INTRODUCTION

Heterozygous 15q13.3 microdeletion syndrome is a clinical syndrome with high variability in expression and penetrance of symptoms. Heterozygous 15q13.3 deletion is frequently inherited (reported as inherited in approximately 85.4% of individuals who have this deletion who have data available on inheritance in a review of large number of cases), but may also occur de novo. Commonly reported associations include developmental delay or intellectual disability, epilepsy or seizures, speech problems, autism spectrum disorder, schizophrenia, mood disorders, and attention deficit hyperactivity disorder. Serious congenital anomalies are uncommon. A subset of individuals appears unaffected and is essentially healthy appearing neurotypical individuals. Some individuals have a mild phenotype with attention deficit disorder, learning disability or psychiatric or behavioral difficulties. More severely affected individuals may have autistic features or more severe cognitive impairment. Deletions in this region can vary in size, with the most typical size deletion approximately 1.5-2.0 Mb, approximately between 30.5 and 32.5 Mb, human genome build 19. Smaller deletions (<700 kb) and larger deletions (~3.9 Mb) can also occur.

Homozygous 15q13.3 deletion is a rare finding. In contrast to individuals with the heterozygous deletion,

**FIGURE 1** Facial appearance of proband
individuals with a homozygous 15q13.3 microdeletion consistently have shown a severe phenotype that includes encephalopathy, diffuse hypotonia, severe developmental delay, cortical vision impairment, and epilepsy or abnormal EEG. Although the number of affected patients reported with homozygous 15q13 microdeletion is small, the features have been highly consistent among the known patients. We report here an additional patient with homozygous 15q13.3 microdeletion to provide further information and discussion of this rare syndrome.

2 | CASE PRESENTATION

Our patient was initially evaluated in neurology clinic due to concerns of hypotonia and developmental delay. She was the

| TABLE 1 | Summary of clinical findings in known patients with homozygous 15q13.3 deletion |
|----------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Age           | Our patient                     | Masurel‐Paulet et al 2010 & 2014 | Masurel‐Paulet et al 2014       | Masurel‐Paulet et al 2014       | LePichon et al 2010 |
|               | 11 mo                           | 9 y                             | 4 y                            | 30 mo                           | 10 y                           |
| Sex           | Female                          | Male                            | Male                           | Male                            | Male                           |
| Deletion size | 2.0 Mb/2.0 Mb                   | 1.5 Mb/1.5 Mb                   | 1.5 Mb/1.5 Mb                  | 1.5 Mb/1.5 Mb                   | 1.5 Mb/1.5 Mb                  |
| Breakpoints   | hg19 30 938 341‐32 926 776      | hg19 30 938 215‐32 510 863       | hg19 30 938 215‐32 510 863     | hg19 30 938 215‐32 510 863     | hg19 28 718 936‐30 701 573     |
| Inheritance   | Biparental                      | Biparental                      | Biparental                     | Biparental                      | Biparental                      |
| Paternal phenotype | ADHD                        | Mild ID                         | No ID, but stopped school studies at 16 | Healthy                         |
| Maternal phenotype | Healthy                     | Mild ID                         | No ID, but stopped school studies at 16 | Healthy                         |
| Hypotonia     | +                               | +                               | +                               | +                               | +                               |
| Developmental delay | +                            | +                               | +                               | +                               | +                               |
| Visual impairment | +                           | +                               | +                               | +                               | +                               |
| Abnormal optic nerve | +                         | +                               | +                               | +                               | +                               |
| ERG           | Abnormal                        | Abnormal                        | Abnormal                        | Abnormal                        | Abnormal                        |
| EEG           | Abnormal                        | Abnormal                        | Abnormal                        | Abnormal                        | Abnormal                        |
| Seizures      | –                               | + refractory                     | + eye version and partial crises | + absence and clonic         | + refractory                     |
| magnetic resonance imaging (MRI) | Delayed myelination at 4 mo | Retrocerebellar arachnoid cyst  | Dysmorphic corpus callosum     |                                  |                                  |

Note: Age indicates oldest age listed in clinical report.
Abbreviations: −, symptom absent; +, symptom present; ADHD, attention deficit hyperactivity disorder; Blank, data not available; hg18, Human Genome hg18 Build 36; hg19, human genome hg19 Build 37; ID, intellectual disability; Mo, months; y, years.
product of her mother's second pregnancy. Maternal age was 24 years, and paternal age was 21 years. She had a generally healthy 5-year-old maternal half-sister with normal developmental milestones. Her father reported a history of attention deficit hyperactivity disorder. Her mother was in generally good health with no clinical or developmental concerns. The pregnancy was uncomplicated until around 36 weeks gestation when there was concern of decreased rate of head growth on ultrasound. Delivery was by induced vaginal delivery at 41 weeks gestational age. Birth weight was 6 pounds and 10 ounces, and birth length was 20-1/2 inches.

Our patient had long eyelashes, epicanthal folds, and mildly anteverted nares but was not significantly dysmorphic. (See photo of proband in Figure 1). On neurologic exam, pupils were isocoric and reactive to light. She did not appear to be able to fix or track objects or faces. Eye movements were...
conjugate but frequently roving with intermittent upward rolling. In the first few months of life she also had occasional brief horizontal pendular nystagmoid intrusions. Motor exam was notable for prominent diffuse hypotonia, with low muscle bulk throughout, but no clear wasting or weakness. Muscle stretch reflexes were absent at the biceps and 1:4 at the quadriceps. Formal ophthalmology exam at 5 months of age showed optic nerve hypoplasia and delayed visual maturation.

Magnetic resonance imaging (MRI) of the brain showed normal structure and volume, with mildly delayed myelination for age. EEG revealed prominent and nearly continuous high-amplitude occipital slowing (2–4 hertz when awake, 1–3 hertz when asleep), usually bilateral and synchronous, but intermittently asymmetric without a clear predilection for one hemisphere over the other. Intermittent focal spike waves were observed as well. At 7 months old these appeared over the right occipital region but also less frequently independently over the left occipital. At 11 months old intermittent spike waves were less frequent and seen primarily over the bilateral paracentral region, often synchronous or with shifting laterality. Cardiology evaluation revealed a normal electrocardiogram and echocardiogram. Aberrant right subclavian artery was detected by MRI.

Her serious clinical concerns prompted further diagnostic work-up. Clinical SNP whole-genome array revealed two alterations: a homozygous copy number loss of 2.0 Mb at 15q13.2q13.3 (30 938 341-32 926 776) and small single copy number gain of 122 Kb on 9q34.3 (137 595 462-137 717 991).

Parental studies were undertaken to determine if the imbalances were de novo or inherited. Parental SNP whole-genome array revealed both parents carried identical heterozygous deletions at 15q13.2q13.3. There was no known consanguinity. Clinical testing was deferred until a later age for her half-sister as she had no clinical or developmental concerns at the time of evaluation.

The family had another pregnancy after the diagnosis of the proband. They elected to undergo amniocentesis with SNP whole-genome array, which revealed an unaffected fetus with normal copy number at 15q13.3.

2.1 | Diagnostic investigation

A whole-genome array of genomic DNA was performed on the proband and her parents (CombiMatrix, Irvine) using a custom-designed Illumina single-nucleotide polymorphism (SNP) array (Illumina) with >845 000 SNP markers covering both coding and noncoding human genomic sequences. This revealed two alterations on the proband’s genome: a homozygous copy number loss of 2.0 Mb at 15q13.2q13.3 (30 938 341-32 926 776) and small single copy number gain of 122 Kb on 9q34.3 (137 595 462-137 717 991). The minimum/maximum genomic coordinates for the deletion on 15q13.2q13.3 fall between 30 928 895-32 522 589 (minimum) and 30 385 284-32 922 385 (maximum). Genomic imbalances are reported using UCSC human genome build 19 (NCBI build 37, Feb 2009). Genes within the deletion at 15q13.2q13.3 included LOC100288637, HECTD2P10, FAN1, MTMR10, MIR211, TRPM1, LOC102725022, LOC283710, KLF13, OTUD7A, CHRNA7, GOLGA8K, ULK4P3, ULK4P1, ULK4P2, GOLGA8O, WHAMMP1, LOC100996255, GOLGA8N, LOC101928042, and ARHGAP11A. The duplication at 9q34.3 partially overlapped the gene COL5A1.

3 | DISCUSSION

Only a small number of patients with homozygous 15q13.3 deletion are reported so far in the clinical literature. Despite the small number, the clinical phenotype has been consistent. A clear phenotype of encephalopathy, hypotonia, developmental delay, cortical vision impairment, epilepsy, and abnormal EEG findings has emerged. See Table 1 for a comparison of features in our patient and previously reported patients.

The small duplication at 9q34.3 was paternally inherited. This duplication partially overlapped the gene COL5A1. We suspected this duplication to be more likely benign and did not anticipate a partial duplication of COL5A1 to have significant clinical consequence unless it was in a region disruptive to another allele or gene.

These patients have helped spur discussion of which genes may underlie the key features of this phenotype. They may also help bring greater understanding of the roles of these genes in the heterozygous phenotype as well. Two key genes involved in the phenotype appear to be CHRNA7 (Cholinergic Receptor, Neuronal Nicotinic, Alpha Polypeptide 7) and TRPM1 (Transient Receptor Potential Cation Channel, Subfamily M, Member 1).8

It has been posited that in the heterozygous deletion, the variability in the phenotype may depend on variation in the remaining allele of key genes such as CHRNA7. The severe phenotype when there is no second allele of CHRNA7 appears supportive of this hypothesis. However, Masurel-Paulet et al sequenced CHRNA7 in a cohort of individuals with heterozygous 15q13.3 deletion and found no sequence variants to explain the variability in phenotype.3 Of course, other variations among the other approximately 20 000 genes in the genome may also play compensatory roles. Elucidating potential key players may be inherently difficult, though candidates may also play compensatory roles. Elucidating potential key players may be inherently difficult, though candidates may also play compensatory roles. Elucidating potential key players may be inherently difficult, though candidates may also play compensatory roles.

TRPM1 has been nominated as playing a role in the ophthalmologic findings.10 Alterations in the gene TRPM1 are known to cause autosomal recessive congenital stationary
night blindness. TRPM1 channel opening is essential for rod bipolar pathway establishment in development, making it a plausible initial candidate.\textsuperscript{11} Mausurel-Paulet et al noted that among the patients with smaller homozygous deletions that did not include TRPM1, the visual component of the phenotype was absent. Our patient's deletion includes TRPM1, and she has clear ophthalmologic findings including optic nerve pallor and cortical vision impairment. However, patients who have a deletion that does not include TRPM1 have been reported to have other visual concerns such as difficulty with visual tracking. TRPM1 may play a role at the level of the retina and the optic nerve, but it is possible CHRNA7 may play a role at the cortical level.

Additionally, we noted that this case further supports the use of chromosome microarray in the initial steps of genetic work-up of children with profound neurological symptoms.\textsuperscript{12} Assessment of chromosome copy number variants is an important initial step in the genetic evaluation and should be considered early in the genetic evaluation process. Not only does this provide an opportunity for better prognosis and management decisions, it also allows for family planning and evaluation decisions for the patient's family and their relatives. The information regarding recurrence risk and early testing was valuable for our patient whose parents were still in the active family planning stage. It will provide testing options to determine recurrence risks for her sister when she is of family planning age.

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CONFLICT OF INTEREST

None reported.

AUTHOR CONTRIBUTIONS

JS, KS, RF, and ALY drafted and edited manuscript. JM wrote the description of neurological exam. ALY coordinated the group and oversaw drafting, editing and responded to reviewer comments.

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