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Short clinical report

12q21 Microdeletion in a fetus with Meckel syndrome involving *CEP290/MKS4*

Arnaud Molin [a,*], Guillaume Benoist [c], Corinne Jeanne-Pasquier [b], Nadia Elkartoufi [d], Julie Litzer [d], Matthieu Decamp [a], Nicolas Gruchy [a], Marion Durand-Malbruny [a], Marianne Begorre [b], Tania Attie-Bitach [d,e,f], Nathalie Leporrier [a]

[a] *Service de Génétique, laboratoire de Cytogénétique, CHU de Caen, Université Caen Basse-Normandie, France*
[b] *Service d'Anatomopathologie, CHU de Caen, Université Caen Basse-Normandie, France*
[c] *Service de Gynécologie-Obstétrique, CHU de Caen, Université Caen Basse-Normandie, France*
[d] *Département de Génétique, Assistance Publique – Hôpitaux de Paris – Necker Enfants Malades, Paris, France*
[e] *INSERM U-781 et Fondation IMAGINE, Hôpital Necker-Enfants Malades, Paris, France*
[f] *Université Paris Descartes, Paris, France*

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ABSTRACT

We report on a fetus with Meckel syndrome diagnosed during the 21st gestational week, hydrocephalus and bilateral hyperechogenic kidneys were then detected on ultrasonography. Fetal pathological examination showed facial dysmorphism, occipital meningoencephalocele, characteristic renal cysts, mild hepatic ductal dysplasia, hydrocephalus in association with extreme cerebellar vermis hypoplasia and brainstem anomalies. Molecular and cytogenetic analysis identified a paternally inherited *CEP290/MKS4* (MIM611134) (12q21) nonsense mutation and a maternal 12q21 microdeletion. Two cases with such a mechanism have previously been described in the literature, one of them involves an inherited microdeletion. The observation of such cases highlights the existence of a pathogenic mechanism which involves deletion and point mutation, and illustrates how homozygosity can hide hemizygosity when usual sequencing methods are used. The identification of hemizygosity enables to determine precisely the molecular mechanism and to understand some phenotypic variations. As they act as complete loss of function allele, deletions might give indication on the severity of the associated point mutation. This clinical report highlights the importance of fetal pathology following termination of pregnancies in order to guide molecular analysis and the potential role of cytogenetic cryptic disorders in autosomal recessive disease. The use of polymorphic marker analysis in association with FISH or arrayCGH provided an accurate identification of molecular mechanisms, accurate genetic counseling and optimized strategy for next pregnancies or preimplantation diagnosis.

1. Introduction

Meckel syndrome (MKS, MIM249000), also known as Meckel–Gruber syndrome, firstly described in 1822, is a lethal autosomal recessive disease characterized by a combination of renal cysts, developmental anomalies of the central nervous system, classically an occipital encephalocele, hepatic ductal dysplasia, postaxial polydactyly and variably associated features including bowing of the long bones, cleft palate, ocular anomalies, heart and genital malformations. Its prevalence is estimated between 1 and 10 per 150,000 births in general population, but it goes up to 1 per 9000 births in Finland [1]. There is a great genetic heterogeneity in MKS as 10 different genes have already been involved in the disorder between 2006 and 2011. This genetic heterogeneity is associated to a clinical variability as at least 6 of these genes are also involved in Joubert syndrome (JBS, MIM213300) and a variable spectrum of malformation in between these two phenotypes might be observed [4–6,9]. All JBS/MKS genes encode proteins involved in primary ciliary function, and MKS therefore belongs to the group of so called "ciliopathies".

2. Clinical report

We report on the case of a non-consanguineous healthy Caucasian couple (27 and 28 years old) (Gravida 1 Para 0) referred

* Corresponding author. CHU de Caen, Service de Génétique – laboratoire de Cytogénétique, Avenue de la Côte de Nacre, CS30001, 14033 CAEN Cedex 9, France. Tel.: +33 231065097; fax: +33 231064508.
E-mail address: molin-a@chu-caen.fr (A. Molin).

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to our prenatal diagnosis center during the 21st gestational week after the detection of a major hydrocephalus (19 mm) on ultrasonography and bilateral hyperechogenic kidneys. There was no family history of congenital malformation. The mother denied any exposure to teratogenic agents, irradiation or infectious disease. The pregnancy aborted spontaneously at 21.5 weeks of gestation and a fetal pathological examination was practiced with parents' consent. The external examination showed an eutrophic female fetus with facial dysmorphism (slight hypertelorism and dolichocephaly) and a small occipital meningoencephalocele. She had bilateral renal cysts characteristic of MKS at histology, and mild hepatic ductal dysplasia (Fig. 1) The neuropathological examination confirmed the presence of occipital meningoencephalocele and hydrocephalus in association with extreme cerebellar vermis hypoplasia and brainstem anomalies ("molar tooth" appearance of the cerebral and superior cerebellar peduncles, fragmented dentate nucleus, asymmetric anomalies of corticospinal tracts, hypoplastic inferior olives). This association led to a diagnosis of Meckel syndrome and the parents received genetic counseling. Skin and placenta samples were cultured for cytogenetic analysis and molecular analysis with parental consent. The chromosomal analysis performed according to standard techniques using RHG and GTG banding showed a 46,XX karyotype. Because of the absence of polydactyly, *TMEM67*/*MKS3* (MIM609884) (8q22.1) was first sequenced but no mutation was identified. Direct sequencing of the 53 coding exons of *CEP290*/*MKS4* (MIM611134) (12q21) showed an apparently homozygous nonsense mutation located in exon 41, p.Gly1890X. Parental analysis revealed that only the father was carrying this mutation, at the heterozygous state. Study of several polymorphic markers within and flanking the *CEP290* gene revealed the absence of maternal contribution at the locus, in a minimal region of 850 kb (Table 1). The suspected maternal deletion was confirmed by fluorescent in situ hybridization (FISH) analysis using BAC RP11-88N10 localized in 12q21.32 (88,002,936-88,173,339 pb hg19), on both fetus' and maternal cells (46,XX.ish del(12q21.32)(RP11-88N10 × 1)) (Fig. 1). CGH-array (Agilent© 60K) on maternal DNA confirmed existence of a 1.9 Mb deletion encompassing *CEP290* and five other genes (*MGAT4C*, *MKRN9P*, *C12orf50*, *C12orf29* and *TMTC3*) (46,XX.arr12q21.33(86,988,872-88,826,736) × 1 hg19) (Fig. 2)

3. Discussion

Considering the great genotypic heterogeneity in MKS, involving at least 10 loci to date, several studies have tried to make genotype-phenotype correlations and to evaluate contribution of each locus. While complete forms of MKS combining encephalocele, polydactyly, cystic kidneys, bile duct proliferation are observed in *MKS1*–*MKS6* mutations, this "full" phenotype is quite constant for *MKS1* [2] and is often associated to a cleft palate, a bone dysplasia or intrauterine growth restriction (IUGR) [3]. Conversely, postaxial polydactyly is rare in *TMEM67*/*MKS3* mutated cases (10%) [3,4], and present in respectively 50% of CEP290/MKS4 [5] and 75% of *CC2D2A*/*MKS6* (MIM612013) mutated fetuses [6]. *MKS1*, *TMEM67*/*MKS3*, and

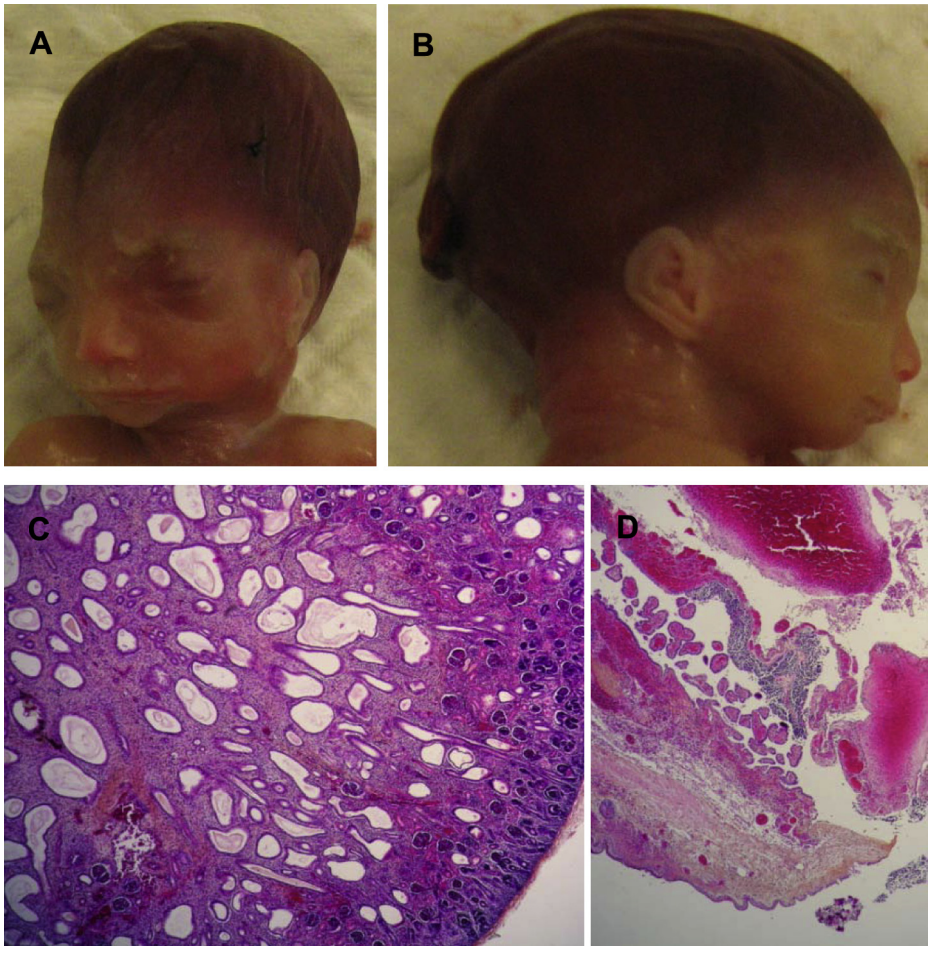

Fig. 1. A and B: facial dysmorphism (slight hypertelorism and dolichocephaly) and a small occipital meningoencephalocele; C: characteristic renal cysts of Meckel syndrome, larger in the medulla; D: histolopathological examination of meningocele showing continuity between skin and meninges.