6q21q22.2 Deletion Syndrome with Ataxia and Congenital Ocular Motor Apraxia (Cogan´s Syndrome)

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Abstract: Congenital oculomotor apraxia, also known as Cogan´s syndrome [Cogan-type congenital ocular motor apraxia (COMA, OMIM 257550)], is a rare hereditary disease that affects the eye insofar as it cannot make horizontal movements voluntary. Of unknown etiology, it was described by Cogan in 1952 and, classically considered as a sporadic disease with autosomal dominant inheritance in some cases, and as an indicator of partial metabolic alterations or defects of neurological development in others. We present a newborn with 6q21q22.1 microdeletion, result of gestation after *in vitro* fertilization, which clinically manifests movement disorders including ataxia and characteristic clinical picture of Cogan´s syndrome (oculomotor apraxia); highlighting microcephaly and peculiar phenotype characterized by small eyes, sparse hair, broad nasal root with epicanthus and hypoplasia of nasal wings. Cerebral ultrasound showed Cysts of the Subependymal**.** Germinal Matrix.

The 6q deletions are infrequent, with around 100 cases described, associated with variable phenotypes, including dysmorphic features, growth retardation, upper limb malformations, and Prader-Willi (PW)-like features; and few of them studied with high resolution cytogenetic techniques. Recently, in the study of three patients (one with ataxia and two with movement disorders), the 6q22.1 region has been proposed as critical (including the MARCKS, HDAC2, and HS3ST5 genes), a region that is also affected in our patient, and correlated with the ataxia phenotype, as the most outstanding data. So, from these results, the genetic heterogeneity of Cogan syndrome is inferred. In this article we also review the bibliography related to oculomotor apraxia associated with other movement disorders such as ataxia.

Keywords: Ataxia, Array-CGH, Copy-number, candidate genes, Congenital ocular motor apraxia, Cogan´s syndrome, Cysts Subependymal Germinal Matrix, Germinal cysts, Deletion 6q21q22.2, Deletion 6q21, Deletion 6q22 MARCKS gen, HDAC2 gen, HS3ST5 gen, Newborn, Oculomotor apraxia, Subependymal cysts, Subependymal pseudocysts.

1. INTRODUCTION

Congenital oculomotor apraxia (OMIM 257550), first reported by Cogan in 1.952 [1] is characterized by (1) defective or absent horizontal voluntary eye movements, and (2) defective or absent horizontal ocular attraction movements; so they must turn their heads to see the sides, next to blink at the beginning of said movements. In some cases it has been associated with different malformations of the CNS, such as agenesis of corpus callosum, porencephalic cysts, trunk tumors, etc. and other disorders with CNS involvement such as neurofibromatosis type I and juvenile form of Gaucher disease. Cogan in 1972 [2] suggest that dominant inheritance cannot be rejected out of hand. However, the etiology of this syndrome is still not well clarified at present, although it has been reported as associated with chromosomal abnormalities (deletion on one 2q13 chromosome and a point mutation of the NPHP1 gene [3], duplication 5p1.3 [4]). We present a newborn with the characteristic clinical picture associated with Cogan's syndrome, ataxia and a 6q21q22.1 microdeletion.

The 6q interstitial deletions are infrequent, with about 100 cases described and very variable phenotype; and few of them are studied with high-resolution cytogenetic techniques (microarray-based comparative genomic hybridization). Classically, three phenotypes have been differentiated: proximal (6q11 to q16), intermediate (6q15 to q25), and terminal (6q25 to qter) deletions [5]. The only universal finding among all patients was intellectual disability. Other common findings included ear abnormalities (90%), hypotonia (82%), postnatal growth retardation (68%), and ocular functional alterations. Nevertheless, phenotype-refined genotype correlations were impossible due to the relatively low resolution of chromosomal band techniques.

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Recent developments of cytogenetic molecular methods improve fine genotype-phenotype correlations. Rosenfeld JA, *et al*. [6], in a study of genotype-phenotype correlation in 12 patients with 6q interstitial deletions, described three patients with movement disorders (one with ataxia) and proposed the 6q22.1q22.2 region of 4.1-Mb, as a critical region for the disorders, including as genes candidate MARCKS, HDAC2, and HS3ST5, region also affected in our patient and correlated with the phenotype of ataxia and nystagmus, as the most outstanding data. This region and the genes mentioned above (especially MARCKS and HDAC2) were also affected in our patient with ataxia and the oculomotor apraxia phenotype, making it compatible with the 6q22.1q22.2 critical region for movement disorders. In conclusion, it is a new case of COMA with a chromosomal disorder that is not described in the literature, and therefore we think that it can be added to the list of anomalies associated with this entity.

2. CLINICAL REPORT

The patient is the second daughter of healthy, non-consanguineous parents, and the result of pregnancy through assisted reproductive technology (IVF). The pregnancy was uneventful, negative for the TORCH screen, and resulted in an uncomplicated delivery at 40 weeks gestation. The Apgar score was 9/10. The propositus had a birth weight of 3.060 g, length of 51cm, and occipital-frontal circumference (OFC) of 32 cm (<3rd centile). After home discharge from the hospital she presents hypoactivity and choking crisis, which is the why we enter objective pathological neurological examination (hypoactivity with overall decrease in general movements). She presented microcephaly and facial dysmorphism characterized by small eyes, sparse hair, broad nasal root with epicanthus and hypoplasia of nasal wings.

Complete blood count (CBC), coagulation, biochemical liver and kidney function, muscle enzymes, serum bone profile (Ca/P/F alkaline) and thyroid hormones were all normal. The neurometabolic study of inborn errors of metabolism was also normal [including amino acids and organic acids, alterations of fatty acids of beta-oxidation, biotinidase test, SAICAR test, Congenital Disorders of Glycosylation (CDG) and long chain fatty acids]. Abdominal Ultrasound was normal. Cerebral ultrasound showed, at the level of both caudothalamicsulcuses, cystic sonographic appearance images compatible with germinal cysts of subependymal germinal matrix and discrete enlargement in both lateral ventricles, mainly in the frontal horns. There was nodisplacement of the midline or mass effect. The visualized portion of cerebral parenchyma and posterior fossa had no significant sonographic finding (see Figure **1**). Cerebral-Spinal MRI showed symmetrical lateral ventricles with bilateral

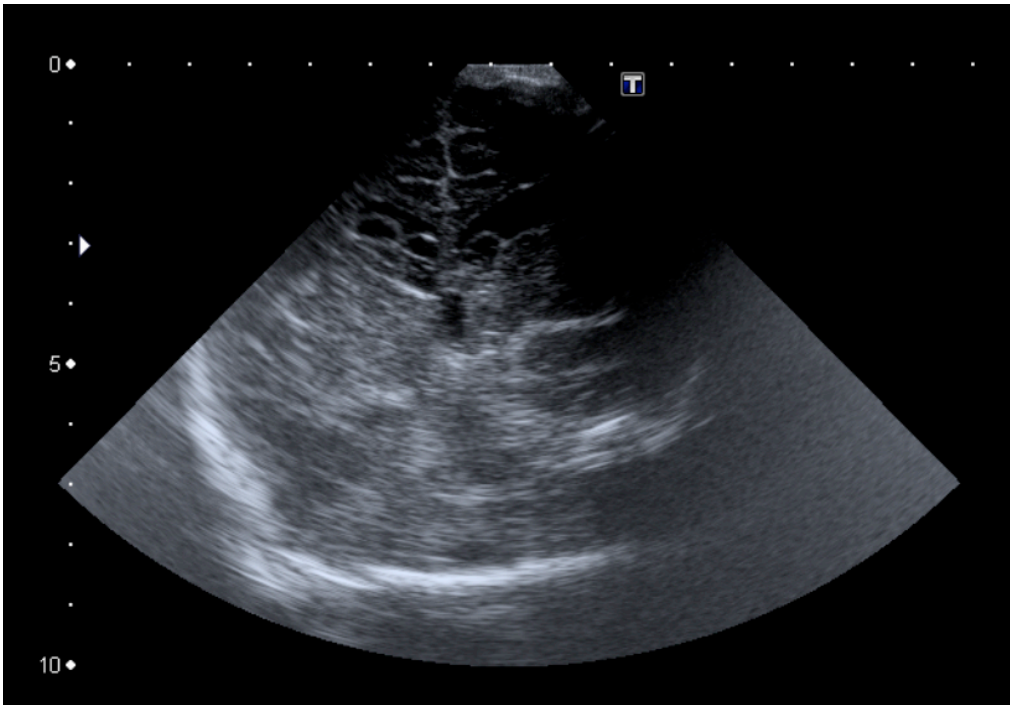

Figure 1: Cerebral ultrasound showed, at the level of both caudothalamicsulcuses, cystic sonographic appearance images compatible with germinal cysts of subependymal germinal and discrete enlargement in both lateral ventricles, mainly in the frontal horns.

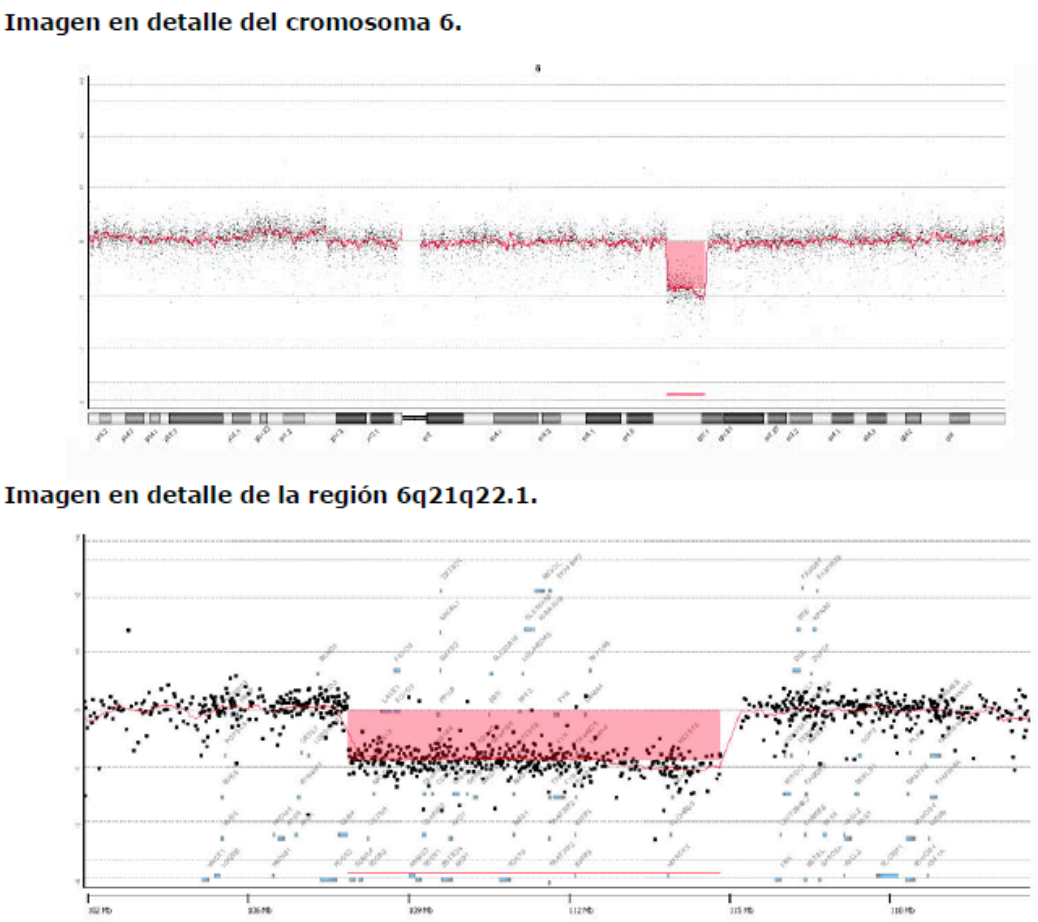

Figure 2: Arraycgh revealing an interstitial deletion, of approximately 7.21 Mb (genome coordinates chr6:108,002,702-115,212,782) in the chromosome 6 region 6q22.1q22.2.

subependymal cysts as isolated finding (two well defined lesions of rounded morphology are visualized in close contact with both frontal horns of the lateral ventricles; they have an approximate size of 8 mm on the right side and 10 mm on the left side, presenting a signal intensity similar to the CSF in all the sequences) and slightly delayed myelination, without other pathological findings and with normal cerebellum. Other features such as neurophysiological studies, including electroencephalography, auditory and visual evoked potentials were normal.

2.1. Evolution

Global delay of the development of psychic predominance with evolution to progressive microcephaly; and hypotonia that causes delayed motor milestones in the first months of life, achieving stable sitting at 13 months and since then truncal ataxia associated with it. Abnormal ocular movements, initially nystagmus, that evolve to oculomotor apraxia and tendency to strabismus of the left eye. Along with the motor delay, mild intellectual disability is also observed. Evolution of cerebral ultrasound: at 25 months the presence of subependymal cystic images described in previous reports is no longer observed in relation to their resolution. In our case, the neuroradiological presence of large bilateral QS, and its unfavorable evolutionary clinical course, forced the expansion of studies using Array-CCG, detecting a 6q21q22.1 micro deletion.

3. METHODS: CYTOGENETIC AND MOLECULAR ANALYSIS

Karyotyping was performed on metaphase spreads prepared from peripheral blood lymphocytes by conventional methods. Chromosome analysis showed a normal female karyotype: 46,XX.

We performed a 400k aCGH revealing an interstitial deletion (Figure **2**), of approximately 7.21 Mb (genome coordinates chr6:108,002,702-115,212,782) in the chromosome 6 region6q21q22.2 (AMAD 14693, Agilent Technologies, Santa Clara, CA,USA, according to the manufacturer's specifications). Commercial reference

female DNA was used as a control (Promega Biotech, Madison WI). Bioinformatic analysis was performed using the statistical ADM-2 (0.5 Mb window, A = 6) as a parameter for detecting the number of copies of DNA present for the different probes. Additionally, we established a threshold of five consecutive probes to accept an altered region as valid, estimating an average resolution of approximately 40 kb. The deleted region includes 27 OMIM genes, which are shown in Table **1**.

4. DISCUSSION

4.1. Interstitial 6Q22.1–Q22.2 Deletions

Genomic studies have demonstratedthat the human genome contains many regions which can contain copy number variations (CNVs) [7-9]. These CNVs represent around 12% of the whole genome, and around 14.5% of the genes contained in CNVs develop genetic diseases. With this concept, it can be easily deduced that CNV analysis must be a crucial part of genetic health research, including complex hereditary diseases and sporadic dysmorfic features [9]. With this idea, the concept “reverse genomics” arises, it means that, after CNV genome studies (using genomic tools such as array-CGH), patients can be grouped due to recurrent CNVs, which make it easier to correlate genotype to a specific syndrome, describing evolution, features and/or treatment, including prenatal counselling, in previously non characterized phenotypes.

By using array CGH for genome-wide screening analysis we have detected an interstitial deletion of

Table 1: The Deleted Region Includes 27 OMIM Genes

Genomic Coordinates		Gene	Description	OMIM
108188960	108279393	SEC63	sec63,s.cerevisiae, homolog of	608648
108041408	108074736	OSTM1	Osteopetrosis-associated transmembrane protein 1	607649
108166057	108188808	NR2E1	Nuclear receptor subfamily 2, group e, member 1	603849
108211216	108261259	SNX3	Sorting nexin 3	605930
108559822	108684768	FOXO 3	Forkhead box o3a	602681
108986436	109094504	SESN1	Sestrin 1	606103
109366513	109382558	CD164	cd164 antigen	603356
109761931	109765122	SMPD2	Sphingomyelin phosphodiesterase 2,neutral membrane	603498
109444061	109465967	MICAL1	Microtubule-associated monooxygenase, calponin and lim domains-containing1	607129
109691215	109825430	Figure 4	Figure 4 s.cerevisiae, homolog of; phosphoinositide 5-phosphatase	609390
109978255	109980719	GPR6	g protein-coupled receptor 6	600553
110099816	110198873	WASF1	was protein family, member 1	605035
110180420	110232219	CDC40	Cell division cycle 40	605585
110392179	110415549	DDO	d-aspartate oxidase	124450
110424586	110476640	SLC22A16	Solute carrier family 22 (carnitine transporter 2)	608276
110814620	110895712	AMD1	Adenosylmethionine decarboxylase 1	180980
110958559	110967887	GTF3C6	General transcription factor iiic subunit 6	611784
111087502	111227124	SLC16A10	Solute carrier family 16 member 10	607550
111299030	111483714	REV3L	Rev3 like, dna directed polymerase zeta catalytic subunit	602776
111555377	111606873	TRAF3IP2	Traf3 interacting protein 2	607043
111660331	111873451	FYN	Fyn proto-oncogene, src family tyrosine kinase	137025
112052812	112069685	WISP3	wnt1 inducible signaling pathway protein 3	603400
112070656	112087547	TUBE1	Tubulin epsilon 1	607345
112107930	**112254721**	LAMA4	Laminin subunit alpha 4	600133
113857334	**113863474**	MARCKS	Myristoylated alanine rich protein kinase c substrate	177061
113936155	**113971194**	HDAC2	Histone deacetylase 2	605164
114055585	**114342387**	HS3ST5	Heparan sulfate-glucosamine 3-sulfotransferase 5	609407

7.21 Mb in the chromosome band 6q21q22.2 in a patient with dysmorphic features, developmental delay including mild intellectual disability, ataxia and eye movement abnormalities (oculomotor apraxia).

In humans, interstitial deletions of 6q are associated with variable phenotypes including intellectual disability, hypotonia, growth retardation, cardiac anomalies, and variable facial dysmorphic characteristics, so as Prader-Willi-like features. Some genotype–phenotype correlations have been suggested for interstitial 6q deletions. Hopkin et al. [5] proposed phenotypic groups according to the location of the deletion:

- Proximal deletions (6q11–6q15) are commonly associated with hernias, upslanting palpebral fissures, and thin lips;
- Medial/intermediate deletions (6q15 to 6q25) are commonly associated with intrauterine growth retardation, abnormal respiration, hypertelorism, and the 6q21 region has been associated with split-hand defects [10]; and alsodeletion of SIM1 at 6q16.3 has been proposed as the cause of a Prader-Willi-like phenotype;
- and terminal deletions (6q25–6qter) are commonly associated with cleft palate, retinal abnormalities, and genital hypoplasia.

Recently, there has been an increase in the detection of interstitial deletions affecting the intermediate (6q15 to q25) region, but only a minority of cases in the literature has been diagnosed by molecular cytogenetic techniques; to date, the interstitial deletion of 6q21-22 has been previously reported in 12 individuals [6, 11-14]. The deletion detected in our patient was compared with the previously reported cases:

- Common clinical features of 6q21–22 deletion include, in most patients, a variablefacial dysmorphism: ear abnormalities, hyper- or hypotelorism, long philtrum or wide nasal bridge, micro/retrognatia, a thin upper lip, a high-arched palate, a small mouth.
- Neurological disorders: intellectual disability (90-100%), alterations of cerebral morphogenesisas microcephaly (detected in 67% of these patients) and dysplasia of the corpus callosum (50%) and cerebellum (33%); and movement disorder/ ataxia (25-40%).
- The eye abnormalities include more frequently strabismus (40%) and nystagmus (10%); and to a lesser extent, oculomotor apraxia in the subject 6 reported by Rosenfeld JA [6] and our current patient (which totals a 15%).
- Cardiac abnormalities were also detected in 5 of these 12 patients, including ventricular septal defect (VSD), pulmonary atresia, coarctation of aorta (CoA), double outlet right ventricle and patent ductus arteriosus.

In the DECIPHER database (see Figure **3**), no deletion is the same as our case, but case 250580 (with chr6: 110606987-117050937, and of 6.44 Mb including 60 genes) presented DI, ataxia, seizures, nystagmus, loss of pain sensation and facial dysmorphisms such as microcephaly, hypertelorism, prominent ears, arched eyebrows and bulbous tip of the nose as well as arachnodactyly. If we delimit the coordinates of this patient with ours (https://decipher.sanger.ac.uk/browser#q/6:110606987-115212782/location/6:110481987-115337782), only 19 genes are included, among which we find the three candidate genes proposed by Rosenfeld [6], although none of the three figures is the origin of pathology in humans, the haploinsufficiency of two of them in experimental animals leds to alterations in the development of the CNS:

- MARCKS: (* 177061, Myristoylated Alanine-rich Protein Kinase C Substrate) it plays a vital role in the normal processes of neurulation development, hemisphere fusion, formation of the forebrain commissure and formation of cortical and retinal laminations [15].
- HDAC2 (* 605164, Histone Deacetylase 2) in mammals is a zinc-mediated transcription factor that acts as a positive and negative regulator of transcription. HDAC2 associates and reduces histone acetylation of important genes for learning and memory. Montgomery et al. (2009) [16], developed a mice with a deletion of Hdac1 and Hdac2 directed to the central nervous system. The deletion of both Hdac1 and Hdac2 led to greater abnormalities of cortical, hippocampal and cerebellar development, whereas the suppression of any of them individually had no apparent effect on neuronal development.

4.2. Cogan's Syndrome

Cogan-type congenital ocular motor apraxia (COMA, OMIM 257550). Ocular motor apraxia (OMA) is the absence or defect in the control of intentional voluntary eye movement. Children with this condition have difficulty in moving their eyes horizontally and, therefore, saccadic movements (normal, rapid and

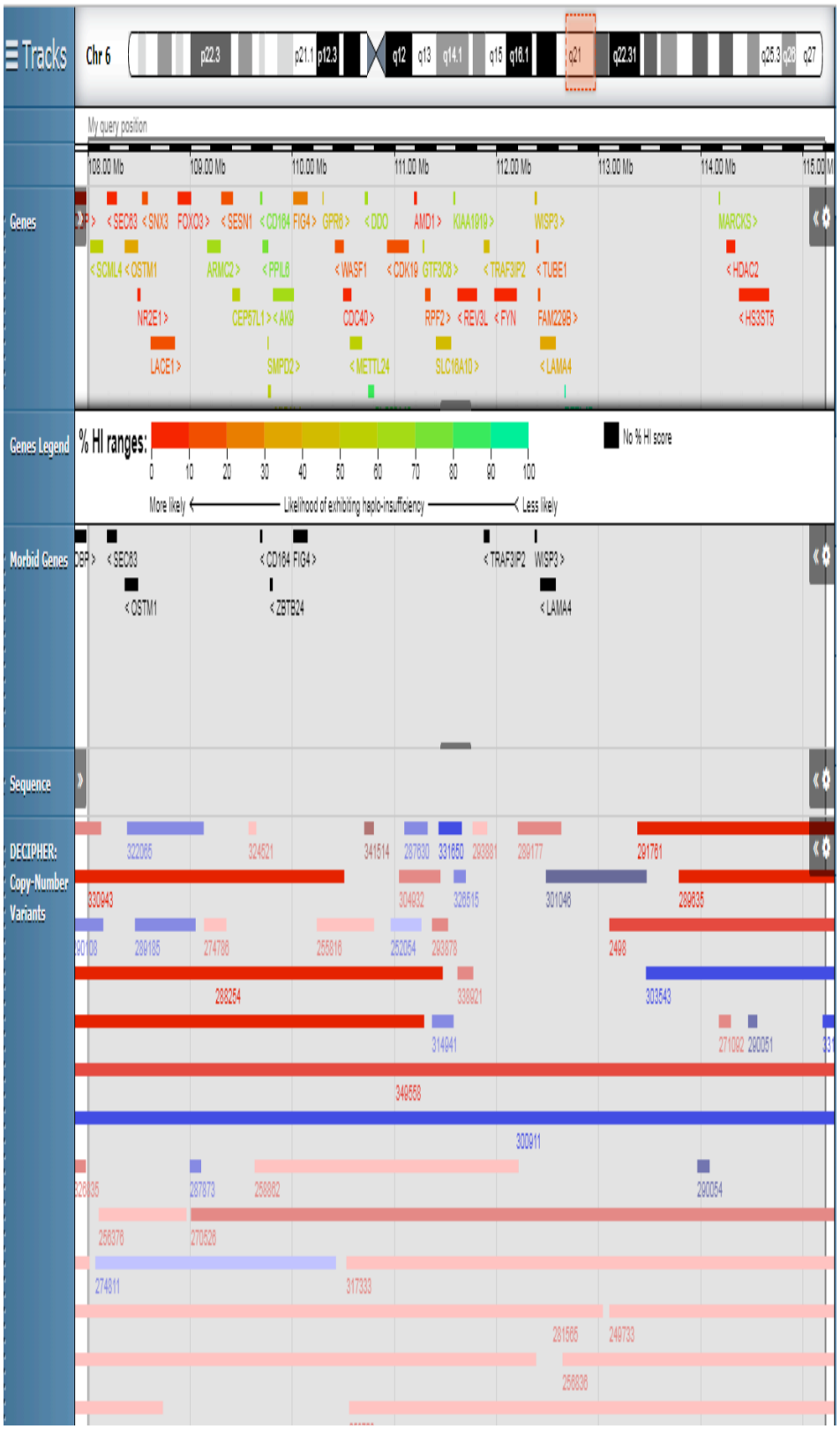

Figure 3: Decipher database: there were no deletions equal to our case, https://decipher.sanger.ac.uk/browser#q/6:108002702-115212782/location/6:107877702-115337782.

simultaneous movement of both eyes in the same direction) are abnormal. Because of this, most patients with AOM have to turn their heads to follow objects looking sideways. They should use a push of the head to compensate for this inability to initiate horizontal eye movements away from the forward looking position. Usually, the vertical movements of the eye are not affected. The source of Cogan´s syndrome is in the brain. The procedure of initiating eye movements is a complex neural pathway that involves many different structures. Neuro imaging with magnetic resonance imaging (MRI) is commonly conducted when OMA is evaluated. The findings may be normal or may reveal poor development of specific regions of the brain, particularly the corpus callosum, the cerebellum and / or the fourth ventricle (vermis hypoplasia, Joubert syndrome, Dandy-Walker malformation, vermis astrocytoma, vermis cyst), but other malformations have been described as microcephaly, hydrocephalus, porencephalic cyst, and megalocephaly.

Sometimes OMA is considered secondary and it is attributed to insults occurring either during the perinatal period or the first 6 months of life. The clinical associations may include perinatal hypoxia, periventricular leukomalacia, cerebral palsy, meningitis, septicemia, herpes encephalitis, and seizures.

Oculomotor apraxia occurs in ataxia-telangiectasia [17], and also has been observed in the neuronopathic form of Gaucher disease (type III; OMIM 231000) [18, 19]. But other hereditary diseases with CNS involvement can exist with OMA (Krabbe'sleuco-dystrophy, Pelizaeus Merzbacher disease, GM1 gangliosidosis, Infantile Refsum's disease, propionic academia, Bardet-Biedl syndrome, carotid fibro muscular hypoplasia, Cornelia de Lange syndrome, and microphthalmos).

In addition, congenital ocular motor apraxia (COMA) has also been described associated with chromosomal abnormalities. Betz et al. [20] identified 2 patients with Cogan-type and associated nephronophthisis-1 (NPHP1; 256100). One patient had a deletion on each chromosome 2q13, and the other patient had a deletion on one 2q13 chromosome and a point mutation of the NPHP1 gene in the other. The authors suggested that COMA may be a defect in a contiguous gene with NPHP1 and that it may be an autosomal dominant condition. We have also seen it associated with a patient with duplication 5p1.3 [4]. The 6q22.1q22.2 chromosomal disorder has been associated with different ocular abnormalities such as strabismus, nystagmus and bilateral colobomas, but its association to Cogan´s syndrome has also been referred to another patient (subject 6 of Rosenfeld [6]), and therefore we think that it can be added to the list of anomalies associated with this entity.

5. ATAXIA-OCULOMOTOR APRAXIA (AOA)

5.1. The ADULT ONSET of Ataxia-Oculomotor Apraxia

(AOA) is well known. In a classical way, two syndromes have been described; they are two processes that share some characteristics but that differ in the moment of their presentation, in some clinical manifestations, in their evolution, and in the affected genes. Both are characterized by the development of progressive mobility problems. The main manifestation is the difficulty of motor coordination (cerebellar ataxia), which is usually the first symptom. Approximately half of the cases suffer from difficulty in ocular lateral movement (oculomotor apraxia). The two types of ataxia with oculomotor apraxia have in common, in addition to ataxia and oculomotor apraxia, involuntary movements (choreoathetosis), spontaneous muscle contractions (myoclonus) and neurological alterations (neuropathy). The ataxia-oculomotor apraxia type 1 usually has an earlier onset of symptoms (around 7 years), whereas type 2 usually has a later onset (around 15 years). Choreoathetosis and myoclonus usually disappear gradually in type 1, while they persist in type 2. Neuropathy is more evident in type 1, affecting mobility, accompanied by muscular and neurological degeneration (atrophies), and occasionally develops deformities in extremities, which causes functional disability, while individuals affected by type 2 tend to fend for themselves for longer. Intelligence is not usually affected in either type, but some patients have difficulty in concentrating or coordinating the development of various activities. Those affected with type 1 have hypoalbuminemia, and increased serum cholesterol so they may have heart problems. In contrast, those affected by type 2 have normal concentrations of albumin and cholesterol, but they have high concentrations of serum alpha-fetoprotein.

From the genetic point of view, both types follow an autosomal recessive pattern, which implies that both parents have an altered copy of the gene in each cell, without showing signs or symptoms of affectation.

5.1.1. Ataxia-Oculomotor Apraxia 1

(AOA1, OMIM 208920): ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia EAOH), also named as cerebellar ataxia, early-onset, with hypoalbuminemia (EAOH), it is caused by homozygous or compound heterozygous mutation in the gene encoding aprataxin (APTX; OMIM 606350) on chromosome 9p21 [21]. This gene encodes the protein "aprataxin", present in various tissues (brain, spinal cord, muscles...), and its function is to repair the damage suffered by DNA. At least 18 mutations that introduce changes in the sequence of the protein have been described, with the result that it loses its functionality.

5.1.2. Ataxia-Oculomotor Apraxia 2

(AOA2. OMIM 606002) or autosomal recessive spinocerebellar ataxia-1 (SCAR1) is caused by homozygous or compound heterozygous mutation in the SETX gene (*608465). This gene is found on the long arm of chromosome 9 (9q34.13), and encodes the "Senataxin" protein, also present in several tissues. This protein also participates in the repair of DNA, as part of proteins called "helicases" that bind to DNA, unwinding the two spiral chains, to allow other proteins to attach to the unrolled chains [22,23].

However, it is possible that with the new molecular genetic techniques, the list of genes involved in diseases with a different phenotype but in which ataxia and OMA are included will be expanded. So, recently it has been shown that the biallelic mutations in the human XRCC1 gene are associated with ocular motor apraxia, axonal neuropathy, and progressive cerebellar ataxia [24]. Other rare pathologies include mitochondrial diseases such as SANDO (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; OMIM 607459), it is an autosomal recessive disease with mitochondrial DNA deletions, caused by homozygous or compound heterozygous mutation in the nuclear-encoded DNA polymerase-gamma gene (POLG) [25].

5.2. Congenital Forms of Ataxia-Oculomotor Apraxia

Congenital forms of ataxia-oculomotor apraxia have been related to other diseases that occur with ataxia, among which we highlight:

5.2.1. Ataxia-Telangiectasia

(AT, OMIM 208900) is caused by homozygous or compound heterozygous mutation in the ATM gene on chromosome 11q22. It is presented in early childhood, and classically, AT is associated with cerebellar ataxia, oculo-cutaneoustelangiectasia and oculo-motor apraxia as well as immune defects, and a predisposition to malignancy. Telangiectases typically develop between 3 and 5 years of age. The earlier ataxia can be misdiagnosed as ataxia cerebral palsy before the appearance of oculocutaneoustel-angiectases. A characteristic oculomotor apraxia, i.e., difficulty in the initiation of voluntary eye movements, frequently precedes the development of telangiectases [26].

5.2.2. Joubert Syndrome

(JBTS) is a clinically and genetically heterogeneous group of disorders characterized by hypoplasia of the cerebellar vermis with the characteristic neuroradiologic 'molar tooth sign,' and accompanying neurologic symptoms, including dysregulation of breathing pattern, developmental delay, hypotonia, ataxia and oculomotor apraxia. Other variable features include retinal dystrophy and renal anomalies. Joubert syndrome is believed to be a representative of a new group of disorders named ciliopathies. JBTS-1 is caused by homozygous mutation in the INPP5E gene on chromosome 9q34, but with a great genetic heterogeneity in which has got involved up to thirty-three causal genes. (NPHP1, AHI1, CEP290, RPGRIP1L, TMEM67/MKS3, ARL13B, CC2D2A…) [27].

5.2.3. Methylglutaconic Aciduria Type V

(MGCA, OMIM 5610198), also called dilated cardiomyopathy with ataxia syndrome (DCMA), is a rare mitochondrial condition caused by homozygous mutation in the DNAJC19 gene (608977) on chromosome 3q26. Associated with early-onset dilated cardiomyopathy (sometimes accompanied by long QT syndrome), prenatal or postnatal growth failure, and non-progressive cerebellar ataxia causing significant motor delays; in which they have also referred disorders of ocular motility [28].

5.2.4. Poretti-Boltshauser Syndrome

(PTBHS, OMIM 615960) is caused by homozygous or compound heterozygous mutation in the LAMA1 gene (150320) on chromosome 18p11; it is characterized by cerebellar dysplasia, cerebellar vermis hypoplasia and cerebellar cysts in most patients. The most prominent clinical features included cerebellar ataxia, intellectual disability, and delayed language development, so as high myopia, variable

retinal dystrophy (with retinal atrophy, increased pigment, or macular heterotopia), and eye movement abnormalities (including strabismus, oculomotor apraxia, amblyopia, and/or nystagmus) [29, 30].

5.2.5. Birk-Landau-Perez Syndrome

(BILAPES, OMIM 617595) is caused by homozygous mutation in the SLC30A9 gene on chromosome 4p13. Perez et al. in 2017 [31] reported a large multigenerational Bedouin kindred in which 6 patients had onset of different combinations of intellectual disability, oculomotor apraxia, muscle weakness included limb and truncal ataxia, and nephropathy in early childhood.

5.2.6. 6q22.1q22 Syndrome

Although both ataxia and oculomotor apraxia have been described in patients with interstitial deletion 6q22.1q22.2, the association of ataxia and oculomotor apraxia has only presented in combination in our patient so far.

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NOTE

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