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Supernumerary Marker of Chromosome 15 Associated with Paternal Uniparental Disomy in a Case with Angelman Syndrome

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Abstract

Angelman syndrome is a rare neurogenetic disorder that usually is clinically associated with global developmental delay including absence of speech, seizures, ataxic gait and frequent smiling. Its genetic bases is complex even though normally it may be attributed to epigenetic alterations of chromosomal region 15q11.2~13. We present a girl of 7 years who was referred with delayed neurological development, speech impairment, and some minor facial anomalies, such as microcephaly and open mouth. Clinical symptoms suggested the diagnosis of Angelman syndrome. Cytogenetic results showed a karyotype 47,XX,+ mar in all 30 analyzed metaphases. Fluorescence *in situ* hybridization studies revealed origin and size of the small supernumerary marker chromosome as an inv dup(15)(q11.1) not including any euchromatin. Microsatellite analyses revealed that both chromosomes were derived exclusively from the father and thus the clinical diagnosis of Angelman syndrome was supported. Angelman syndrome caused by paternal uniparental disomy is rare, although it has been reported by other researchers, associated with supernumerary marker chromosome as well as other complex chromosomal rearrangements. It has to be always in mind also for genetic counseling that chromosomal aberrations can be a hint on epigenetic alterations. This article reviews eight previously published comparable cases of literature.

Keywords: Angelman syndrome; Small Supernumerary Marker Chromosomes (sSMC); Uniparental disomy; Genetic counselling

Abbreviations: AS: Angelman Syndrome; FISH: Fluorescence *in situ* Hybridization; PWARC: Prader Willi/Angelman Syndromes; sSMC: Supernumerary Marker Chromosome; UPD: Uniparental Disomy

Introduction

Angelman Syndrome (AS, OMIM # 105830) is a rare neurogenetic disorder that is clinically characterized by global delay of development with speech impairment, seizures, ataxic gait and unmotivated smiles. Physical abnormalities such as micro-brachycephaly, macrostomy, protruding tongue and cutaneous hypo-pigmentation are also described. The disease causing gene *UBE3A* is subject to different methylation patterns depending on their maternal or paternal origin. 70% of cases are due to deletions of this region in maternal derived chromosome 15q11.2~13, 5% of cases occur as a result of paternal uniparental disomy (UPD) and the rest is due to mutations of the imprinting center, the *UBEA* gene, and other mechanisms [1,2].

UPD may be due to chromosomal alterations – one possibility is the presence of a *de novo* small supernumerary chromosomal marker chromosome (sSMC). They occur with a frequency of 0.043 per hundred live births and approximately 0.075 per hundred prenatal diagnoses; they are also seven times more frequent in patients with intellectual disabilities than in normal population [3,4].

Approximately 50% of sSMC derive from chromosome 15 [4,5]. From the cytogenetic point of view, two fundamental types of chromosome 15 markers are distinguished: sSMC(15) without euchromatic material, which lacks especially the critical region for the Prader Willi/Angelman Syndromes (PWARC) being generally associated with a normal phenotype, and a large sSMC(15) containing euchromatin including PWARC and being usually associated with an abnormal phenotype [6,7].

The characterization of an sSMC is always a clinical and diagnostic challenge since they can be associated with complex phenotypes or lack clinical repercussion. This is dependent on the sSMC size, euchromatic content, mosaic state and its possible relation to UPD of sSMC's normal sister chromosomes. To establish all these characteristics requires molecular cytogenetic studies [8]. In the present case, a girl with neurodevelopmental delay, dysmorphism and an sSMC the diagnosis of Angelman Syndrome was established compared with cases reported in the literature.

Case Presentation

A female patient of six years of age, derived from the Neuropediatric service with a diagnosis of global neurodevelopmental delay. She is the first daughter of a 19-year-old mother and a 22-year- old father at conception. It was a gestation product without prenatal alterations and normal delivery at 39 weeks, with a birth weight of 2200 grams. During the first two years of life he attended with hypotonia, delayed psychomotor development and sleep disorders associated with aggressive behavior. The cephalic support was achieved at the age of six months, the sitting was reached at twelve months and the

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ambulation began at the age of two and a half years. At the time of genetic counseling, the girl does not emit words, presents frequent drooling, controls sphincters and fulfills very simple orders. The physical examination shows: size: 107 cm (- 3rd percentile) weight: 19 kg (10th percentile), head circumference: 45 cm (-2 SD), prognathism, open mouth, ocular squint, slightly ataxic gait. No hypo pigmentation of skin and hair. The simple skull tomography was normal along with cardiological, audio, and abdominal scanning scans. Clinically there are no signs of epilepsy although the electroencephalogram has been delayed due to the patient's poor cooperation and the risks of sedation. Thyroid hormonal profile, like muscular enzymes were normal. They were considered regarding differential diagnosis of hypotonia.

Banding cytogenetic analysis

The karyotype of the girl and her parents was carried out by culture of peripheral blood lymphocytes in RPMI-1640 medium (GIBCO – Thermo Fisher Scientific, Waltham Massachusetts, United States). Chromosome preparations were obtained using standard techniques and analyzed by GTG banding with twenty metaphases was counted. Subsequently, fluorescence *in situ* hybridization (FISH) and molecular analysis of chromosome 15 were performed.

Fluorescence *in situ* Hybridization (FISH)

FISH analysis was performed according to standard procedures on metaphase derived from cultured lymphocytes [9] applying the commercially available probes for centromeric regions of chromosome 14 and 22 (D14/22Z1) (ZYTOVISION, Bremerhaven - Germany) and chromosome 15 (D15Z3) (ABBOTT, Wiesbaden - Germany).

Microsatellites analysis

DNA extraction from the index case and from their parents was performed using the Qiamp Blood Mini Kit (QIAGEN, Germantown – United States). Microsatellite analysis was done as previously reported [9]. Molecular markers applied were D15S817 in 15q11.2, D15S128 in 15q11.2, D15S122 in 15q11.2~12, D15S986 in 15q12, D15S822 in 15q12, D15S214 in 15q14, D15S1049 in 15q21.3, D15S216 in 15q23, D15S818 in 15q24 and FES in 15q26.1. The parents expressed their approval to carry out the present study by means of informed consent.

Results

The cytogenetic analysis revealed a karyotype with 47 chromosomes including an sSMC in all metaphases analyzed 47,XX, +mar(40) (Figure 1). The parental cytogenetic studies did not find the sSMC neither in father nor in mother in 20 metaphases, each By FISH the sSMC could be characterized as heterochromatic sSMC derived from chromosome 15: 47,XX, +inv dup(15)q11.1) (Figure 2). Regarding the polymorphic microsatellite markers, four of them were informative (D15S128, D15S122, D15S1234, D15S822) and their analysis revealed that both chromosomes 15 were inherited from the father, identifying paternal UPD (Figure 3). According to Table 1 and Figure 3, there is a mixed hetero/isodisomy of both chromosomes 15.

Discussion

It is important to note that the association of SMC and UPD is not yet fully understood, as to whether it occurs by coincidence or consequence [10]. However the recent finding that trisomic rescue and sSMC formation may be achieved by chromothripsis, make genotype-phenotype correlation for sSMC more complicated [11-13]. Until date, the most complete reference describing cases similar to ours is available at http://ssmc-tl.com/sSMC.html [14].

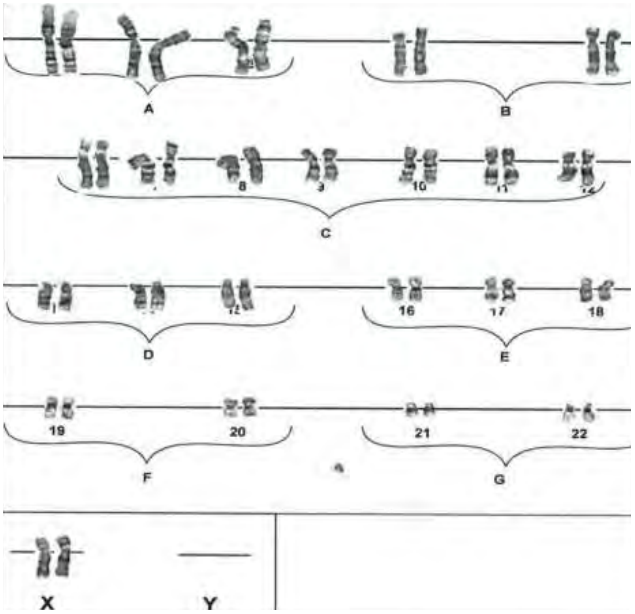

Figure 1: Karyotype with GTG banding of female patient with supernumerary chromosomal marker: 47XX + mar.

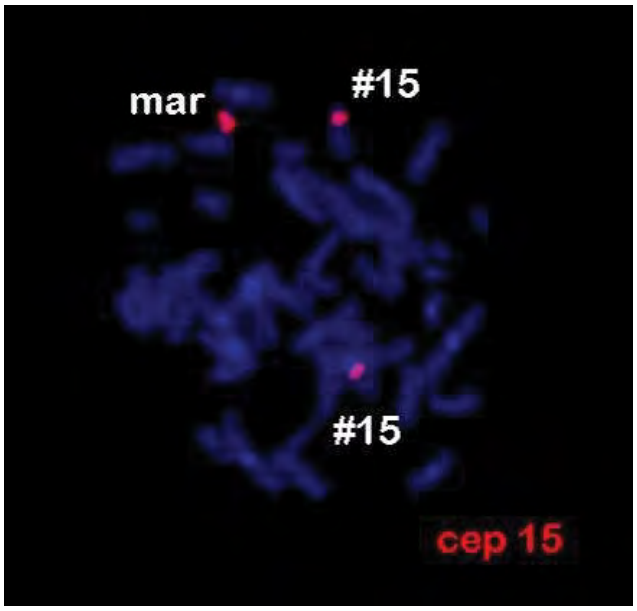

Figure 2: Fluorescence *in situ* hybridization (FISH) on metaphase shows three signals for the pericentromeric region of both chromosomes 15 (paternal) and chromosomal marker (mar).

In this work, we describe the 8th case of an Angelman syndrome connected with UPD and sSMC presence (Table 2). We consider that the mechanism of formation of a UPD + sSMC in this case, considering what was suggested by Kotzot and extended by Liehr T, would be the union of a heterodisomal paternal gamete, product of error in meiosis I, to the maternal one that contains the SMC only, instead of the corresponding homologous chromosome, due to the partial chromosome fragmentation during meiosis. Thus constituting an embryo 47 XN plus SMC, in pure line [8,10,15].

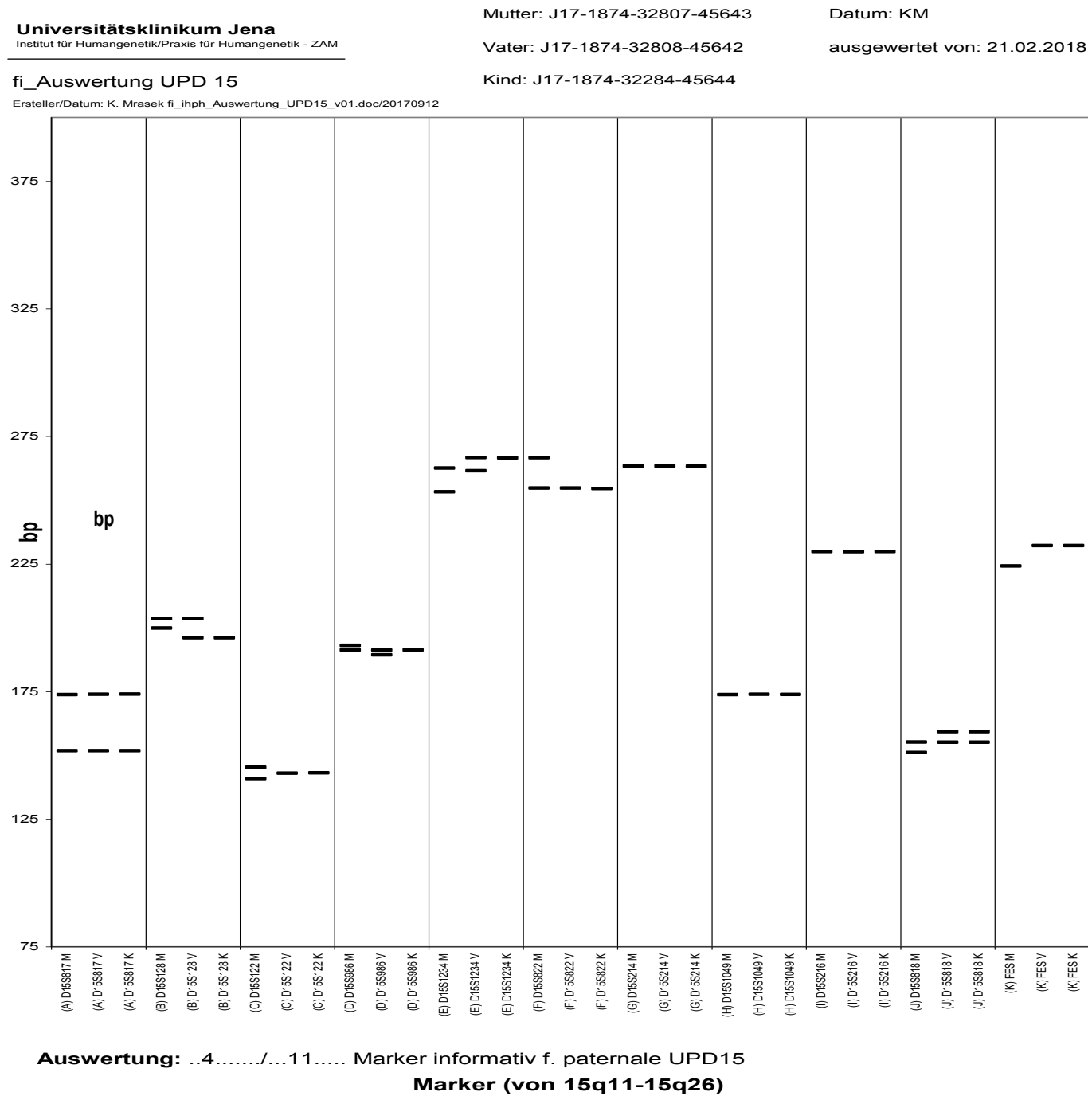

Figure 3: Schematic representation of the analysis of the microsatellite markers showing in lanes 2, 3 ,5 and 6 exclusively paternal inheritance (UPD).

	Mother		Father		Daughter	
Genetic marker	**Allele Size 1**	**Allele Size 2**	**Allele Size 1**	**Allele Size 2**	**Allele size 1**	**Allele Size 2**
D15S128	199.89	203.61	196.11	203.63	196.14	
D15S122	140.9	145.34	143.05		143.6	
D15S1234	253.32	262.59	261.58	266.71		266.66
D15S822	254.79	266.67	254.76		254.76	

Table 1: Segregation analysis using STS 15q11-q26 markers in parents (Father and mother) and daughter.

Clinical features	P1[21]	P2[21]	P3[21]	P4[21]	P5[21]	P8[12]	P9*	Index P
Years old at diagnosis	4 years	18 months	1 year	Prenatal	?	15 years	4 years	6 years
Sex	Male	Male	Female	Male	Female	Male	Male	Female
Phenotype	AS	AS	AS	AS	AS	AS	AS	AS
Cytogenetic Characteristics								
% SMC submission	60	100	100	80	100	100	70	100
Inherited or *De Novo* character of the sSMC	*De Novo*	*De Novo*	N A	N A	*De Novo*	*De Novo*	*De Novo*	*De Novo*
Parental origin of the sSMC	N A	N A	N A	N A	N A	N A	N A	N A
Parental origin of UPD	Paternal	Paternal	Paternal	Paternal	Paternal	Paternal	Paternal	Paternal
Type of UPD (Hól)	NA	NA	NA	NA	NA	Isodisomy	Isodisomy	Heterodisomy
Shape of sSMC	NA	inv/dup 15q11.1	inv/dup 15q11.1	inv/dup 15q11.1	inv/dup 15q11.1	NA, NOT PWARC	inv/dup 15q11.1	inv/dup 15q11.1

AS = Angelman Syndrome; NA = Not Applicable; sSMC = Supernumerary Marker Chromosome; H = Heterodisomy; I = Isodisomy; inv = Inversion; dup = Duplication; PWARC = Prader Willi/Angelman Syndromes

Table 2: Clinical and cytogenetic characteristics of the patients informed with SA by DUP + SMC15 in comparison with the index patient.

Conclusion

We conclude that our case suffer from Angelman syndrome caused by paternal uniparental disomy associated with the *de novo* sSMC from Chromosome 15 and shows a milder phenotype. Angelman syndrome caused by paternal uniparental disomy is rare, although it has been reported by other researchers, associated with supernumerary marker chromosome as well as other complex chromosomal rearrangements. It has to be always in mind also for genetic counseling that chromosomal aberrations can be a hint on epigenetic alterations.

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