Improving the Early Detection of Rare Craniofacial Genetic Disorders Through Convolutional Neural Networks and Machine Learning using Facial Images

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Abstract – This project improves the early detection of rare craniofacial genetic disorders, like Down Syndrome and Williams Syndrome, through Deep Convolutional Neural Networks using facial images. The early detection of rare craniofacial genetic disorders is crucial for the management/treatment of associated medical complications and health issues. This project focuses mainly on Down Syndrome and Williams Syndrome. Studies have found that the current screening tests are not adequate, and in many cases, detection is missed until a few years after the child is born. A new machine learning based system, named AI4GenetX, was developed to predict whether a child has a rare craniofacial genetic disorder from simple facial images. This system uses Deep Convolution Neural Networks, and a desktop/mobile Graphical User Interface (GUI) with real-time facial detection and tracking implementation. The new system achieved an accuracy of 92.3%.

I. INTRODUCTION

The purpose of the experiment and project was to improve the early detection of rare craniofacial genetic disorders through convolutional neural networks using facial images. The early detection of rare craniofacial genetic disorders will help to earlier manage and treat potential health complications and issues associated with the disorders.

If missed before birth, early detection of rare craniofacial genetic disorders is crucial for the management and potential treatment of associated medical complications and health issues. According to Children's National Health System, one of the top 5 children's hospitals in the United States, six hundred thousand people are diagnosed with a rare craniofacial genetic disorder, in the United States alone. Children's National treats hundreds of patients with rare craniofacial genetic disorders every year. They define the term, "Craniofacial Genetic Disorder", as malformations of the face and skull that results from birth defects and genetics. One of the most common craniofacial genetic disorders is Down syndrome (DS). Each year, about 6,000 babies are born with Down syndrome; that's nearly 1 in every 700 babies born (Birth Defects, 2017). The percentage of babies born with Down syndrome has been increasing by around 1% every year since 1979 (Birth Defects, 2017). Another rare craniofacial genetic disorder is Williams Syndrome. Williams syndrome affects nearly 1 in 10,000 people worldwide and an estimated 20,000 to 30,000 people in the United States (What is Williams Syndrome?, 2018).

Down Syndrome is the most common cause of birth defects while Williams Syndrome is quite rare. These two genetic disorders produce alterations in physical growth, medical complications, and intellectual disability. Detecting Down Syndrome and Williams Syndrome early in an individual's life is crucial for the management and potential treatment of the associated medical complications. However, the diagnostic accuracy for pediatricians prior to cytogenetic results is moderate and the access to specialists is limited in many low-economic areas (Zhao, Q. et. al., 2014).

A. Down Syndrome Overview

Down Syndrome is one of the most common chromosomal diseases with inherited mental disability. Currently, the most common form of Down Syndrome is known as trisomy 21 (Crosta, P., 2017). Trisomy 21 is a genetic condition where individuals have 47 chromosomes in each cell instead of the normal 46 (Crosta, P., 2017). Trisomy 21 is caused by an error in cell division called nondisjunction, which leaves an extra copy of chromosome 21 (Crosta, P., 2017). Every cell in the body contains genes that are grouped along chromosomes in the cell's nucleus.

There are normally 46 chromosomes in each cell, 23 inherited from the mother and 23 from the father. When some or all of a person's cells have an extra full, or partial, copy of chromosome 21, the result is Down Syndrome. (Crosta, P., 2017).

Individuals with Down Syndrome often have very distinct physical features, health issues, and variability in cognitive development. These physical characteristics include eyes that have an upward slant, oblique fissures, epicanthic skin folds on the inner corner, and white spots on the iris; short neck; flat nasal bridge; and a protruding tongue (Crosta, P., 2017).

In addition to the physical features, Down Syndrome can result in various developmental delays. Individuals with Down Syndrome most likely can have mild to moderate intellectual disability (Crosta, P., 2017). Crosta explains, Children with Down Syndrome often reach developmental milestones later than their peers. There may be a delay in acquiring speech. A child may need speech therapy to help them gain expressive language. Fine motor skills may also be delayed. They can take time to develop after gross motor skills have been acquired. For example, a child with Down Syndrome learns to sit independently at 11 months old while typically children can sit at 8 months old. Down Syndrome children learn to crawl at 17 months, while typically children learn at 9 months. Children with Down syndrome start walking at 26 months, but typical children are walking by 14 months (Crosta, P., 2017).

There are health issues associated with Down Syndrome. Currently, around half of all people with Down Syndrome have a congenital heart defect (Crosta, P., 2017). A congenital heart defect occurs when a person is born with a fault in the structure of the heart or the main arteries (Nordqvist, C., 2018). Down Syndrome may also bring about a higher risk of respiratory problems, hearing difficulties, Alzheimer's disease, childhood leukemia, epilepsy, and thyroid conditions (Crosta, P., 2017). Down Syndrome can also bring a lower risk of hardening of the arteries, diabetic retinopathy, and most kinds of cancer (Crosta, P., 2017).

It is crucial to detect Down Syndrome, and really all the rare craniofacial genetic disorders, early to start the management of health issues and to improve the quality of each patient's life. Generally, on average, when the disorder is detected early, the average life expectancy of an individual with Down Syndrome increases from 25 (in 1983) to more than 50 years today (Sara, S. 2008).

B. Williams Syndrome Overview

Williams Syndrome, or Williams-Beuren Syndrome, is a rare craniofacial genetic disorder that is caused by the spontaneous deletion of the 26-28 genes on chromosome 7. Williams Syndrome is characterized by "growth delays before and after birth (prenatal and postnatal growth intellectual disability), short stature, a varying degree of mental deficiency, and distinctive facial features that typically become more pronounced with age" (rarediseases.org). As Williams Syndrome is a craniofacial disorder, there are major facial features that are prominent in Williams Syndrome individuals. These abnormal features may include "a round face, full cheeks, thick lips, a large mouth that is usually held open, and a broad nasal bridge with nostrils that flare forward (anteverted nares). Affected individuals may also have unusually short eyelid folds (palpebral fissures), flared eyebrows, a small lower jaw (mandible), and prominent ears. Dental abnormalities may also occur including abnormally small, underdeveloped teeth (hypodontia) with small, slender roots." (rarediseases.org).

In addition to physical symptoms, Williams Syndrome can result in various personality and health symptoms. A large percentage of individuals with Williams Syndrome have some type of heart or blood vessel problem (What is Williams Syndrome?, 2018). Explained by the United States National Williams Syndrome Association, "Typically, there is narrowing in the aorta producing supravalvular aortic stenosis (SVAS) or narrowing in the pulmonary arteries. There is a broad range in the degree of narrowing, ranging from trivial to severe (requiring surgical correction of the defect). Since there is an increased risk for development of blood vessel narrowing or high blood pressure over time, periodic monitoring of cardiac status is necessary." (What is Williams Syndrome?, 2018). In addition to heart or vessel problems, Williams Syndrome can cause elevation in the blood calcium level, called hypercalcemia. Usually, hypercalcemia can cause extreme irritability or "colic-like" symptoms (What is Williams Syndrome?, 2018). Low birth-weight and/or slow weight gain is also associated with Williams Syndrome. Most children with Williams Syndrome have a slightly lower birth-weight than their brothers or sisters (What is Williams Syndrome?, 2018). Slow weight gain is also a common weight problem and many Williams Syndrome children are diagnosed as "failure to thrive". Another condition that children with Williams Syndrome may have is sensitivity to certain frequencies or loud noises. These loud noises or frequencies can be painful and/or startling to the child. Williams Syndrome individuals may also have musculoskeletal problems. Young children with Williams Syndrome often have joint laxity and low muscle tone (What is Williams Syndrome?, 2018). As the Williams Syndrome children get older, joint stiffness (contractures) may develop (What is Williams Syndrome?, 2018).

Williams Syndrome also brings about psychological problems to many individuals. Most individuals with Williams Syndrome have a mild to severe learning differences and cognitive challenges (What is Williams Syndrome?, 2018). Young children with Williams Syndrome often experience developmental delays. Like children with Down Syndrome, children with Williams Syndrome will reach certain milestones, such as walking, talking and toilet training, often later than what is considered normal (What is Williams Syndrome?, 2018). "Older children and adults with

Williams syndrome often demonstrate intellectual "strengths and weaknesses." There are some intellectual areas (such as speech, long term memory, and social skills) in which performance is quite strong, while other intellectual areas (such as fine motor and spatial relations) show significant weakness." (What is Williams Syndrome?, 2018).

C. Current Solutions/Methods/Issues for Down Syndrome Detection

Down Syndrome can currently only be identified through screening tests and diagnostic tests. Most screening tests administered during pregnancy can only estimate the probability if a child will have Down Syndrome, however some diagnostic tests can tell whether the fetus has the condition (Crosta, P., 2017). An example of a diagnostic test is a karyotype test. A karyotype test can be administered to evaluate the size, shape, and number of chromosomes in a sample of body cells; which can help identify the extra chromosome that causes Down syndrome. After birth, screening is a cost-effective and less invasive way to determine if more invasive diagnostic tests are needed. However, unlike diagnostic tests, they cannot confirm whether Down syndrome is present. In general, diagnostic tests are more accurate in detecting Down syndrome and other problems.

Individuals with Down Syndrome receive care for their health problems, just as other people do. Early intervention can help a Down Syndrome individual maximize their potential, improve the quality of their life, and prepare them to take an active role in the community. Children who have specific difficulties with learning and development may be eligible for educational support, either in a mainstream or specialized school. In recent years, the tendency has increasingly been to attend mainstream schools, often with additional support to help them integrate and progress. Some children will have an Individualized Education Plan (IEP), supported by various specialists.

D. Current Solutions/Methods/Issues for Williams Syndrome Detection

Like Down Syndrome, Williams Syndrome can currently only be determined through blood tests and some diagnostic tests. A clinical diagnosis of Williams Syndrome can be confirmed with a blood test (Frequently Asked Questions about Williams Syndrome and the WSA., 2017). The technique known as "fluorescent in situ hybridization (FISH), a diagnostic test of the DNA detects the elastin deletion on chromosome 7 in more than 98% of individuals with Williams Syndrome" (Frequently Asked Questions about Williams Syndrome and the WSA., 2017). The United States National Williams Syndrome Association describes a new diagnostic test for Williams Syndrome called micro-array analysis. This test not only identifies the elastin deletion (as FISH does) but can provide additional information on the precise size of the deleted area on chromosome 7.

Because of the rarity of the syndrome, most individuals with Williams Syndrome remain undiagnosed or are diagnosed at a relatively late age (Frequently Asked Questions about Williams Syndrome and the WSA., 2017). Never being diagnosed or being diagnosed at a late age is especially concerning since individuals with Williams Syndrome can have significant and possible progressive medical problems (Frequently Asked Questions about Williams Syndrome and the WSA., 2017).

E. Convolutional Neural Networks (CNNs) Overview

A Convolutional Neural Network (CNN) is a class of deep neural networks, most commonly applied to analyzing visual imagery. CNNs use a variation of multilayer perceptrons designed to require minimal preprocessing. CNNs are a type of supervised learning, which is a machine learning task of learning a function that maps an input to an output based on example input-output pairs. It infers a function from labeled training data consisting of a set of training examples.

F. Experiment Overview

For the experiment, I built a Convolutional Neural Network Model to classify a given facial image into three classifications: Normal, Down Syndrome, and Williams Syndrome. If missed before birth, the early detection of Down Syndrome and Williams Syndrome (and really all Rare Craniofacial Genetic Disorders), is crucial for the management and potential treatment of medical complications and health issues associated with the disorders.

In addition to this model, a desktop application, named AI4GenetX, was developed to my model as a screening tool that would provide a less invasive, cheaper, quicker, and just as accurate alternative to the current screening tools.

II. MATERIALS AND METHOD

A. Materials

Below, the materials needed to complete the experiment are provided:

- 4,200 Normal Facial Images (images captured from videos and sources are cited in References)
- 4,200 Down Syndrome Facial Images (images captured from videos and sources are cited in References)
- 4,200 Williams Syndrome Facial Images (images captured from videos and sources are cited in References)
- Python 3.7 Programming Language
- Keras 2.2.4 Python Neural Network Library (open-source library licensed under MIT)

- TensorFlow 1.11.0 Library (open-source licensed under Apache License 2.0)
- Intel Core i7-8th Gen, 64GB RAM, Windows 10 Pro, GTX 1080 Ti GPU Accelerated Full Computer Tower

B. Procedure

My project is a Machine Learning project, so it has a relatively different procedure than traditional scientific experiments. My project consisted of three major parts: Preprocessing (collection, cleaning, and labeling of data), Training and Testing of my model, and Inference /Predictions. Below is an in-detail explanation of each part:

1. **Preprocessing**: In this step, I built a Python script (using the Python 3.7 programming language with OpenCV) that took a YouTube video and converted it to a group of facial images (extracted from the video). I collected YouTube videos: videos with normal faces, Down Syndrome faces, and Williams Syndrome faces (Note: I used these YouTube videos under the YouTube Fair Use Policy and are cited in the References section). After converting all the YouTube videos to photos and going to each image and ensureing it represented the accurate classification, I ended up with 4,200 images of each classification (Down Syndrome, Williams Syndrome and Normal) for a total of 12,600 images.

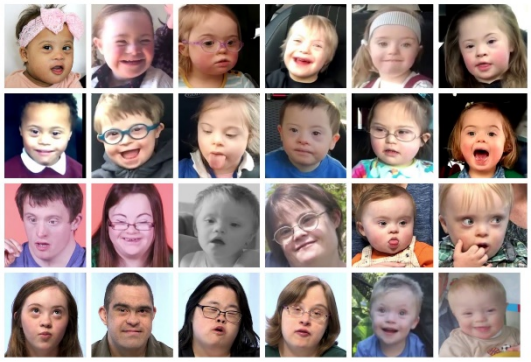

Fig.1. Down Syndrome sample facial images

Fig. 2. Williams Syndrome sample facial images

Fig. 3. Normal sample facial images

I resized the images to 244 by 244 pixels and added a label to each image.

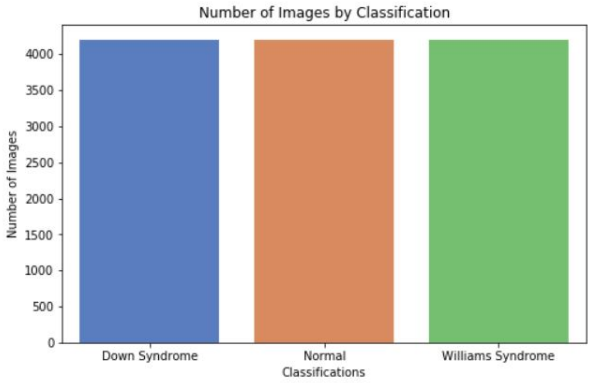

Fig. 4. Number of Images by Classification

After adding labels, I divided the images into an 80% training category and 20% testing category. This is done so that a portion of the images will be reserved for the testing of the model.

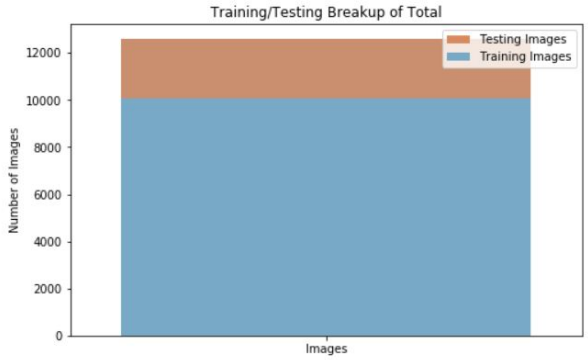

Fig. 5. Training and Testing Breakup of the Total Images

2. **Training and Testing**: I built different CNN models (using Keras with a backend of TensorFlow), but my final model (the one with the highest accuracy) was a modified version based upon the VGGNet (VGG16) model from the ImageNet competition (Russakovsky et. al.). My model has 16 layers (refer to figure 4 for a full

model summary and the name and output shape of each layer in my model). I trained my model to the training images for 100 epochs (1 epoch means that the computer looked through the data 1 time). I then saved my trained model.

3. **Inference/Predictions**: I used Python to build a GUI named AI4GenetX (stands for Artificial Intelligence for Genetics). Using the saved model from my training step, AI4GenetX allows a user to either select a photo from their file system or take a photo in real time with a camera. I implemented facial detection and facial tracking into both these options to crop the image to a face, and both options display a predicted classification (using my model from the training step) and the percentage predicted for each class.

III. RESULTS AND DISCUSSION

I built a version of a Convolutional Neural Network to classify facial images into 3 different classifications: 2 different rare craniofacial genetic disorder classes and a normal class. The model I built was a standard Convolutional Neural Network. For my final model (after trying various architectures of CNNs), I used a modified version of the VGG16, or VGGNet, neural network architecture. The VGGNet neural network performed very well in the ImageNet Large Scale Visual Recognition Challenge in 2014 (Russakovsky et. al.). It scored first place on the image localization task and second place on the image classification task. The adapted VGG16 model architecture I used is displayed in figure 3 below.

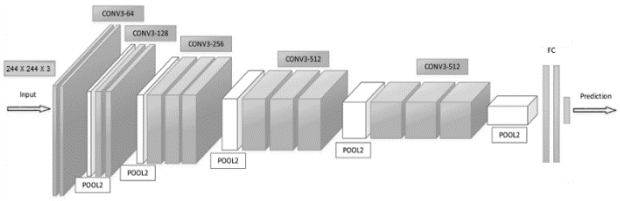

Fig. 6. VGG16 CNN Model Architecture (adapted from Khiyari, H. E. et. al.)

I built my final model using the Python programming language and the machine learning library: Keras (with a TensorFlow backend). Adapted from the VGG16 network architecture, my model had a total of 16 layers. Below, the model summary is shown:

Layer (type)	Output Shape	Param #
zero_padding2d_1 (ZeroPaddin	(None, 246, 246, 3)	0
conv2d_1 (Conv2D)	(None, 244, 244, 64)	1792
zero_padding2d_2 (ZeroPaddin	(None, 246, 246, 64)	0
conv2d_2 (Conv2D)	(None, 244, 244, 64)	36928
max_pooling2d_1 (MaxPooling2	(None, 122, 122, 64)	0
zero_padding2d_3 (ZeroPaddin	(None, 124, 124, 64)	0
conv2d_3 (Conv2D)	(None, 122, 122, 128)	73856
zero_padding2d_4 (ZeroPaddin	(None, 124, 124, 128)	0
conv2d_4 (Conv2D)	(None, 122, 122, 128)	147584
max_pooling2d_2 (MaxPooling2	(None, 61, 61, 128)	0
zero_padding2d_5 (ZeroPaddin	(None, 63, 63, 128)	0
conv2d_5 (Conv2D)	(None, 61, 61, 256)	295168
zero_padding2d_6 (ZeroPaddin	(None, 63, 63, 256)	0
conv2d_6 (Conv2D)	(None, 61, 61, 256)	590080
zero_padding2d_7 (ZeroPaddin	(None, 63, 63, 256)	0
conv2d_7 (Conv2D)	(None, 61, 61, 256)	590080
max_pooling2d_3 (MaxPooling2	(None, 30, 30, 256)	0
zero_padding2d_8 (ZeroPaddin	(None, 32, 32, 256)	0
conv2d_8 (Conv2D)	(None, 30, 30, 512)	1180160
zero_padding2d_9 (ZeroPaddin	(None, 32, 32, 512)	0
conv2d_9 (Conv2D)	(None, 30, 30, 512)	2359808
zero_padding2d_10 (ZeroPaddi	(None, 32, 32, 512)	0
conv2d_10 (Conv2D)	(None, 30, 30, 512)	2359808
max_pooling2d_4 (MaxPooling2	(None, 15, 15, 512)	0
zero_padding2d_11 (ZeroPaddi	(None, 17, 17, 512)	0
conv2d_11 (Conv2D)	(None, 15, 15, 512)	2359808
zero_padding2d_12 (ZeroPaddi	(None, 17, 17, 512)	0
conv2d_12 (Conv2D)	(None, 15, 15, 512)	2359808
zero_padding2d_13 (ZeroPaddi	(None, 17, 17, 512)	0
conv2d_13 (Conv2D)	(None, 15, 15, 512)	2359808
max_pooling2d_5 (MaxPooling2	(None, 7, 7, 512)	0
flatten_1 (Flatten)	(None, 25088)	0
dense_1 (Dense)	(None, 256)	6422784
dropout_1 (Dropout)	(None, 256)	0
dense_2 (Dense)	(None, 256)	65792
dropout_2 (Dropout)	(None, 256)	0
dense_3 (Dense)	(None, 3)	771

Total params: 21,204,035
Trainable params: 21,204,035
Non-trainable params: 0

Fig. 7. Summary of Each Layer in the CNN Model

I used this 16-layered model and ran 10,080 images (80% of the total images of Normal, Down Syndrome, and Williams Syndrome: each had 4,200 images) through it to train it to the rare craniofacial genetic disorder data.

After running the training for 100 epochs (meaning the model looked through all the training data 100 times) which took 2 hours and 55 minutes, I achieved a training accuracy of 99.68% and a loss value of 0.0086.

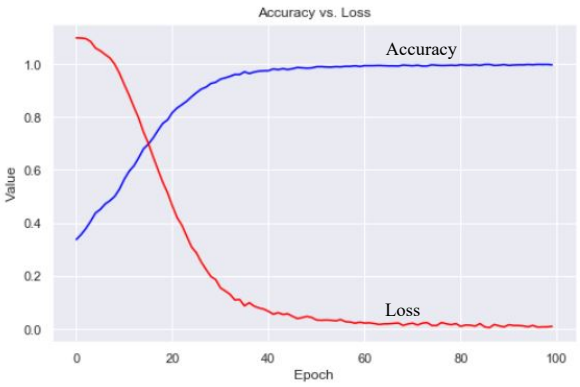

Fig. 8. Accuracy and Loss vs. Epoch Graph

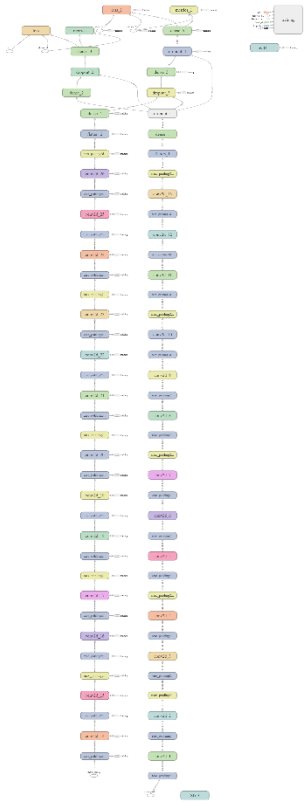

Fig. 9. TensorBoard Generated Model Diagram

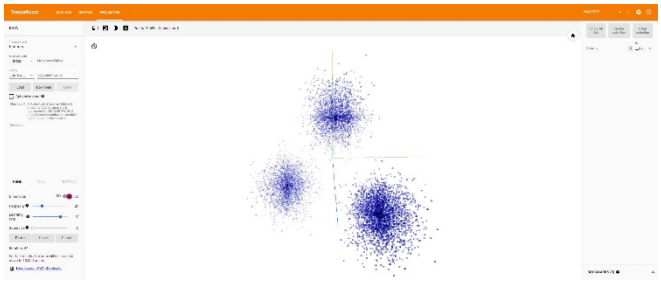

Fig. 10. TensorBoard Generated Model Projector Diagram

I ran my testing using the 20% testing images (2,520 images) through my model to evaluate its performance. I received a global validation accuracy of 91.3% and a loss value of 0.6493. For my model, I also generated a Classification Report (figure 6) and a Confusion Matrix (figure 7). A classification report displays the Precision, Recall, F1-Score, and Support scores for each classification and overall. Below is a description of each score metric:

- **Precision** is defined as the number of true positives divided by the number of true positives plus the number of false positives.
- **Recall** is defined as the number of true positives divided by the number of true positives plus the number of false negatives.
- **F1-Score** is the harmonic mean of precision and recall and is described as the precision multiplied by the recall divided by precision plus recall, multiplied by two.
- **Support** is defined as the number of samples of the true response that lie in that class.

	precision	recall	f1-score	support
Normal - 0	0.94	0.95	0.95	855
Down Syndrome - 1	0.89	0.90	0.89	854
Williams Syndrome - 2	0.91	0.89	0.90	811
micro avg	0.91	0.91	0.91	2520
macro avg	0.91	0.91	0.91	2520
weighted avg	0.91	0.91	0.91	2520

Fig. 11. Classification Report of the Model

A confusion matrix, also known as an error matrix, is a specific table layout that allows visualization of the performance of a supervised algorithm. The confusion matrix reports the number of false positives, false negatives, true positives, and true negatives. Below is a description of each term:

- **False Positive**: Outcome where the model *incorrectly* predicts the *positive* class
- **False Negative**: Outcome where the model *incorrectly* predicts the *negative* class
- **True Positive**: Outcome where the model *correctly* predicts the *positive* class
- **True Negative**: Outcome where the model *correctly* predicts the *negative* class

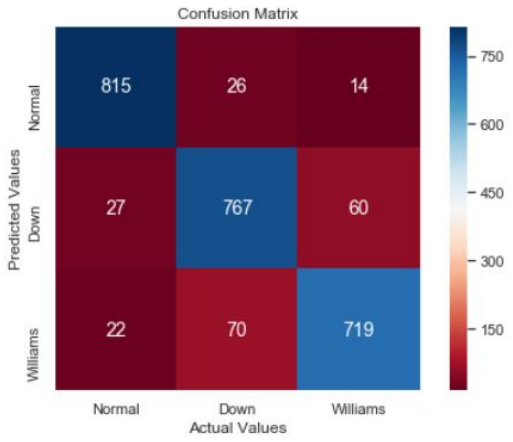

Fig. 12. Confusion Matrix

I developed a GUI (Graphical User Interface) for my model and named it AI4GenetX (stands for Artificial Intelligence for Genetics). AI4GenetX uses my model to classify a given facial image. It provides a user two options: Take Image or Select Image from Computer. The Take Image option allows the user to capture a facial image in real-time, and I have implemented facial detection and tracking into this option. The Select Image from Computer allows the user to select a pre-captured facial image from his or her file system.

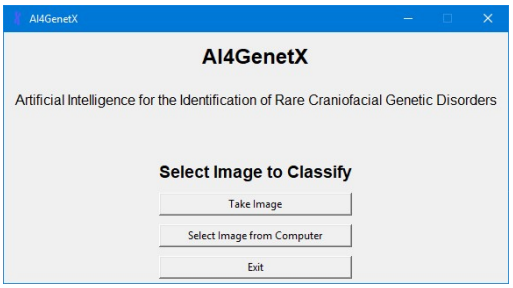

Fig. 13. Home Screen of AI4GenetX Desktop Application

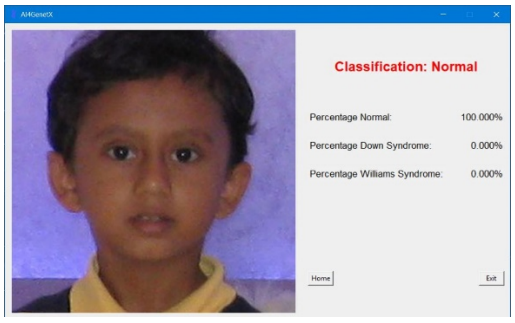

Fig. 14. Inference Screen of AI4GenetX Desktop Application

I also developed an IOS App for my model and also named it AI4GenetX. AI4GenetX uses my model to classify a given facial image. It provides a user two options: Take Image or Select Image from Photo Library. The Take Image option allows the user to capture a facial image in real-time using the device camera. The Select Image from Photo Library allows the user to select a pre-captured facial image from his or her camera roll.

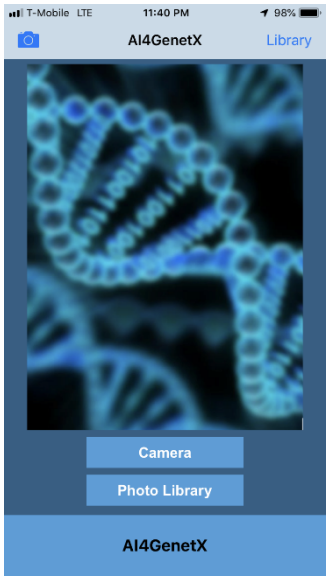

Fig. 15. Home Screen of AI4GenetX App

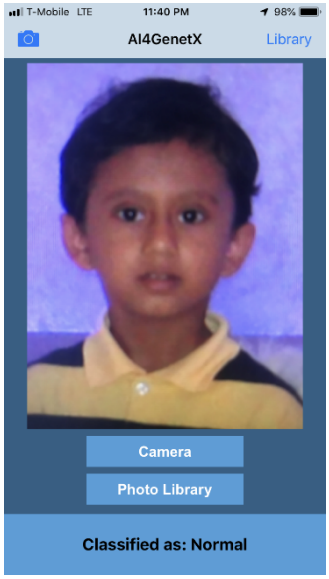

Fig. 16. Inference Screen of AI4GenetX App

IV. CONCLUSION AND FUTURE WORKS

A. Applications

With the development of this model and research, many applications present themselves. The model that was built can be applied in a real-world doctor-patient scenario when a baby is born. This can be a screening tool which can help specific medical specialists or really any medical

professional (nurses, doctors, etc.) quickly and efficiently determine if a child requires additional diagnostic testing.

My system, model, and research can be used in places where medical specialists or personnel are not available (like remote villages in third-world countries) as it only requires a camera and an electronic device.

B. Possible Extensions

At the current state of model development and research, the main issue that can be improved upon is the model accuracy. As explained in detail in the III. Results and Discussion section, I achieved a highest global validation accuracy of 91.3% from both versions of my model. This means that for every 100 photos that the machine sees, it will predict the correct classification of around 91 photos.

A possible extension to this project can be improving the global validation accuracy. I built a model using an adapted version of the VGG16 neural network architecture. The VGGNet (VGG16) architecture is from the ImageNet Competition in 2014 (Russakovsky et. al.). At the time of writing this paper, the VGG16 architecture is four years old, which means that a new model architecture could bring about a higher global validation accuracy.

My system could also be developed into a mobile application or website to make my system easy to use and widely available to use.

V. ACKNOWLEDGMENT

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Ms. Julie White, a Ph.D. Graduate Student at Pennsylvania State University in the Department of Anthropology;

Dr. Marshall Summar, Director of the Rare Disease Institute at the Children's National Medical Center.

VI. REFERENCES

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