



***CNOT2* haploinsufficiency in a 40-year-old man with intellectual disability, autism and seizures**

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11 165 **FIGURE1** Clinical features of the proband and reported variants in *CNOT2*.

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13 166 (a) Left and central panels show facial characteristics of the patient at age 39 including sparse
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19 169 The right panel shows the back (upper part) and the palm (lower part) of his hand, considered
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21 170 normal. (b) The upper part is a schematic representation of the *CNOT2* gene and the lower
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23 171 part shows the localisation of the presently reported deletion compared to the previously
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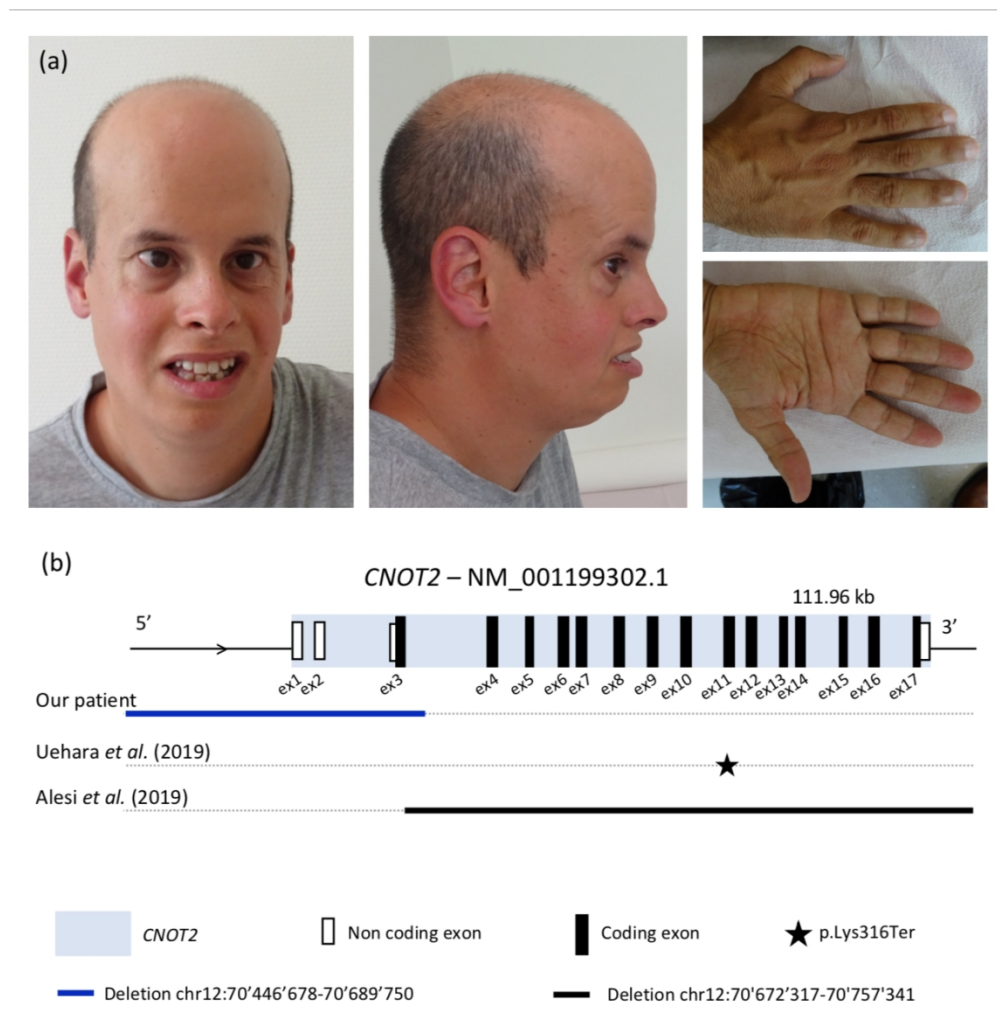
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11 165 **FIGURE1** Clinical features of the proband and reported variants in *CNOT2*.

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13 166 (a) Left and central panels show facial characteristics of the patient at age 39 including sparse
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15 167 lateral eyebrows, slightly upslanted palpebral fissures, strabismus, hypoplastic alae nasi, low
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17 168 hanging columella, smooth philtrum, absent Cupid's bow, misaligned teeth, micrognathia.
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20 169 The right panel shows the back (upper part) and the palm (lower part) of his hand, considered
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22 170 normal. (b) The upper part is a schematic representation of the *CNOT2* gene and the lower
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24 171 part shows the localisation of the presently reported deletion compared to the previously
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26 172 described *CNOT2* pathogenic variants.
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Clinical features of the proband and reported variants in *CNOT2*.

(a) Left and central panels show facial characteristics of the patient at age 39 including sparse lateral eyebrows, slightly upslanted palpebral fissures, strabismus, hypoplastic alae nasi, low hanging columella, smooth philtrum, absent Cupid's bow, misaligned teeth, micrognathia. The right panel shows the back (upper part) and the palm (lower part) of his hand, considered normal. (b) The upper part is a schematic representation of the *CNOT2* gene and the lower part shows the localisation of the presently reported deletion compared to the previously described *CNOT2* pathogenic variants.

457x471mm (72 x 72 DPI)

TABLE 1 Clinical features of patients with predicted loss-of-function variants in *CNOT2*

	Our patient	Uehara et al. (2019)	Alesi et al. (2019)
Type of variant	Partial deletion of <i>CNOT2</i>	Nonsense variant in <i>CNOT2</i>	Partial deletion of <i>CNOT2</i>
Genomic Location (GRCh37)	chr12:70,446,678-70,689,750	chr12:70,732,268:A>T	chr12:70,672,317-70,757,341
Location (NM_001199302.1)	5'UTR - Intron 3-4	c.946A>T,p.(Lys316Ter), Exon 11	Intron 3-4 – 3'UTR
Size of the variant	243-281 kb	1 b	85 kb
Inheritance	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>
Origin	Swiss-French	Japan	Romania
Gender	M	M	M
Age at last evaluation	40 y	6 y	13 y
Delivery	Preterm	Term	Term
Birth weight (kg)	1.580 (P10)	2.798 (-0.7 SD)	2.4 (P3, -1.2 SD)
Birth length (cm)	42 (P10)	49 (mean)	49 (P32)
Birth OFC (cm)	NR	33 (-1.3 SD)	NR
Weight at last evaluation (kg)	59 (P11, -1.2 SD)	24 (+0.5 SD)	34.2 (P<3)
Height at last evaluation (cm)	167 (P9, -1.34 SD)	115.9 (mean)	146.5 (P3-25)
OFC at last evaluation (cm)	55.5 (P61, +0.27 SD)	54 (+3.0 SD)	54 (P25-50)
Hypotonia	NR	-	+
Feeding difficulties	NR	+	+
Developmental delay	+, walked at 30 m, language acquisition at 5 y	+, walked at 20 m, first words at 24 m	+
Nasal speech	-	-	+
Epilepsy	+	NR	NR
Behavior disturbance	Autism	NR	NR
Upper face	Sparse lateral eyebrows, slightly upslanted palpebral fissures, strabismus	Bushy eyebrows, synophris, long eyelashes, upslanted palpebral fissures	Deep-set eyes, upslanted palpebral fissures, hypotelorism
Midface	Hypoplastic alae nasi, low hanging columella	Anteverted nares	Triangular nose, anteverted nostrils
Lower face and mouth	Smooth philtrum, absent Cupid's bow, misaligned teeth, micrognathia	Thin upper lip, micrognathia	Long philtrum, underbite, high-arched palate
Other craniofacial anomalies	-	low-set ears	Elongated, slightly asymmetric face
Hirsutism	-	+	-
Skeletal /extremities anomalies	-	Short 5 th fingers with clinodactyly, broad halluces	Stubby fingers with fleshy pads, flat feet with short 2 nd - 5 th toes, kyphosis and scoliosis
Hypothyroidism	-	NR	-
Heart disease	Aortic and mitral insufficiency (acute rheumatic fever suspected)	NR	Valvular and supravulvar pulmonary stenosis, mild aortic insufficiency
Miscellaneous	Brain MRI: irregular border of the ventricle, left parietal loss of white matter (perinatal hypoxicemic encephalopathy suspected)	NR	Pseudo-hypertrophy of calf muscles, supernumerary nipple, renal dysplasia, chronic renal failure

Abbreviations: b, base pair; kb, kilobase pair; F, female; M, male; -, absent; +, present; NR, not reported; OFC, occipitofrontal head circumference; P, percentile; SD, standard deviation; m, months; y, years

TABLE S1 Clinical features of patients harboring 12q15 heterozygous deletions involving *CNOT2* and other genes

	Schluth <i>et al.</i> (2008)	Vergult <i>et al.</i> (2011) (1)	Vergult <i>et al.</i> (2011) (2)	Vergult <i>et al.</i> (2011) (3)	Lopez <i>et al.</i> (2012)	Alesi <i>et al.</i> (2017)	Uehara <i>et al.</i> (2019)
Genomic location (GRCh37)	chr12:68,582,752-78,553,987	chr12:69,354,696-71,853,018	chr12:70,496,651-73,086,047	chr12:70,515,973-73,086,047	chr12:70,178,509-74,883,975	chr12:70,232,655-70,974,979	chr12:69,433,936-70,758,925
Cytogenetic position	12q15q21.2	12q15q21.1	12q15q21.1	12q15q21.1	12q15q21.1	12q15	12q15
Size of the variant	10.21 Mb	2.50 Mb	2.59 Mb	2.57 Mb	4.71 Mb	0.74 Mb	1.32 Mb
Inheritance	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>	<i>De novo</i>
Origin	NR	Belgium	United Kingdom	Sweden	NR	NR	Japan
Gender	F	M	F	F	F	M	F
Age at last evaluation	5 y	16 y	11 y	21 y	4 y	29 y	12 y
Delivery	Term	Preterm	NR	NR	Term	Term	Term
Birth weight (kg)	2.1 (P3)	2.63 (P25–50)	2.85 (P10)	3.5 (P50)	3.51	3.27	3.15 (+0.8 SD)
Birth length (cm)	45 (P3)	49 (P90)	NR	NR	49.5	51	51 (+1.2 SD)
Birth OFC (cm)	32	33 (P75)	NR	NR	37.5	34	35 (+1.3 SD)
Weight at last evaluation (kg)	NR	56.8 (P10–25)	NR	NR	–2.5 SD	NR	59.5 (+1.5 SD)
Height at last evaluation (cm)	NR	175 (P25–50)	P9	NR	–2.5 SD	NR	162 (+1.5 SD)
OFC at last evaluation (cm)	NR	54 (P25)	56.5 (>P98)	NR	+1.5 SD	NR	56.3 (+1.0 SD)
Hypotonia	+	+	–	–	NR	+	–
Feeding difficulties	+, GER, enteral nutrition	+, with vomiting	+	–	+, severe GER, hiatal hernia, enteral nutrition	+, recurrent vomiting	–
Developmental delay	+, walked at 3 y, delayed speech	+, walked at 23 m	+, Dyspraxia, dyslexia	+	+, walked at 2 y, first words at 4 y	+, mild	+, walked at 2 y, first words at 2 y
Nasal speech	NR	+	+	+	+	+	+
Epilepsy	NR	NR	NR	NR	NR	NR	NR
Behavior disturbance	NR	NR	NR	NR	Frustration intolerance	NR	NR
Forehead anomalies	High/ large forehead	High forehead with bitemporal narrowing	High forehead	High forehead	–	High forehead	–
Upper face	Arched eyebrows, hypertelorism, crescent-shaped eyes, upslanted palpebral fissures, strabismus	Straight eyebrows, mild synophrys, hypotelorism, small horizontal palpebral fissures	Straight eyebrows	Straight eyebrows	Deep-set eyes, long eyelashes	Straight eyebrows, hypotelorism, small eyes	Upslanted and short palpebral fissures
Midface	Anteverted nostrils, linear nose with long columella	Flat face	Midfacial hypoplasia	Flat face/midface hypoplasia	Bulbous nose, broad nasal bridge, wide columella	Midface hypoplasia, high nasal bridge, small columella	–

Lower face and mouth	Long philtrum, large mouth with thin lips, micrognathia	Long philtrum, small mouth, narrow and highly arched palate, small chin	–	–	Wide mouth, thin upper lip vermilion, prognathism	Long and smooth philtrum, oligodontia, posterior open bite, micrognathia	Submucosal cleft palate, malaligned teeth, micrognathia
Other cranio-facial anomalies	Low-set ears	Large anterior fontanel, large ears	Low-set ears, dorsally rotated auricles	Small low-set ears	Triangular-shaped face, short neck, large anterior fontanel	Large anterior fontanel, long expressionless face, small anteriorly rotated ears	Low-set ears, hypoplastic antihelix
Hirsutism	Sacrococcygeal tuft of hair	NR	NR	NR	+ (mild)	NR	–
Skeletal /extremities anomalies	Hands brachydactyly, syndactyly of toes 2-3, mild pectus excavatum, delayed bone age	Straight back, mild scoliosis, cubitus valgus, long and slender hands and fingers, 5 th fingers held in flexion, mild legs asymmetry, S-shaped configuration of tibias, thin legs and feet with hallux valgus, hammer toes	Hammer toes, hypoplastic 5 th toenails	Slender built, normal growth	Delayed bone age, slightly shortened clavicles, clinodactyly of 5 th fingers, large thorax with widely spaced nipples	Slender built, narrow shoulders, asymmetry of pelvis and lower limbs, scoliosis, flat feet, and right valgus knee	Short 5 th fingers, restricted range of supination at her right elbow joint, 2-3 toe syndactyly
Hypothyroidism	–	+ (14 y)	+ (9 y)	+ (during pregnancy)	–	–	–
Heart disease	VSD	NR	NR	NR	–	NR	–
Miscellaneous	IUGR, hypercalcemia	Prone to upper airways infections, surgery for phimosis, removal of tonsils and adenoids, and repair of the right eardrum	Refractive error, lymphoblastoid leukemia (3 y), cutis marmorata	Anorexia nervosa (late teens), refractive error, recurrent upper airways and middle ear infections	–	Neurosensory hearing loss, left megaureter primary obstruction, upper limbs postural tremor, hyperelastic skin, mild ligaments laxity, recurrent inner ears infections, median retrocerebellar arachnoid cyst, cryptorchidism	Hyperopia

Abbreviations: b, base pair; kb kilobase pair; Mb, megabase pair; F, female; M, male; –, absent; +, present; NR, not reported; OFC, occipitofrontal head circumference; P, percentile; SD, standard deviation; m, months; y, years; GER, gastroesophageal reflux; IUGR, intrauterine growth retardation; VSD ventricular septal defect