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CASE PRESENTATION

The Genetics Journey: A Case Report of a Genetic Diagnosis Made 30 Years Later

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Abstract Mandibulofacial dysostosis with microcephaly (MFDM) is a rare autosomal dominant condition that was first described in 2006. The causative gene, *EFTUD2*, identified in 2012. We report on a family that initially presented to a pediatric genetics clinic in the 1980s for evaluation of multiple congenital anomalies. Re-evaluation of one member thirty years later resulted in a phenotypic and molecularly confirmed diagnosis of MFDM. This family's clinical histories and the novel *EFTUD2* variant identified, c.1297_1298delAT (p.Met433Valfs*17), add to the literature about MFDM. This case presented several genetic counseling challenges and highlights that "the patient" can be multiple family members. We discuss testing considerations for an unknown disorder complicated by the time constraint of the patient's daughter's pregnancy and how the diagnosis changed previously provided recurrence risks. Of note, 1) the 1980s clinic visit letters provided critical information about affected family members and 2) the patient's husband's internet search of his wife's clinical features also yielded the MFDM diagnosis, illustrating the power of the internet in the hands of patients. Ultimately, this case emphasizes the importance of re-evaluation given advances in genetics and the value of a genetic diagnosis for both patient care and risk determination for family members.

Keywords Mandibulofacial dysostosis with microcephaly (MFDM) · *EFTUD2* · c.1297_1298delAT · p.Met433Valfs*17 · Tracheoesophageal fistula (TEF) · Genetic counseling · Patient letters · Internet search

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Introduction

Advances in genetic testing have resulted in the identification of causative genes for genetic syndromes that previously had to solely rely on clinical criteria for diagnosis. Mandibulofacial dysostosis with microcephaly (MFDM) is one of those syndromes and was first described in a cohort of 4 unrelated Brazilian patients (Guion-Almeida et al. 2006; Lines et al. 2012). The major criteria of MFDM (OMIM # 610536) include mandibulofacial dysostosis, microcephaly, malformations of the ear, tracheoesophageal fistula/esophageal atresia and characteristic dysmorphic features (Table 1) (Lines et al. 2012). A diagnosis of MFDM should be suspected in individuals with 3 or more of these major features (Lines et al. 2012, 2014). In 2009, investigation of the first familial case of an affected mother and son suggested that MFDM was inherited in either an X-linked or autosomal dominant manner (Guion-Almeida et al. 2009).

In 2012, *EFTUD2* was identified as the causative gene through whole exome sequencing in four unrelated affected individuals (Lines et al. 2012). The *EFTUD2* gene, located at 17q21.31, encodes a GTPase which is a component in the spliceosome complex (Fabrizio et al. 1997). The gene contains 29 exons and is 972 amino acids in length (Aken et al. 2016). The majority of the pathogenic variants in *EFTUD2* are nonsense, frameshift and splice site variants leading to

Table 1 Major criteria of mandibulofacial dysostosis with microcephaly (MFDM)[a]

1. Mandibulofacial dysostosis
Most commonly characterized by malar and maxillary hypoplasia.
Associated anomalies can also include midline cleft palate, choanal atresia, ear anomalies (see below), and/or lacrimal atresia.
2. Microcephaly
Intellectual disability present in virtually all individuals with varied severity.
3. Characteristic malformations of the middle/outer ear
External ears are abnormal in virtually all individuals
Middle ears are abnormal in some individuals
Hearing loss affects about 75% of individuals (80% is conductive)
4. Esophageal atresia/Tracheoesophageal fistula
5. Characteristic dysmorphic features (including micrognathia, a relatively high nasal root with prominent ridge, everted lower lip, and (frequently) facial asymmetry).

A diagnosis of MFDM should be suspected in individuals meeting three or more criteria

[a] Lines et al. (2014)

premature truncation of the protein, with haploinsuficiency believed to be the disease causing mechanism for MFDM (Huang et al. 2016).

The identification of the *EFTUD2* gene established that MFDM is inherited in an autosomal dominant manner with most cases (75%) the result of de novo pathogenic variants (Huang et al. 2016). This condition is believed to be highly penetrant with variable expressivity as some patients only display minor findings (Lines et al. 2014). As of the most recent report in 2016, there are 107 individuals from 94 kindreds reported with MFDM (Huang et al. 2016).

Here we report a family with three affected individuals with MFDM that originally came to medical attention in the early 1980s. At the time, the family did not receive a definitive diagnosis for the constellation of multiple anomalies. A member of the family was then seen thirty years later and was provided with a clinical and molecular diagnosis of MFDM. The patient's husband, in fact, had raised the possibility of the MFDM diagnosis based on his own internet research. The clinical description of this family adds to the literature describing the variability of the MFDM phenotype and we present the novel pathogenic variant identified.

We also describe challenging genetic counseling issues raised by this case including meeting genetic counseling needs simultaneously of different family members ("who is the patient"), figuring out an undiagnosed condition with the time constraints of an ongoing pregnancy, communicating changes in inheritance information and making decisions about genetic testing when timing and cost are significant considerations. This case also illustrates the impact letters to patients and patient use of the internet can have in making a genetic diagnosis.

Case History

In the early 1980s, our female patient (Mrs. R), then in her early 20s, gave birth to a baby boy with multiple congenital anomalies: tracheoesophageal fistula (TEF), microcephaly, micrognathia, cleft palate, ventricular septal defect (VSD) and malformation of the external ears. Mrs. R, herself, had been born with a TEF, micrognathia, microcephaly and had mild intellectual disability (finished high school with some assistance). Mrs. R's son was evaluated in a pediatric genetics clinic when he was 4 months old. Chromosome analysis of her son revealed a normal male karyotype (46, XY). Following the evaluation, the family was counseled that the likely diagnosis was Pierre-Robin sequence which was potentially inherited in an X-linked dominant manner, based on the fact that Mrs. R had some of the same clinical features as her son.

In the subsequent years, Mrs. R gave birth to two more children: a healthy daughter with no congenital anomalies and another son who had a similar spectrum of anomalies as the first son, but no VSD (Table 2). The family was again seen in the pediatric genetics clinic when the younger son was 1 month of age and were counseled similarly to before; the set of anomalies were best explained by an X-linked dominant disorder. Both sons were given up for closed adoption within their first year of life.

Thirty years later, Mrs. R was seen in the adult genetics clinic with her pregnant daughter. At the time, her daughter was approximately 13 weeks pregnant and was interested in determining her risk to have a child with the same medical issues as her mother and brothers. The daughter was first seen by a prenatal genetic counselor at another hospital who referred her to our genetics clinic to determine recurrence risks. Separately, Mrs. R's husband also contacted our clinic's genetic counselor by email regarding his daughter's pregnancy and shared their family history. Through the use of the

Table 2 Features of the affected family members

Feature	Mrs. R	Son 1	Son 2
TEF	X	X	X
Micrognathia	X	X	X
Microcephaly	X	X	X
Cleft Palate		X	X
Malformed Ears	X	X	X
Ventricular Septal Defect		X	
Malar hypoplasia	X	—	—
Cognitive Impairment	X	X[a]	X*

"X" denotes presence of the feature in the particular individual

"X*" denotes presumed present

"—" denotes not known

[a] Father found a photo on the internet of his son, who was in his 20s, at a special education school

internet, he had located the genetic counselor they saw 30 years ago and sent her an email. This counselor had moved out-of-state in the interim and provided Mrs. R's husband with our clinic's genetic counselor's email.

In Mrs. R's husband's email, he notably provided the results of his own internet research on potential diagnoses. He specifically utilized Online Mendelian Inheritance in Man (OMIM) and GeneReviews to search for the clinical features identified in his wife and sons and raised concern for 2 conditions: MFDM and Pierre-Robin Sequence. He also inquired about the autosomal dominant inheritance of MFDM since the family had been previously counseled about X-linked inheritance. Additionally, Mrs. R wrote the following on our clinic's intake form:

> "*I was born with a TEF and other jaw and head shape issues. I gave birth to a normal healthy girl. I also gave birth to two sons with multiple birth defects, which were more severe than mine. I was originally told that it was an X-linked dominant trait. Thirty years later what has been learned through research? What gene/chromosome is responsible? Could my perfectly normal daughter be a carrier of a recessive trait?*"

This statement captured the questions we hoped to answer: what gene change is responsible for the condition and what is the risk to the pregnancy? When seen in our adult genetics clinic, Mrs. R also expressed significant concern for her daughter's pregnancy echoing the sentiments shared above.

Given the family history, we recommended to the daughter that her mother be evaluated and if possible, that they be seen together. At the time of the visit to our clinic, Mrs. R was 55 years old and her daughter was 29 years old. A family history was obtained (Fig. 1) and no additional family members were reported to be affected. Of note, Mrs. R reported that a paternal male second cousin also had a TEF. He later became blind (unspecified age of onset) and died at age 50 due to pneumonia. To the family's knowledge, he did not have genetic testing and no unifying diagnosis was ever made.

To best provide care for both patients, our clinical team decided to move the daughter to a different room from her mother to obtain the medical histories and perform physical examinations separately. This allowed us to both obtain relevant information efficiently and assess the individual needs of each patient in a confidential manner.

Mrs. R's physical exam confirmed the microcephaly and microretrognathia, although the latter was reportedly more significant prior to surgery for temporomandibular joint (TMJ) dysfunction. Additional dysmorphic features identified included malar flattening, facial asymmetry and a high arched palate. Mrs. R also reported trigeminal neuralgia and hearing loss that had worsened recently. According to Mrs. R's husband, she was seen by an outside audiologist and ENT specialist and has conductive hearing loss, ear canals that are smaller than normal and a deviated septum.

Mrs. R's daughter's maternal family history is documented above. Family history for her paternal side of the family was unremarkable. The daughter had a normal physical exam. This was the daughter's first pregnancy and ultrasound at 12 weeks gestation was normal.

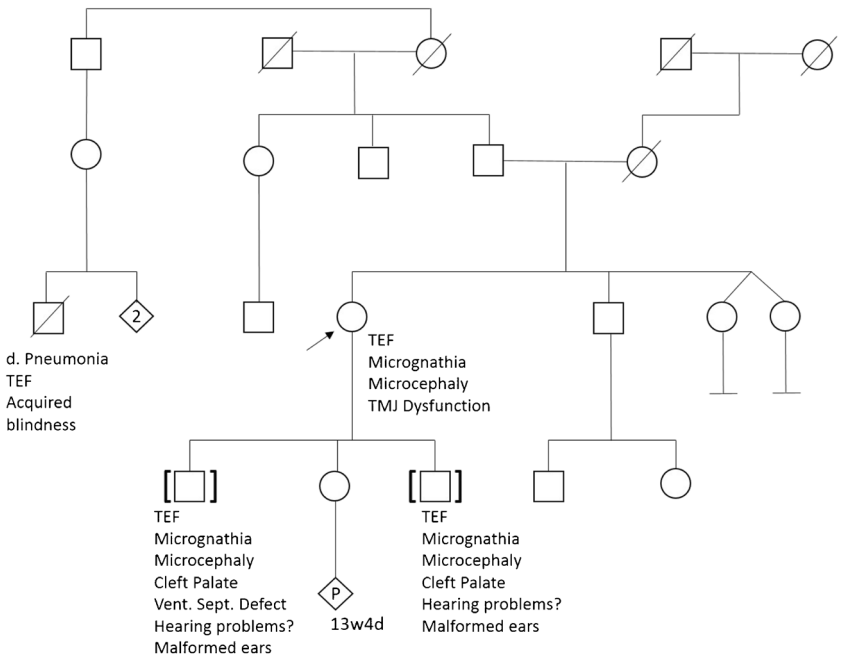

Fig. 1 Pedigree

Diagnostic Considerations

The family notably had copies of the clinic visit letters sent to them 30 years prior, which provided needed documentation about Mrs. R's sons' features and enabled us to develop differential diagnoses. The initial diagnosis provided was Pierre Robin sequence (PRS). PRS formally refers to the association of micrognathia, glossoptosis and respiratory obstruction. Frequently, a secondary cleft palate also co-occurs (Tan et al. 2013). Importantly to note, there are multiple genetic causes of PRS including 22q11.2 deletion syndrome, Stickler syndrome, and MFDM, and each of these conditions can have several additional features (Tan et al. 2013). Confirming the underlying genetic cause is extremely important as the differential diagnoses, as noted below, are conditions with varying inheritance patterns, surveillance recommendations, and treatment strategies (Lalani et al. 2006; Lines et al. 2014; Marcelis and de Brouwer 2009; Meroni 2004; Tan et al. 2013).

The features shared by all three affected individuals in the family (Table 2) are TEF, micrognathia, microcephaly and intellectual disability (per parent report for the two sons). The differential diagnoses we considered are in Table 3 and include MFDM, Feingold syndrome, X-linked Opitz G/BBB syndrome, CHARGE syndrome or a chromosomal microdeletion/microduplication.

The features seen in the family met all of the major diagnostic criteria for MFDM. With respect to the other conditions, there are key characteristic features of each condition which were not seen in the family. Individuals with Feingold syndrome typically have digital anomalies (Celli et al. 2003; Marcelis and de Brouwer 2009). Females with X-linked Opitz G/BBB syndrome rarely express a phenotype more severe than isolated ocular hypertelorism. Additionally, males usually have hypospadias (Meroni 2004; Quaderi et al. 1997). In terms of CHARGE syndrome, notable features missing include coloboma and choanal atresia (Hsu et al. 2014; Lalani et al. 2006; Verloes 2005; Vissers et al. 2004). Chromosomal microdeletions or microduplications remained a diagnostic possibility.

Counseling Issues

Case Management: Who is the Patient?

Although this case was initiated 30 years ago when Mrs. R's first affected son was evaluated, it was Mrs. R's healthy daughter who was now inquiring about risk to her pregnancy and had been referred to our clinic. However, even though the daughter was referred, it was Mrs. R who needed to first have the genetic evaluation in order to assess the risk to her

Table 3 Differential diagnoses

Feature	Mandibulofacial Dysostosis with Microcephaly (MFDM)[a, b, c]	Feingold Syndrome[d, e]	X-linked Opitz G/BBB Syndrome[f, g]	CHARGE Syndrome[h, i, j, k]
TEF	X*	X*	X*	X
Microcephaly	X*	X*	X	
Micrognathia	X*	X	X	
Ear abnormalities	X*			X*
Cleft lip/palate	X		X	X
Heart defects	X	X	X	X*
Malar hypoplasia	X*			X
Cognitive Impairment	X	X	X	X*

"X" denotes presence of the feature in the particular condition

"*" denotes major criteria for the particular condition or features seen in > 80% of individuals

[a] Lines et al. (2012)

[b] Lines et al. (2014)

[c] Huang et al. (2016)

[d] Celli et al. (2003)

[e] Marcelis and de Brouwer (2009)

[f] Quaderi et al. (1997)

[g] Meroni (2004)

[h] Vissers et al. (2004)

[i] Verloes (2005)

[j] Lalani et al. (2006)

[k] Hsu et al. (2014)

daughter and the pregnancy. Recognition of the necessity of Mrs. R being evaluated in addition to her daughter allowed us to enact the proper work-up, make a likely diagnosis and initiate genetic testing in an effective and time-sensitive manner.

The fact that Mrs. R and her daughter were both simultaneously patients impacted case management and results disclosure. Genetic testing decisions and results communication had to meet the needs of both Mrs. R and her daughter. Fortunately, Mrs. R wanted to do the genetic testing and share the results to help her daughter make informed pregnancy decisions. Mrs. R was seen jointly with her daughter to discuss her test results at which time, genetic testing was initiated for her daughter.

We had scheduled an in-person results disclosure for Mrs. R in order to be able to explain the results and their implications and to have the ability to initiate additional genetic testing as soon as possible had results been negative. The in-person results disclosure also allowed us to communicate the results to Mrs. R's daughter in a timely manner so that she could make her genetic testing decision. Mrs. R's daughter needed to know her mother's results to determine whether she could have genetic testing for an identified familial pathogenic variant or whether the pregnancy would be assessed by chromosome microarray analysis and ultrasound evaluation, both with limitations, in the absence of identifying a maternal pathogenic variant. Mrs. R gave verbal consent for us during the visit to provide her daughter with a copy of her genetic test results and this consent was documented.

Undiagnosed Condition and Pregnancy

Mrs. R's daughter's 13-week pregnancy placed a time pressure on this case. It is not known why genetic counseling was not sought prior to conception or earlier in the pregnancy. In the state where the family lived, the legal limit for pregnancy termination is 24 weeks. When Mrs. R's daughter was asked about her pregnancy and whether she would make a decision to not continue the pregnancy should it be affected, she replied that she was unsure. She was certain that she wanted all possible information, however, to make a potential decision.

An undiagnosed condition confounds the ability to provide a specific recurrence risk (see "Risk Assessment" section). Ultimately, genetic testing would be key in confirming a specific diagnosis in Mrs. R and subsequently assessing her daughter's risk. Because of the pregnancy, time was limited to obtain Mrs. R's results, do additional testing if indicated and have the option to test her daughter and/or the pregnancy if a pathogenic variant was identified. It was possible that genetic testing would not yield a result or would identify a variant of uncertain significance.

Risk Assessment

Given three affected individuals, both genders, in two generations, the pattern of inheritance of the condition was consistent with either autosomal dominant or X-linked inheritance (due to the difference in severity of affected males vs. females). Therefore, if Mrs. R's daughter was a carrier, the risk for the pregnancy to be affected was 50%, with potentially milder features in a female if due to X-linked inheritance.

Mrs. R's parents and siblings were unaffected, making it likely that the condition first manifested in Mrs. R as the result of a de novo mutation. While it is notable that a second cousin had a TEF, he, by report, did not have any other anomalies and had normal intelligence. This cousin's TEF was thought to likely be unrelated given that second cousins are fifth degree relatives and only share approximately 3% of their DNA as well as the fact that the four relatives between Mrs. R and the cousin were all unaffected. Isolated TEF/esophageal atresia occurs at an incidence of 1/3500 individuals and it is possible that the cousin represented an isolated case (Shaw-Smith 2006).

Testing Strategy

In determining an optimal testing strategy, two key factors were considered: 1) whether a single test or multiple genetic tests should be ordered and 2) result times given the ongoing pregnancy of the daughter. Given both the clinical findings and the family history, MFDM was the presumptive diagnosis. However, we could not rule out the possibility that a chromosomal microdeletion and/or microduplication could be the underlying etiology.

After the physical exams, we brought the family together and presented two options to confirm the diagnosis in Mrs. R: either perform *EFTUD2* molecular analysis (sequencing followed by deletion/duplication analysis) and a chromosome microarray analysis simultaneously or first perform *EFTUD2* molecular analysis. Expedited *EFTUD2* molecular analysis at extra cost was also offered. The expected turn-around time for *EFTUD2* analysis was 3–4 weeks and with expedited testing was approximately 8 days. The family wished to start with only *EFTUD2* analysis but could not afford to pay for expedited testing. A blood sample was obtained from Mrs. R and sent for *EFTUD2* analysis and at the same time, insurance authorization was requested for both *EFTUD2* analysis and chromosome microarray analysis. Coverage for both genetic tests was subsequently denied and unsuccessfully appealed.

Mrs. R's daughter informed us that she would be having a follow-up ultrasound between 15 and 16 weeks gestation. Should her mother's test results not yet return, we recommended that the daughter consider *EFTUD2* molecular testing and potentially chromosome microarray analysis for the

pregnancy as a contingency plan, especially if ultrasound anomalies were noted (such as polyhydramnios secondary to esophageal atresia, cleft palate, heart defects or other anomalies described in the two sons).

Novel Pathogenic Variant Identified

Mrs. R's *EFTUD2* genetic testing returned after 2 weeks and identified a novel pathogenic variant in the *EFTUD2* gene, c.1297_1298delAT (p.Met433Valfs*17). The identified variant is predicted to result in a frameshift leading to premature termination of the protein either in exon 13 or 14 (depending on which protein transcript is used). Mrs. R's daughter elected to pursue site-specific testing as there remained the small possibility she could have inherited the *EFTUD2* variant given the variable expressivity of MFDM. Site-specific testing returned negative and therefore Mrs. R's daughter and the pregnancy were not at increased risk for MFDM.

It is likely that the *EFTUD2* variant identified was a de novo variant in Mrs. R which was inherited by both of her sons. Given that her sons were adopted out of the family, it is unknown if they have a genetically confirmed diagnosis, but their constellation of features is consistent with the phenotypic spectrum of MFDM.

Discussion

This case illustrates the significant progress of clinical genetics since the early 1980s, which has resulted in both the identification of numerous genetic conditions phenotypically and molecularly. Of note, MFDM was first described in 2006 (Guion-Almeida et al. 2006) and the genes responsible for the syndromes in our differential diagnoses were identified only as early as 1997 (X-linked Opitz G/BBB syndrome) and as recently as 2012 (MFDM) (Celli et al. 2003; Lines et al. 2012; Quaderi et al. 1997; Vissers et al. 2004). These genetic advances in syndrome identification and genetic testing enabled us to give Mrs. R's family the appropriate diagnosis. Our description of Mrs. R's and her sons' phenotypic variability adds to the literature about MFDM. We also identified a novel pathogenic variant, thus adding to the list of documented variants causative of MFDM.

In addition to the advances in genetics, there have been significant changes in the way we gather information, namely use of the internet. The internet houses databases and resources about genetic syndromes, genetics clinics and providers, genetic testing and support/advocacy groups. These sources of information are not just utilized by genetics professionals and health care providers, but by patients as well. In this case, MFDM was first brought to our attention by Mrs. R's husband. He navigated through well-established online genetics resources such as OMIM and GeneReviews to generate possible diagnoses with one of the conditions being the correct diagnosis.

It is important, however, to recognize that most patients do not have the training to distinguish the resources that provide accurate information from those that do not. Additionally, several genetics-specific informational resources available on the internet are not written for the general public but rather for providers which greatly inhibits comprehension of the information by patients and their families. Nonetheless, this case illustrates the power of the internet and the growing opportunities patients and their families have in aiding in the diagnostic process.

The diagnosis was not the most challenging issue in this case however. Mrs. R's daughter's pregnancy placed a time constraint on the entire case. This time constraint was effectively managed by the genetic counselor's recognition that while the daughter was the referred patient, her mother was the key family member to evaluate and therefore also needed to be seen as soon as possible.

Determining "who is the patient" and recognizing that "the patient" can be more than one family member is an important part of case management and can significantly impact the outcome of a genetic evaluation and provision of genetic counseling (Uhlmann 2009). In our case, we had to consider as "patients" Mrs., R, her daughter and even her daughter's pregnancy. "Who is the patient" could also apply to Mrs. R's two more significantly affected sons, who were not available for our evaluation but information about them from clinic letters was critical for our evaluation of Mrs. R, decision-making about genetic testing and provision of risk information.

It has been a long-standing practice in genetics to send patients letters to document the genetic counseling provided and to have as a resource for family members (Baker et al. 2002). The letters provided by Mrs. R and her husband of the evaluations in the 1980s were instrumental in providing us with a clinical description of their two sons, differential diagnoses considered, inheritance patterns discussed and testing that was performed. Considering both sons were adopted out, without these patient letters, we would only have had Mrs. R's and her husband's report of their sons' clinical features since HIPAA regulations would have prohibited us from accessing their sons' medical records without their guardians' permission. The letters allowed us to generate differential diagnoses, identify the likely diagnosis and determine testing options prior to the family's visit.

Decision-making about genetic testing in this case raised the important question: what is the most important factor (i.e. diagnostic yield, time, etc.) when performing testing? Typically, diagnostic yield is the highest priority and one approach to achieve greater diagnostic yield is to order multiple tests. However, selecting multiple tests is usually costlier and

has a higher chance of yielding variants of uncertain significance, which creates challenges in interpretation. Time is paramount to some patients, especially those who are pregnant or making surgical decisions. In terms of cost, it is not uncommon for genetic testing to be denied by insurance and patients often do not have the financial resources to pay for testing (Armstrong 2015; Jewell 2015; Secretary's Advisory Committee on Genetics, Health and Society 2006).

Specific to our patient and her family, a plan for testing needed to provide the greatest opportunity to identify a molecular diagnosis and be completed in time to potentially test the daughter/daughter's pregnancy. The options we offered the family reflected these two factors of diagnostic yield and time; the option of performing *EFTUD2* gene analysis and chromosome microarray analysis concurrently cast a larger net and valued time and yield versus *EFTUD2* gene analysis only, a less expensive option, which cast a smaller net with need of additional testing if negative. In the end, non-expedited *EFTUD2* only analysis was pursued due to financial reasons but fortunately we were still able to obtain a timely diagnostic result with this testing approach.

In this case, the MFDM diagnosis completely changed the understanding and perception of risk of the condition. Originally, Mrs. R and her husband thought their daughter was "in the clear" because she was healthy. With new knowledge, we counseled the family about the presumptive diagnosis of MFDM and autosomal dominant inheritance, which left the possibility that the daughter could be very mildly affected given variable expressivity associated with this condition, and a potential increased risk to the pregnancy. Fortunately, it was learned that their daughter did not carry the pathogenic variant, and there was no increased risk for the pregnancy to be affected. In the end, this was the answer they were hoping for and provided the most relief. Other families undergoing genetic testing to identify the cause or inheritance pattern of a disease describe similar feelings and valued the importance of identifying the causative mutation to provide accurate risk information for other family members (Carstens et al. 2016; Combs et al. 2013).

Mrs. R's genetic testing was denied insurance coverage because it would not affect her management. Testing, however, was a necessary first step to confirm the MFDM diagnosis molecularly in order for the daughter to have the option to test herself/the pregnancy. This situation is analogous to many cases in cancer genetic counseling in which it is recommended to begin testing with an affected individual if available (Berliner et al. 2013; Weissman et al. 2012). Even if management of the affected individual will not be altered, identifying the pathogenic variant is important for diagnosis confirmation, accurate risk assessment and enables at-risk family members to be tested.

Obtaining insurance authorization for genetic testing is a time-involved multistep process and testing approval can be challenging to obtain especially when results will not directly impact patient care (Uhlmann et al. 2017). If Mrs. R had not proceeded with genetic testing because of insurance coverage or other issues, her daughter could have had the pregnancy directly tested. However, this approach would have had significant limitations. If the pregnancy had tested negative, it would not have been known if the pregnancy was negative because a pathogenic variant had not been inherited or negative because, even in Mrs. R, a pathogenic variant would not be identified with today's testing. In regards to obtaining insurance coverage of prenatal genetic testing, it may have been less problematic because of the ongoing pregnancy (Deverka and Dreyfus 2014; Graf et al. 2013; Secretary's Advisory Committee on Genetics, Health and Society 2006). If Mrs. R's daughter did not have insurance coverage for genetic testing and could not afford the out of pocket expense, evaluating the pregnancy would have been limited to using the screening ultrasound that is recommended in all pregnancies at approximately 18 weeks' gestation, and others as clinically indicated (American College of Obstetricians and Gynecologists 2016), in the hopes of identifying some of the MFDM clinical features.

This case effectively demonstrates the quintessential feature about clinical genetics practice: genetics affects not just the patient, but the family. If we had only seen Mrs. R's daughter in our clinic, our evaluation would have been limited and our testing would likely have either been unfruitful or uninformative. Despite this being an extreme case of almost thirty years separating the clinic visits, this case also highlights the importance of encouraging follow-up. Ensuring patients follow-up with genetics, especially given advances in genetic testing, improves the possibility of obtaining a molecular diagnosis and gives some patients what is most needed: a name for their medical condition.

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Compliance with Ethical Standards

Conflicts of Interest Linford A. Williams, Shane C. Quinonez and Wendy R. Uhlmann declare that they have no conflicts of interest.

Human Studies and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Animal Staudies No animal studies were carried out by the authors for this article.

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