementation. Our statistical method represents facial image data in terms of principal component (PC) features and it diagnoses syndromes using these features. We evaluated the accuracy of the method using a leave-one-out cross-validation scheme.

[1] More information about the Mahalanobis distance can be found in Gul's thesis [15].

[2] Many new dysmorphic diseases are described each year in the London Dysmorphology Database (http://www.lmdatabases.com [accessed 25.01.14]).