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CASE STUDY: Using Face2Gene to Support Molecular Diagnostics in a Telehealth Setting - Case 1

In these cases, Face2Gene helped Dr. Omar Abdul-Rahman get patients tested in a more rapid, targeted way, many times before a patient even walked through the door.

WHO

Dr. Omar Abdul-Rahman is the Director of Genetics at the Munroe-Meyer Institute.

BACKGROUND

For many years, the genetics team at the Munroe-Meyer Institute has provided genetic care for patients across Nebraska and surrounding states, sometimes traveling several hours to see patients in remote locations. Upon joining the team, Dr. Abdul-Rahman helped to adopt telehealth services, deploying telehealth cameras to sites around the state.

THE DILEMMA

However, even the best telehealth video isn't the same as being face-to-face. Face2Gene has now become an essential component of the telehealth diagnostic process. "It's making me start to think about other ways we can use [Face2Gene] to get to diagnoses faster, without even going through the formal clinic set-up," said Dr. Abdul-Rahman, "A more rapid way to get patients tested in a more targeted way." This allows Dr. Abdul-Rahman and his team to carefully evaluate the details of patients' faces during the clinical visit, and many times even before the patient walks through the door.

THE SOLUTION

In the telehealth clinic in Scottsbluff, Nebraska, Dr. Abdul-Rahman uses Face2Gene to capture information from families and analyze the patient's face before they come to the clinic, as part of a novel patient intake process. Shortly after implementing this new process, Dr. Abdul-Rahman received the Face2Gene analysis for an incoming patient, which showed a very high similarity to chromosome 22q11.2 deletion syndrome. Seeing this, he decided to adjust his clinical evaluation to focus on evaluation of this differential diagnosis. Using the very limited time available for the telehealth exam, he was able to look for specific clinical features and ask the parents targeted questions to help determine whether the patient may have 22q11.2 deletion syndrome. Sure enough, the clinical history was suggestive of this diagnosis, and although his ability to do a complete visual examination was limited by video quality, his confidence was increased due to the high ranking of this syndrome in Face2Gene.

THE RESULT

With this reassurance, he decided to pursue microarray testing to check for copy number variations, including a 22q11.2 deletion, but the patient's insurance declined to cover the cost of this test. Instead, Dr. Abdul-Rahman ordered FISH testing, which was covered by the patient's insurance, to look just for 22q11.2 deletion syndrome. The result came back confirming the diagnosis.

Dr. Abdul-Rahman concluded, "It helped us get a diagnosis without me ever laying a hand on this patient, who lives literally four or five hundred miles away, and the diagnosis was already suspected before they walked through the door because of that intake process."

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CASE STUDY: Using Face2Gene to Support Molecular Diagnostics in a Telehealth Setting - Case 2

After a successful experience using Face2Gene in his telehealth clinic in Scottsbluff, Dr. Abdul-Rahman decided to start another clinic using the same model, this time even further away in Gordon, Nebraska.

WHO

Dr. Omar Abdul-Rahman is the Director of Genetics at the Munroe-Meyer Institute.

THE DILEMMA

Here they saw a young child, only a few months old with non-specific syndromes, including developmental delay and low muscle tone.

THE SOLUTION

He had no specific syndrome in mind for the patient, and Face2Gene gave a pretty broad differential, so he ordered a microarray analysis. A couple of weeks later, he received results showing that the patient had a microdeletion in the Prader Willi/Angelman syndrome critical region. Though these syndromes present differently, they may be hard to differentiate at a very young age. Reviewing his clinical notes, he found nothing to really pinpoint the diagnosis one way or another, but he did see that Angelman was one of the highly ranked syndromes in Face2Gene, and Prader Will was not on the list of highly ranked results. When the family returned to the telehealth clinic months later, he saw further clinical signs to support the diagnosis of Angelman syndrome.

THE RESULT

Although the family's insurance refused to cover confirmatory testing, Dr. Abdul-Rahman felt confident in making a clinical diagnosis of Angelman syndrome, backed up by the results of the patient's Face2Gene analysis.

"Now we're talking to our faculty about more telehealth clinics, and to me, this is the model that works," said Dr. Abdul-Rahman,"We can interact with the patient. We can talk with them and get a history. But when it comes to the physical exam, using Face2Gene as an adjunct tool is really critical."

Though the use of Face2Gene in telehealth clinics is an approach unique to Dr. Abdul-Rahman's genetics team, the challenges they are facing are not unique. This novel telehealth approach could have a great impact on many patients and families in remote areas.

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CASE STUDY: Using Face2Gene to Make Sense of a Medical Mystery

In this case, Face2Gene helped Dr. Li target analysis of a gene which otherwise would not have been analyzed, ultimately identifying the diagnostic variant.

WHO

Dr. Hong Li is a clinical and biochemical geneticist at Emory University specializing in the diagnosis and treatment of inherited metabolic disorders, lysosomal storage diseases, genetic disorders with dysmorphic features and intellectual disability.

THE DILEMMA

For several years, the Emory Genetics team had been following a young female patient who remained undiagnosed. First seen by Genetics at age 5, the patient presented with global developmental delay, predominant speech delays, and microcephaly, but with otherwise normal growth. She also had early-onset epilepsy, starting at 1 year old and well-controlled on Keppra. Her MRI was essentially normal except for the left hippocampus with a globular configuration and abnormal folding pattern, but showed no abnormal signals or atrophy. Worried that there may be additional health issues on the way, the parents of this young girl were eager to get a diagnosis to prepare and provide the best care for their daughter. The patient's neurologist ordered a NGS epilepsy gene panel, including analysis of over 100 genes before her consultation with Genetics. The panel returned several variants of uncertain significance and prompted various additional clinical work-ups in the pursuit of clinical correlation. However, none of these VUS results seemed to fit the patient's clinical presentation.

When the patient returned to Genetics for her next visit at 8 years of age, Dr. Li saw the patient and noticed some very unique facial features. She saw that the patient had hypotelorism and a slightly beaked nose. Though these features were not dramatic, they are not common, and therefore caught Dr. Li's attention.

THE SOLUTION

Having recently started using Face2Gene, Dr. Li decided to analyze this patient's facial image. One of the top results returned was a syndrome associated with the DYRK1A gene, which was the second ranked result and showed a moderate facial match. The fact that this syndrome was associated with her patient's very unique features caught Dr. Li's attention, and the Face2Gene heatmap helped to confirm these areas of strong facial similarity. Upon further review, Dr. Li was intrigued to see that the clinical features of this syndrome — including microcephaly, hypotelorism, pointed nose, and various neurological features — fit her patient's clinical history very well.

She reached out to Dr. Lora Bean in the EGL Genetics lab, where the epilepsy panel had been completed, to see whether that panel had included analysis of the DYRK1A gene. Though the gene had not been included in the panel, Dr. Bean was able to go back to the raw NGS data to look specifically at this gene.

THE RESULT

Sure enough, she found a suspicious variant. After analysis of parental samples, Dr. Bean confirmed that this was a *de novo* variant in the patient, which helped to classify this variant as "likely pathogenic" and causative for this patient's clinical phenotypes.

CASE STUDY: Using Face2Gene to Make Sense of a Medical Mystery

The family of this young girl were relieved to have an answer, ending the diagnostic odyssey for their child. Finally having a diagnosis allowed Dr. Li and the parents of this patient to set aside their worries about additional serious health issues.

Dr. Li continues to use Face2Gene to support her diagnostic evaluations, particularly when the patient has dysmorphic features. “Face2Gene is an integral part of my clinical evaluation,” said Dr. Li, “It’s a powerful tool that not only reaffirms my suspicion of a particular syndrome, but has also pointed me towards syndromes I typically wouldn’t have considered, which have then resulted in the correct diagnosis.”

Dr. Li went on to add, “In this case, without the clues from Face2Gene, it was hard to consider any targeted testing due to the patient’s non-specific presentation. My next step would have been to order trio exome sequencing, but the integration of information from Face2Gene saved me this exome step.”

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CASE STUDY: Using Face2Gene to Focus Analysis on the Relevant Gene Based on Phenotype

In this case, Face2Gene helped Dr. Lynne Bird focus analysis on a single variant in a setting where the patient had limited financial support for genetic testing.

WHO

Dr. Lynne Bird is a dysmorphologist and clinical geneticist at Rady Children's and a long-time user of Face2Gene. She regularly uses the app to help in her clinical evaluation of patients with dysmorphic facial features where the correct diagnosis is not obvious. She also uses the Face2Gene analysis to help guide her test selection and support her clinical correlation of reported results.

THE DILEMMA

Like many geneticists, Dr. Bird sometimes has very few options when it comes to ordering genetic testing for her patients, as many insurance companies will only cover certain types of tests or only tests from certain laboratories. For example, in a recent case, the patient's insurance limited the laboratory she could use and what tests she could order. The patient presented with intellectual disability, behavior problems, and some dysmorphic facial features. Based on the patient's insurance, Dr. Bird knew she would only get coverage for testing at one particular lab. When she tried to get authorization to order an exome sequence, it was not approved. She instead ordered an intellectual disability gene panel, which included several genes and reflexed to a clinical exome, including about 5,000 genes.

It was no surprise to Dr. Bird that the results came back showing two variants of uncertain significance (VUS). Both were in genes that can be associated with intellectual disability, but based on the available information about these variants, there was no good way to determine which one was most likely to be a causative variant for Dr. Bird's patient. Fortunately, the lab offered free analysis of parental samples. Unfortunately, this offer was only available for one of the two variants.

THE SOLUTION

To help make the decision about which VUS to pursue, Dr. Bird analyzed the case in Face2Gene, and the results showed KBG syndrome as the top hit and a very strong match for the patient. One of the two VUS results was in ANKRD11, the gene which causes KBG syndrome. Dr. Bird discussed this with the family, explaining that, "there are two reported variants here, but we can only get free parental testing on one. Based on the strength of the fit for KBG syndrome in Face2Gene, that's the one I suggest we prioritize."

THE RESULT

The results of parental testing showed that the ANKRD11 variant was a *de novo* variant in the patient. Finding that a VUS is *de novo* often motivates a change in the variant classification, elevating it to "likely pathogenic". In this case, the lab felt that they could not rule out nonpaternity, so they did not alter the variant classification. For Lynne, it made a huge difference and made her feel a lot more confident in deciding on this as the diagnosis. "Finding that it was *de novo* in this patient, in combination with Face2Gene pushing me in that direction, made me feel that I had solved this case."

"I don't have a great 'feel' for KBG syndrome. I think I have seen now a total of two cases with this diagnosis. I suspect this syndrome is a lot more common than we think, but in most cases its not very distinctive. Yet the computer obviously sees something way more clearly than the human brain (at least mine) can."

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CASE STUDY: Using Face2Gene to End a 12-Year-Long Diagnostic Odyssey for Mother and Daughter

In this case, Face2Gene helped Dr. Cyndy Curry by motivating targeted genetic testing for a family that had long gone undiagnosed, saving significant time and money in the process.

WHO

Dr. Cyndy Curry is a geneticist at UCSF Fresno with many years of experience in the clinic, and often uses Face2Gene to support her clinical evaluations.

THE DILEMMA

Dr. Curry had a patient she had followed since birth, who was originally referred for a genetics evaluation because she was thought at birth to be dysmorphic. The patient's mother has mild to moderate intellectual disability, and she had two other daughters, both intellectually normal. When the patient was 12 years of age, the family returned to genetics after a six-year gap requesting a diagnosis.

Initially, the patient had multiple hemangiomas, which dominated her clinical phenotype. These resolved without treatment. She also had mild generalized hypertrichosis. She walked at 18 months and combined words at 4 ½ years. She does not read and has only beginning math skills. She needs some assistance with self-help skills. She has not yet entered puberty. Her general health is good.

Prior evaluations included normal Fragile X analysis, a normal SNP microarray, and a non-diagnostic MRI. Findings at her most recent visit included a weight at the 15th percentile and height at the 21st percentile, her head circumference was 51.75 cm, and she had a strikingly triangular face, mild hypertelorism, heavy eyebrows with synophrys, bulbous nasal tip, mild facial asymmetry and brachycephaly, low posterior hairline, poorly defined philtral ridges, overbite, high narrow palate and a bifid uvula. Her resemblance to her mother was more obvious than in previous visits. Her mother had coarse features and a poorly defined philtrum and a thin upper lip with widened cupids bow.

THE SOLUTION

Before proceeding with exome sequencing, Dr. Curry reviewed the patient case with her residents, and they entered both the patient and her mother independently into Face2Gene. In both the patient and her mother, there was a very high gestalt match for KBG syndrome. The team reviewed KBG syndrome in detail and decided, based on this match and detailed analysis of the KBG phenotype, to order single gene analysis for ANKRD11 rather than costly exome sequencing. Results confirmed a pathogenic variant in ANKRD11 (p.Arg1462Lysfs*). At the time of results disclosure, the clinical team examined the patient and her mother's teeth, as macrodontia is a characteristic feature of the syndrome. While the patient's mother's teeth were clearly of normal size, the patient's teeth were borderline large and prominent due to her malocclusion. Only 69% of patients with KBG have macrodontia.

THE RESULT

Use of Face2Gene and the comparison of mother and child's nearly identical gestalt matches directed us to perform a single gene analysis that was diagnostic.