Case Report

8q22.2q22.3 Microdeletion Syndrome Associated with Hearing Loss and Intractable Epilepsy

Alejandra Rincon,1 Paola Paez-Rojas,1,2 and Fernando Suárez-Obando1,2

1Instituto de Genética Humana, Facultad de Medicina, Pontificia Universidad Javeriana, Colombia
2Javesalud, Colombia

Correspondence should be addressed to Fernando Suárez-Obando; fernando.suarez@javeriana.edu.co

Received 2 October 2018; Revised 7 November 2018; Accepted 2 December 2018; Published 10 January 2019

Copyright © 2019 Alejandra Rincon et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

8q22.2q22.3 microdeletion syndrome has been described in only seven patients. We present a new case from Colombia. The characteristicsof this condition are developmental delay, microcephaly, seizures, and typical facial dysmorphism. We discuss the clinical phenotype of the patient presenting relevant findings like hearing loss and severe epilepsy and the possible relations between the phenotype and the genes involved in the microdeletion. We describe a female with developmental delay, microcephaly, epilepsy, severe short stature, impaired speech, facial dysmorphism, and congenital deafness. A minimal/maximal deletion of 5.238 Mb and 5.374 Mb, respectively, at 8q22.2q22.3 was diagnosed using a genome-wide array. The clinical phenotype is similar to the others seven patients previously reported; however, the severity of epilepsy and the concomitant hearing loss is remarkable, characteristics previously observed independently in only two patients. The KCNS2 gene is located in the deleted regions (8q22.2). Therefore it is a possible candidate for explaining the complex neurologic phenotype.

1. Background

Developmental delay and intellectual disability (DD/ID) associated with abnormal phenotype are common indications for genetic referral [1]. In developing countries like Colombia, the diagnostic approach is usually based on clinical approach, neurological assessment, conventional karyotyping, and screening tests for metabolic diseases. However, until recently the clinical availability of MLPA (multiplex ligation-dependent probe amplification) [2], FISH (fluorescent in situ hybridization), and CGH (Comparative Genomic Hybridization) has facilitated the detection of submicroscopic chromosome aberrations. The molecular approach improves the etiological diagnostic of DD/ID, which is only achieved in around 30% of the evaluated cases [3]. Using this diagnostic method, we present molecular and clinical data of the first case of 8q22.2q22.3 microdeletion syndrome in Colombia.

This chromosome aberration is a clinically recognizable condition described worldwide in only seven patients [4–6]. The principal features of this syndrome are facial dysmorphism, ptosis, blepharophimosis, very short stature, developmental delay, and microcephaly. This report also lets us confirm the usefulness of molecular and cytogenetic analysis in the clinical approach of patients with idiopathic dysmorphism associated with DD/ID. The localization of the deleted genes and clinical phenotype are discussed.

2. Case Presentation

The patient was a 10-year-old girl referred to our genetic department because of developmental delay, microcephaly, epilepsy, severe short stature, impaired speech, facial dysmorphism, congenital deafness, and skeletal abnormalities. She was the second of two born children of healthy non-consanguineous parents and was born at 36 weeks due to intrauterine growth restriction and oligohydramnios, with a birth weight of 1,800 g and length of 42 cm (both below 2SD). She presented her first epileptic crisis at five months of age; it was characterized by generalized tonic-clonic seizures accompanied by eye deviation. By the age of 8 months,
Deletion of the 8q22.2q22.3 region has been associated with a clinically recognizable condition described worldwide in only seven patients. We present a new case comparing clinical and molecular data with previously reported cases. The deleted region comprises at least 25 clinical relevant genes, including the KCNS2, GRHL2, and COH1, that could be relevant in the pathogenesis of this syndrome. Table 1 comprises all clinical data from patients previously reported and this new case. The ratio between male and female cases of 8q22.2q22.3 deletion syndrome seems to be skewed toward an excess of females (males: 2, females: 6). There is no evident aged-factor maternal or paternally related, and all cases are sporadic. Our patient had intrauterine growth restriction (IGR) diagnosed at the time of the delivery; it seems that IGR is not a common finding since seven out of the eight reported patients had uneventful pregnancy. Short stature and microcephaly are common findings in this condition, 3 out of 8 patients developed postnatal microcephaly, and 3 out of 8 had postnatal short stature.

All eight patients have a developmental delay of variable degrees; 4 out of 8 have a severe developmental delay, and developmental language delay seems to be a common factor in almost all the patients (Table 1). However, there is not a correlation between microcephaly, the size of the deletion, and severity of developmental delay. Our patient has a severe language developmental delay, probably worsened by her bilateral hearing loss. Our patient presents classical facial dysmorphism of an 8q22 deletion syndrome, including ptosis, blepharophimosis, epicanthus, thin upper lip vermilion, and down-turned corners of the mouth. There is no phenotype-genotype correlation for ptosis and blepharophimosis. However, there is a proposed critical region related to ptosis which has a protein-coding gene ZFHX4 (Zinc Finger Homeobox 4) in 8q21.11 [7], a gene that is out of the deleted area in the reported patients. It could play a positional or close regulation effect related to the deleted region. Table 2 comprises molecular data (deleted region) from patients previously reported and this new case. Seizures and epilepsy are a remarkable diagnosis for almost all the cases since seven out eight patients have presented seizures.

Our patient has been affected by generalized tonic-clonic seizures and absence seizures since her first year of life. We do not have electroencephalographic details of the epileptic crisis of the others patients; however, according to the Kuechler et al. report, one of the patients had absence seizures, and another one presented two epileptics crisis at six years old. In addition, Kuroda et al. [5] describe an 8-year-old patient, who has had difficult-to-manage seizures since age 10 months. Our patient has been very symptomatic all of her life, and her treatment had been difficult; she has been treated with multiple medicines. Nevertheless, she presents at least one absence seizure per day. Some of the genes in
Table 1: Clinical phenotype of the seven reported cases carrying an interstitial microdeletion of 8q22.2q22.3. Patient 8 is the new Colombian case reported.

| Patient | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 | Patient 8 |
|---------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Sex     | F         | M         | F         | F         | F         | M         | F         |
| Age mother/father | 20/21 | 24/30 | 38/36 | 35/31 | n.d | n.d | 22/25 | 38/37 |
| Weeks of gestation | 37 | 42 | 40 | 37 | 40 | 39 weeks and 4 days | 41 or 42 | 36 |
| Birth weight (g) | 2,240 (-1.7 SD) | 4,000 (+0.8 SD) | 3,350 (-0.3 SD) | 2,550 (-1 SD) | 2,700 (-1.8 SD) | 2,702 (-1.3 SD) | Over 3,600 | 1,800 (-2 SD) |
| Birth length (cm) | 45 (-1.9 SD) | n.d | 50 (-0.8 SD) | 43.5 (-2.5 SD) | 48 (-1.7 SD) | 47.5 (-1.2 SD) | 57 (+3.66 SD) | 42 (-2 SD) |
| Birth OFC (cm) | 32 (-1.4 SD) | 36 (+0.1 SD) | 34 (-0.7 SD) | 31.5 (-1.7 SD) | 33 (-1.5 SD) | 33.5 (0 SD) | n.d | n.d |
| Age | 6 years | 3 years 6 months | 8 years 6 months | 8 years | 20 years | 8 years | 40 years | 10 years |
| Height (cm) | 111 (-1.2 SD) | 97 (-1 SD) | 116 (-2.7 SD) | 102.5 (-4.5 SD) | 131 | 124.8 (-0.7 SD) | 170.9 | 110 (-2 SD) |
| Weight (Kg)/BMI (kg/m2) | 20 (-0.6 SD)/16.2 | 16.1 (+0.3 SD)/17.1 | 20 (-2 SD)/14.9 | 15.4 (-2.9 SD)/14.7 | 73.5/32 | 24.35 (-0.8 SD)/15.6 | 99/33.9 | 17 (-1.5 DS)/14 |
| OFC (cm) | 48.5 (-1.6 SD) | 49 (-1.2 SD) | 48.7 (-2.1 SD) | 46 (-3.9 SD) | 53 (-1.4 SD) | 51.6 (+0.5 SD) | 59.7 (+3.45 SD) | 46 (-2 SD) |
| Developmental delay/ID | Severe | Moderate | Severe | Severe | Moderate | Moderate/severe | Moderate | Moderate |
| Sits independently (Months) | 12 | n.d | Between 24 and 36 | 24 | 9 | 7 | n.d | 7 |
| Walks independently (Months) | 27 | 17 | 60 | 90 | 24 | 24 | 13 | 30 |
| First Words (Months) | No words | n.d | No words | No words | 18-20 | 46 | n.d | 24 |
| Seizures | + | - | + | + | + | ++ | + | + |
| Autistic behavior | + | + | - | + | + | + | + | - |
| Temper tantrums | n.d | + | - | + | + | n.d | + | - |
| Sleep disturbances | + | n.d | - | n.d | + | n.d | n.d | - |
| Low sensitivity to pain | + | n.d | - | n.d | n.d | n.d | n.d | - |
| Autoaggressiveness | + | + | - | n.d | + | n.d | + | - |
| Restlessness | + | + | - | n.d | + | n.d | n.d | + |
| Poor facial expression | + | + | - | + | - | + | - | + |
| Blepharophimosis | + | + | - | + | - | - | + | + |
| Telecanthus | + | + | - | + | - | + | - | + |
| Ptosis | - | - | + | - | - | + | - | + |
| Epicanthus | + | + | - | n.d | - | - | + | - |
In conclusion patients with a submicroscopic deletion of 8q22.2q22.3 are characterized by a facial phenotype with blepharophimosis, telecanthus, epicantus, flat malar region, thin upper lip vermilion, and down-turned corners of the mouth. Other clinical manifestations associated with 8q22.2q22.3 deletion syndrome can be a moderate to severe developmental delay, language development delay, absent speech, deafness, microcephaly, seizures, short postnatal stature, and congenital diaphragmatic hernias, especially when FPM2 (Zinc Finger Protein, FOG Family Member 2) is involved [4]. Until the present report, there is not a clear correlation between the size of the deletion and developmental delay, short stature, microcephaly, or seizures (Table 2).

| Table 1: Continued. |
|---------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                     | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** | **Patient 5** | **Patient 6** | **Patient 7** | **Patient 8** |
| **Eyebrows**        | Sparse, broad | Rather sparse | Rather sparse | Bushy/ Mild Synofris | Mild Synofris | Sparse and wide | Sparse | Sparse |
| **Flat nasal tip**  | +             | +             | +             | +              | -             | Slightly      | -              | +              |
| **Down-turned corners of the mouth** | +       | +            | +             | +              | +             | -              | +              | +              |
| **Ears**            | Small ear     | Poor modeled ears | Poor modeled ears | Low set posteriorly rotated | Small ears | n.d             | Overfolded and asymmetrical in length | Low set posteriorly rotated |
| **Hands/Feet**      | n.d           | Short thumbs and toes | Short hands with proximal implanted thumbs, mild cutaneous syndactyly bilateral proximal radio-ulnar synostosis | Single crease, bilateral clinodactyly of the 2nd and 5th fingers | Small hands with tapering fingers, II–III cutaneous syndactyly of feet | n.d           | n.d           | Short hands and feet, short thumbs, bilateral fifth finger clinodactyly |
| **Congenital malformations** | -          | Large hiatal hernia, pylorus stenosis glandular hypospadias | n.d           | Diaphragmatic hernia | -             | -             | Congenital heart disease, Hypoplastic auditory canals | -             |
| **Minimal deletion size (Mb)** | 5.26   | 6.10          | 5.26          | 6.44           | 1.92          | 1.36          | 3.35          | 5.23          |

+ denotes feature present; - denotes feature absent; n.d. denotes not documented.

ID: intellectual disability.

In conclusion patients with a submicroscopic deletion of 8q22.2q22.3 are characterized by a facial phenotype with blepharophimosis, telecanthus, epicantus, flat malar region, thin upper lip vermilion, and down-turned corners of the mouth. Other clinical manifestations associated with 8q22.2q22.3 deletion syndrome can be a moderate to severe developmental delay, language development delay, absent speech, deafness, microcephaly, seizures, short postnatal stature, and congenital diaphragmatic hernias, especially when FPM2 (Zinc Finger Protein, FOG Family Member 2) is involved [4]. Until the present report, there is not a clear correlation between the size of the deletion and developmental delay, short stature, microcephaly, or seizures (Table 2).
the deleted region are implied in seizures and epilepsy. For instance, KCNS2 (potassium voltage-gated channel, modifier subfamily S, and member 2) encodes a neuronal modulatory alpha subunit Kv9.2, associated with the transmission across chemical synapse, with the Dopamine-DARPP32 Feedback into the CAMP pathway, the regulation of the resting membrane potential, and the control of the shape and frequency of action potentials [8]. Kv9.2 is highly expressed in the brain (olfactory bulb, cerebral cortex, the hippocampus, and the cerebellum) retina and spinal cord [8]. We could only hypothesize that epilepsy is somehow related to the absence of KCNS2 expression although it is not an entirely satisfactory explanation given the lack of retinal or cerebellar disease in the reported cases.

Our patient shares the majority of the clinical features described in the preceding report, including congenital hearing loss described in only one patient previously by Sinajon et al. [6] (Table 1). Interestingly, the GRHL2 gen (Grainyhead-like 2) at 8q22.3 [9] is associated with an autosomal dominant form of progressive non syndromic sensorineural hearing loss with a highly variable age of onset and progression. Homozygous GRHL2B mutant zebrafish embryos have enlarged otocysts, thinner otic epithelium, and smaller or eliminated otoliths [9].

Apparently, there is no relationship between this gene and epilepsy. However, loss of GRHL2 in zebrafish induces neural apoptosis and extinction of midbrain – hindbrain boundary (MHB) markers [10]. The VPS13B or COH1 gene (vacuolar protein sorting 13 homolog B (yeast)) is also located in the deleted region, Cohen syndrome is caused by mutations in the VPS13B gene [11], and it has an important role in eye, hematological, and nervous central system development. Despite the clinical variability of Cohen syndrome, our patient does not present phenotypic signs of Cohen syndrome, as truncal obesity, chorioretinal dystrophy, myopia, neutropenia, or classical facial dysmorphism. In only one of the previously reported cases, Cohen syndrome was suspected. However, VPS13B was not involved in that patient’s deletion.

**Data Availability**

No data were used to support this study.

**Consent**

Informed consent was obtained from parents on behalf of the patient before writing this case report. The consent is filed in the patient’s electronic medical record.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**References**

[1] B. A. Pletcher, H. V. Toriello, S. J. Noblin et al., “Indications for genetic referral: A guide for healthcare providers,” *Genetics in Medicine*, vol. 9, no. 6, pp. 385–389, 2007.

[2] A. Medina, L. Piñeros, C. Arteaga et al., “Multiplex ligation-dependent probe amplification to subtelomeric rearrangements in idiopathic intellectual disability in Colombia,” *Pediatric Neurology*, vol. 50, no. 3, pp. 250–254, 2014.

[3] L. Cabarcas, E. Espinosa, and H. Velasco, “Etiology of mental retardation in children: Experience in two third level centers,” *Biomedica*, vol. 33, no. 3, pp. 402–410, 2013.

[4] A. Kuechler, K. Buyssse, J. Clayton-Smith et al., “Five patients with novel overlapping interstitial deletions in 8q22.2-q22.3,” *American Journal of Medical Genetics Part A*, vol. 155, no. 8, pp. 1857–1864, 2011.

[5] Y. Kuroda, I. Ohashi, T. Saito et al., “Refinement of the deletion in 8q22.2-q22.3: The minimum deletion size at 8q22.3 related to intellectual disability and epilepsy,” *American Journal of Medical Genetics Part A*, vol. 164, no. 8, pp. 2104–2108, 2014.

[6] P. Sinajon, T. Gofine, J. Ingram, and J. So, “Microdeletion 8q22.2-q22.3 in a 40-year-old male,” *European Journal of Medical Genetics*, vol. 58, no. 11, pp. 569–572, 2015.

[7] T. F. W. McMullan, J. A. Crolla, S. G. Gregory et al., “A candidate gene for congenital bilateral isolated ptosis identified by molecular analysis of a de novo balanced translocation,” *Human Genetics*, vol. 110, no. 3, pp. 244–250, 2002.

[8] M. Salinas, F. Duprat, C. Heurteaux, J.-P. Hugnot, and M. Lazdunski, “New modulatory α subunits for mammalian Shab K+ channels,” *The Journal of Biological Chemistry*, vol. 272, no. 39, pp. 24371–24379, 1997.

[9] B. Vona, I. Nanda, C. Neuner, T. Müller, and T. Haaf, “Confirmation of GRHL2 as the gene for the DFNA28 locus,” *American Journal of Medical Genetics Part A*, vol. 161, no. 8, pp. 2060–2065, 2013.
[10] S. Dworkin, C. Darido, S. R. Georgy et al., “Midbrain-hindbrain boundary patterning and morphogenesis are regulated by diverse grainy head-like 2-dependent pathways,” *Development*, vol. 139, no. 3, pp. 525–536, 2012.

[11] S. Douzgou and M. B. Petersen, “Clinical variability of genetic isolates of Cohen syndrome,” *Clinical Genetics*, vol. 79, no. 6, pp. 501–506, 2011.