European Journal of Medical Genetics 59 (2016) 367–372

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Two male sibs with severe micrognathia and a missense variant in *MED12*

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ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form
31 May 2016
Accepted 2 June 2016
Available online 7 June 2016

Keywords:
MED12
Intellectual disability
X-linked
Mental retardation
Micrognathia

ABSTRACT

Missense variants in *MED12* cause three partially overlapping dysmorphic X-linked intellectual disability (XLID) syndromes: Lujan-Fryns syndrome (also known as Lujan syndrome), FG syndrome (also known as Opitz-Kaveggia syndrome) and X-linked Ohdo syndrome. We report a family with two severely micrognathic male sibs, a 10½ year old boy and a fetus, in which hemizygosity for a previously unreported missense variant in exon 13 of *MED12* (NM_005120.2), c.1862G > A, p.(Arg621Gln) was detected by whole exome sequencing. The affected sibs shared no other rare variant with relevance to the phenotype. X-chromosome inactivation in blood was completely skewed (100:0) in the unaffected heterozygous mother, most likely as a result of preferential inactivation of the X-chromosome harbouring the missense variant in *MED12*. Neither the unaffected brother nor the unaffected maternal grandfather carried the missense variant in *MED12*. In the 10½ year old boy, upper airway obstruction secondary to Pierre Robin sequence necessitated a tracheostomy for the first 10 months of life. He has mild to moderate intellectual disability and some dysmorphic features seen in *MED12*-related syndromes. In addition, he has a horizontal gaze paresis, anomalies of the inner ear, and a cervical block vertebra. This report contributes to the expanding phenotypic range associated with *MED12*-mutations.

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1. Introduction

Missense variants in *MED12* cause three partially overlapping dysmorphic X-linked intellectual disability (XLID) syndromes: Lujan-Fryns syndrome, also known as Lujan syndrome (OMIM #309520), FG syndrome, also known as Opitz-Kaveggia syndrome (OMIM #305450) and X-linked Ohdo syndrome (OMIM #300895). Shared features include a tall prominent forehead, down-slanting palpebral fissures, a high narrow palate, micrognathia/retrognathia, hypotonia in infancy and behavioural issues. Macrocephaly, or relative macrocephaly, and hypoplasia/agenesis of the corpus callosum are typical of Lujan-Fryns syndrome and FG syndrome. In FG syndrome constipation or anal anomalies, a frontal hair upsweep, small ears and broad first digits are characteristic whereas a marfanoid habitus and hypernasal voice are often present in Lujan-Fryns syndrome. Five individuals with *MED12*-associated X-linked Ohdo syndrome were reported in 2013 (Vulto-van Silfhout et al., 2013). All had blepharophimosis and sparse eyebrows whereas short stature and microcephaly were inconsistent findings. Facial features tended to coarsen with time and were most suggestive of Ohdo syndrome in young boys. Although ascertainment bias cannot be excluded, in all three of these *MED12*-associated XLID syndromes, carrier females are typically unaffected.

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http://dx.doi.org/10.1016/j.ejmg.2016.06.001
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A frameshift mutation in *MED12*, c.5898dupC in exon 41, which results in generation of an abnormal isoform, was described in a single large family with XLID (Lesca et al., 2013). All hemizygous males were severely intellectually impaired and dysmorphic. Shared features included a high forehead, long face, high nasal bridge, flat malar region and short philtrum. Nine non-dysmorphic heterozygous females were cognitively impaired, most often mildly. In two of the five heterozygous females for whom it could be established, the X-chromosome inactivation (XCI) pattern in blood was 88:12 and 96:4 respectively. Skewed X-chromosome inactivation is defined as preferential inactivation of one of a female's two X-chromosomes in at least 75–80% of cells. The XCI pattern is considered extremely skewed when one X-chromosome is preferentially inactivated in 90–95% of cells (Ørstavik, 2009).

Graham and Schwartz summarized differences and similarities in the clinical features in these four X-linked conditions in 2013 (Graham and Schwartz, 2013). More recently, missense variants in *MED12* were reported in three unrelated male sib pairs; one pair with hydrops or demise in infancy, short humeri and Ohdo-like dysmorphic features (Isidor et al., 2014); another pair with moderate intellectual disability (ID), short stature and microcephaly (Tzschach et al., 2015); and lastly a pair with mild to severe ID, dysmorphic facial features, feeding difficulties, gastro-oesophageal reflux and penile chordee (Langley et al., 2015). Partial phenotypic overlap notwithstanding, none of the six males was considered to have X-linked Ohdo syndrome, Lujan-Fryns syndrome or Opitz-Kaveggia syndrome.

Missense variants in *MED12* in the heterozygous, homozygous and hemizygous state, but no nonsense variants in any state, are registered in the Exome Aggregation Consortium (ExAc) (Cambridge, MA (URL: http://exac.broadinstitute.org) database as of 31.03.16; constitutional nonsense mutations which occur early in the gene and whole gene deletions may well be embryonically lethal in males. Reported variants correlate to some extent with the clinical phenotype. Hemizygosity for the recurrent mutation c.2881C > T, p.(Arg961Trp) is associated with FG syndrome (Clark et al., 2009; Graham et al., 2010; Risheg et al., 2007), as is c.2873 G > A, p.(Gly958Glu) (Rump et al., 2011): both these mutations are located in exon 21. Hemizygosity for a mutation in exon 22, c.3020A > G, p.(Asn1007Ser) (Schwartz et al., 2007; Tarpey et al., 2009) causes Lujan-Fryns syndrome. The mutation, c.3443G > A in exon 24, p.(Arg1148His), has been detected in two unrelated families with X-linked Ohdo syndrome (Isidor et al., 2014; Vulto-van Silfhout et al., 2013). In the report describing *MED12* mutations as causative of X-linked Ohdo syndrome, c.3493C > T in exon 25, p.(Ser1165Pro), was found in two brothers and c.5185C > A in exon 37, p.(His1792Asn), in a simplex case (Vulto-van Silfhout et al., 2013). Several reports of other deleterious, or possibly deleterious, missense variants in individuals with ID contain limited phenotypic information (Callier et al., 2013; Hu et al., 2009, 2016; Huang et al., 2012; Tzschach et al., 2015).

Somatic mutations in exons 1–2 of *MED12* are common in uterine myoma, fibroadenomatous disease of the breast (Makinen et al., 2011) and in the middle of the gene in a small proportion of prostate cancers (Barbieri et al., 2012). Somatic mutations have been detected at very low frequencies in other tumor types (Forbes et al., 2015). An increased risk of cancer has not been documented in *MED12*-related syndromes although there is one report of early onset prostate cancer in an individual with X-linked Ohdo syndrome (Vulto-van Silfhout et al., 2013).

Features in the affected individuals in the family we report that expand the clinical spectrum of *MED12*-related disorders include severe micrognathia, structural anomalies of the inner ear, cervical block vertebra and horizontal gaze paresis.

2. Ethics

This study was approved by the regional committee for medical and health research ethics in Norway (REK Sør-Øst, reference 2010/1152) and under protocols approved by Institutional Review Board for Human Subjects Research at Baylor College of Medicine, Houston TX USA (H-29697- Genome Sequencing to Elucidate the Causes and Mechanisms of Mendelian Genetic Disorders). The molecular analyses were performed in accordance with the Norwegian Biotechnology Act. Written informed consent including consent for whole exome sequencing as well as for publication of clinical information, pedigree and photographs, was obtained from the parents who also consented on behalf of their children under age 16 years.

3. Cases

The family structure is illustrated in Fig. 1. The proband (Fig. 2a,b,c) has an unaffected younger brother and healthy non-consanguineous Norwegian parents. There is no history of congenital malformations or intellectual disability in the extended family. The mother, age 41 years, has had three first trimester miscarriages. The parents chose to terminate a sixth pregnancy after detection of severe isolated fetal micrognathia, first suspected on ultrasound scan in the 14th week of pregnancy and clearly present in the 16th week. At autopsy, the only anomaly noted was micrognathia in the absence a palatal cleft (Fig. 2d,e). A post-mortem skeletal survey revealed midline clefting of the mandible but was otherwise unremarkable.

The proband, a friendly empathetic 10½ year old boy, has mild to moderate intellectual disability. His gross motor development was

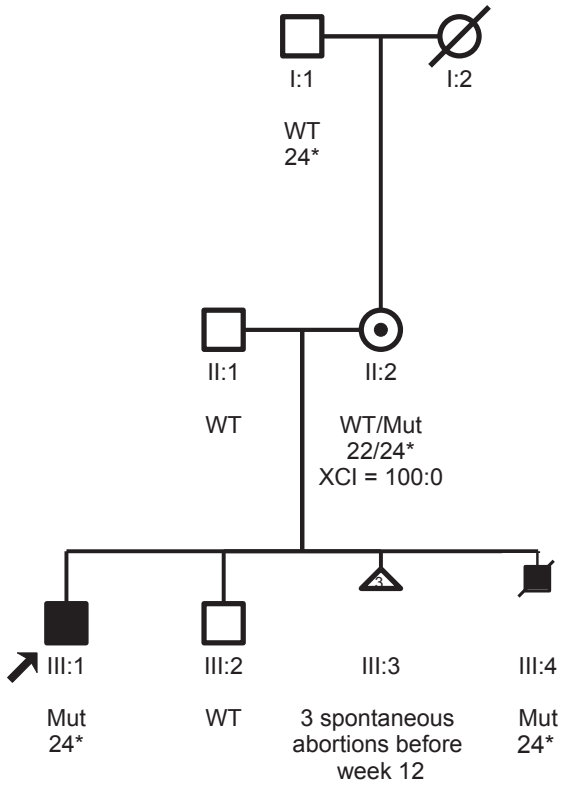

Fig. 1. Pedigree. Arrow indicates proband. Symbols and abbreviations: WT = *MED12* wild type, Mut = *MED12* variant c.1862G > A, * = number of CAG repeats in the androgen receptor (*AR*) gene, XCI = X-chromosome inactivation pattern.

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