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Proximal Deletion 12q with a New Insight to Growth Retardation

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Established Facts

- Proximal deletions of the long arm of chromosome 12 have been described in about 20 patients with growth and developmental delay. No clear candidate gene has been identified yet.
- The *ARID2* gene has been associated with intellectual disability and a Coffin-Siris-like phenotype.

Novel Insights

- The present case contributes to the common phenotypic features for patients with proximal deletion 12q such as developmental delay, growth retardation, broad forehead, large low-set ears, broad nasal bridge and/or nose, long philtrum, and widely spaced nipples.
- *ARID2* is the only gene in common for patients described with a deletion at 12q12q13.1 and growth retardation (<–2 SD).
- *ARID2* single nucleotide variants do not correlate with severe growth retardation.

Keywords
ARID2 · Deletion 12q12q13.11 · Developmental delay · Growth retardation · SNP array

Abstract
Proximal deletion of the long arm of chromosome 12 is a rare chromosomal abnormality described in about 20 patients. Known deletions span the region from 12q11 to 12q13 and include the genes *YAF2*, *AMIGO2*, and *NELL2*. These are suggested as candidate genes for the key phenotypic features such as growth and psychomotor retardation. Here, we present a case with a 3.1-Mb interstitial deletion at 12q12q13.11. The clinical observations of our patient overlap with the major common findings for published cases. The deletion detected in our patient does not involve the previously suggested candidate genes *YAF2* and *AMIGO2*. We draw a correlation between proximal deletion 12q and *ARID2* deficiency by comparing patients carrying gross deletions with a cohort of patients carrying small intragenic *ARID2* deletions as well as patients with single nucleotide variants (SNVs) in *ARID2*. Growth retardation <–2 SD is present in cohorts with both gross and small deletions spanning *ARID2*. However, *ARID2* SNVs do not correlate with severe growth retardation.

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Chromosome 12q deletions are a heterogeneous group of genetic conditions that can be clustered into 3 major subgroups: (i) proximal deletions with breakpoints in 12q11q13; (ii) intermediate deletions with breakpoints in 12q15q21, and (iii) distal deletions with breakpoints in 12q22q24. Moreover, a defined 12q14 microdeletion syndrome has been described in the literature [Lynch et al., 2011]. A variable degree of developmental delay as well as intellectual impairment was noted for most of the published cases. This fact is in agreement with the general observation that the majority of chromosomal rearrangements are associated with developmental and intellectual retardations as well as a broad spectrum of dysmorphisms.

Proximal deletions of the long arm of chromosome 12 have been described in about 20 patients. Five of these share a well-defined phenotype characterised by developmental delay with cognitive impairment, growth retardation, and decreased head circumference as well as a broad forehead, large low-set ears, broad nasal bridge and/or nose, long philtrum, and widely spaced nipples [Tonoki et al., 1998; Miyake et al., 2004; Failla et al., 2008; Carlsen et al., 2015; Weng et al., 2018]. All these patients have an overlapping deleted region at 12q12, where *YAF2*, *AMIGO2* and *NELL2* were suggested as candidate genes for growth and psychomotor retardation. However, no strong correlation or experimental proof have been shown for these genes to be associated with the mentioned phenotypic abnormalities.

In this study, we report a patient with a 3.1-Mb deletion at 12q12q13.11 contributing to the cohort of patients with proximal deletions at 12q. The present deletion does not span previously suggested candidate genes *YAF2* and *AMIGO2.* Instead it delineates a minimal critical region for moderate to severe growth retardation with *ARID2* as a candidate gene. We also compare this cohort with patients carrying *ARID2* gene disruption and for the first time propose *ARID2* as a candidate gene for moderate to severe growth retardation (<–2 SD). We notice that *ARID2* single nucleotide variants (SNVs) do not correlate with severe growth retardation, which may indicate diverse effects of different types of genetic variants on ARID2 protein function.

Case Presentation

The male patient was born at term after an unremarkable pregnancy and delivery; Apgar scores were 9-10-10. Birth weight was 3,210 g (15th centile/–1 SD) and length 47 cm (<10th centile/–2 SD). He had difficulties with breastfeeding and did not take on weight as fast as expected. The boy came to medical attention because of failure to thrive. Although his target height is around 1.80 m (±0 SD), he has been growing on –3 SD for length, a bit below –2 SD for weight, and has a head circumference of –1 SD (Fig. 1A). Early on, he showed signs of developmental delay, especially in terms of oral motor function and expressive speech development. At 6 years of age, he is drooling and is still eating mashed food. He started walking unsupported at 18 months and still has some difficulties with fine motor activities. According to the parents, he was more like a 2-year-old at 3 years of age. He was toilet trained at 3.5 years of age and is wearing diapers at night at the age of 6.5 years.

Because of a slight strabismus, he is followed up by an ophthalmologist. Hearing is reported to be normal. Psychological assessment performed at age 6 concluded an expressive language delay, difficulties with transitions and changes of routines. Overall, it was concluded that he showed an impaired ability to social reciprocity and communication that was assessed to give a clinically significant functional impairment. However, there was no clear sign that he exhibited any stereotypical, limited or repetitive interests, and therefore he fulfilled the diagnostic criteria for atypical autism according to ICD-10.

At examination, one notices a short boy with a scaphocephalic head shape, long face, prominent forehead, slight strabismus, broad nose and nasal bridge, long philtrum, thin upper lip, high-arched palate narrowed ventrally, widely spaced nipples, broad-based fingers, and hypoplastic toenails (Fig. 1B–F). He has a decreased muscular tone. For a detailed clinical description see Table 1.

Method and Results

In view of the growth retardation, a hormone screening was performed at age 3.4 years. Thyroid function test was within the normal range (TSH 1.77 (0.7–6.0) mlE/L, FT4 16.4 (12.3–23) pmol/L, FT3 5.7 (3.7–8.5) pmol/L), as well as the insulin growth factor 1 (IGF-1, 38 (27–172) ug/L, and 58 ug/L at age 3.5 years).

The patient was referred for genetic testing because of developmental delay and dysmorphism. Chromosomal microarray analysis was performed using CytoScan HD (Thermo Fisher) following the manufacturer's instructions. The analysis identified a 3.1-Mb interstitial deletion in the long arm of chromosome 12, arr[GRCh37] 12q12q13.11(43889138_47011108)x1. FISH analysis was performed on metaphase spreads from cultured blood lymphocytes using BAC probe RCPI-11 95K16 (Empire Genomics) located within the deleted region and standard techniques. TelVysion 12q (Abbot), located at subtelomeric region 12q, was used as a control probe. Parental metaphase FISH-analysis could not detect any deletion or any other rearrangement of the named region (data not shown).

Discussion

In this study we describe a de novo deletion at 12q12q13. The deleted region in our patient partially overlaps with previously described deletions in 5 independent cases

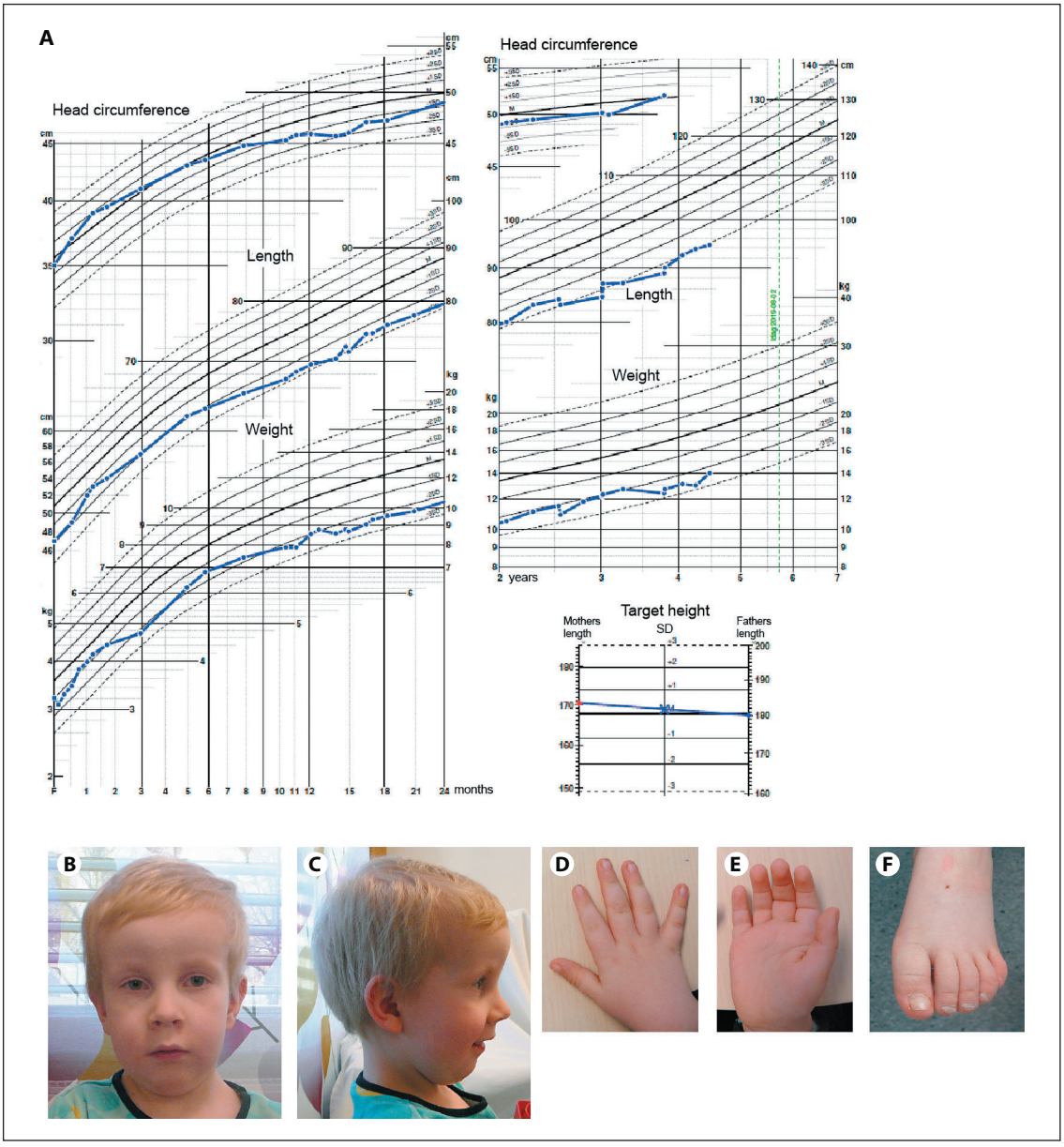

Fig. 1. A Growth curve representing the patient's growth parameters as well as a target height. **B–F** Pictures of the patient (facial and profile views , right hand and left foot) at age 6 years 7 months.

(Fig. 2) [Tonoki et al., 1998; Miyake et al., 2004; Failla et al., 2008; Carlsen et al., 2015; Weng et al., 2018]. Four cases, including our patient, presented with psychomotor developmental delay, short stature, decreased head circumferences, as well as large low-set ears, strabismus, broad nasal bridges and/or noses, long philtrums, down-turned corners of the mouth, and widely spaced nipples (Table 1). The patient described by Carlsen et al. [2015] showed most of the above-mentioned clinical features, although he had small ears, a wide mouth and rather an increased head circumference. At a clinical investigation at age 10 years, his height and weight were within the normal range (10th centile).

Fifth-finger clinodactyly as well as small hands and/or feet were common features present in all of the 5 previously described cases, however, not present in our patient. Hypoplastic toenails as well as broad-based fingers were observed for our patient, but not reported for the

Table 1. Clinical features of individuals with proximal 12q deletions

	Present patient	Weng et al., 2018	Carlsen et al., 2015	Failla et al., 2008	Miyake et al., 2004[a]	Tonoki et al., 1998
Position (size)	12q12q13.1 (3.1 Mb)	12q12 (3.18 Mb)	12q12 (1.13 MB, no *ARID2* deletion)	12q12 (4.5 Mb)	12q11q13 (~10.5 Mb)	12q12q13.12 (~6.3 Mb)
Molecular coordinates (hg19)	43,889,138–47,011,108	43,418,911–46,601,627	44,830,147–45,964,945	~42,000,000–~47,000,000	~38,033,557–~48,566,447	~41,826,511–~48,084,277
Age/gender	5 ys 3 m/M	3 m/F	10 ys/M	10 ys/M	20 m/unk	2 ys/M
Height/weight, SD	–3/–2.2	–3/–3	–1/–1 (10th centile both)	–3.6/–2	–3/–3	–3/–5
Length/weight at birth, SD	–2/–1	–3/–	–1/–0.5 (10th/25–50th centile)	–1/–1.5 (10–25th/<10th centile)	–/–	–3/–3
Head circumference, SD	–1	–3	+2	–4	NA	–2
Hypotonia	+	NA	+	+	Hypertonia (lower limbs)	+
Behaviour	Autism (atypical)	NA	ADHD	NA	NA	NA
Delayed motor development	Mild (oral), dyspraxia	NA	+	+	+	+
Cognitive delay	+	+	+	+	+	+
Speech delay	++ (expressive)	NR	+	+	NA	NA
Intellectual disability	Border line	NR	Moderate	Moderate	NA	Severe
Head	Broad forehead /scaphocephaly	**Broad forehead**	Broad forehead	Microcephaly/ brachycephaly	Broad forehead	Microcephaly
Face	Long	NA	–	NA	NA	NA
Large/low-set ears	+/–	+/+	small/+	+/+	+/+	+/+
Hypertelorism	–	+	+	–	NA	+
Strabismus	Slight	NA	+	+	+	+
Palpebral fissures	Horizontal	Up-slanting	Down-slanting	Horizontal	Up-slanting	Down-slanting
Flat/broad nasal bridge	Broad	Broad/depressed	Low/depressed	–/–	NA	NA
Abnormal nose shape	–	**High-inserted columella**	–	Broad	Short/broad	Short/broad
Anteverted nares	–	+	–	–	+	+
Long philtrum	+	+/**smooth**	+/**smooth**	+	NA	+
Mouth size/chin	Micrognathia	Small	Wide	**Wide**	Small	Small
Mouth shape	Thin upper lip	Downturned corners	**Thin upper lip**	**Thin upper lip**, downturned corners	Downturned corners	Downturned corners
Cleft/high-arched palate	+ (high)	NA	NA	+	+	+
Widely set nipples	+	+	+	+	+	+
Small hands/feet	–/–	+/+	+/+	–/+	+/NA	+/+
Hypoplastic nails	+ (toes)	NA	NA	NA	NA	NA
5th finger clinodactyly	–	+	+	+	+	+
Cardiac malformations	NA	+ (ASD)	+	NA	NA	–
Feeding difficulties	+	+	+	+	NA	+
Other	Small pectus excavatum	Small pectus excavatum				

[a] Case 1 adapted from Gallego et al. [2000] as cited in Miyake et al. [2004]. ADHD, attention deficit hyperactivity disorder; ASD, atrial septal defect; m, months; NA, not assessed; NR, not relevant; ~, deducted position according to annotated deleted genes [Failla et al., 2008] or BAC-probes [Miyake et al., 2004]; unk, unknown; ys, years; +, present; –, absent. Bold print indicates information assessed from previously published patients' photos.

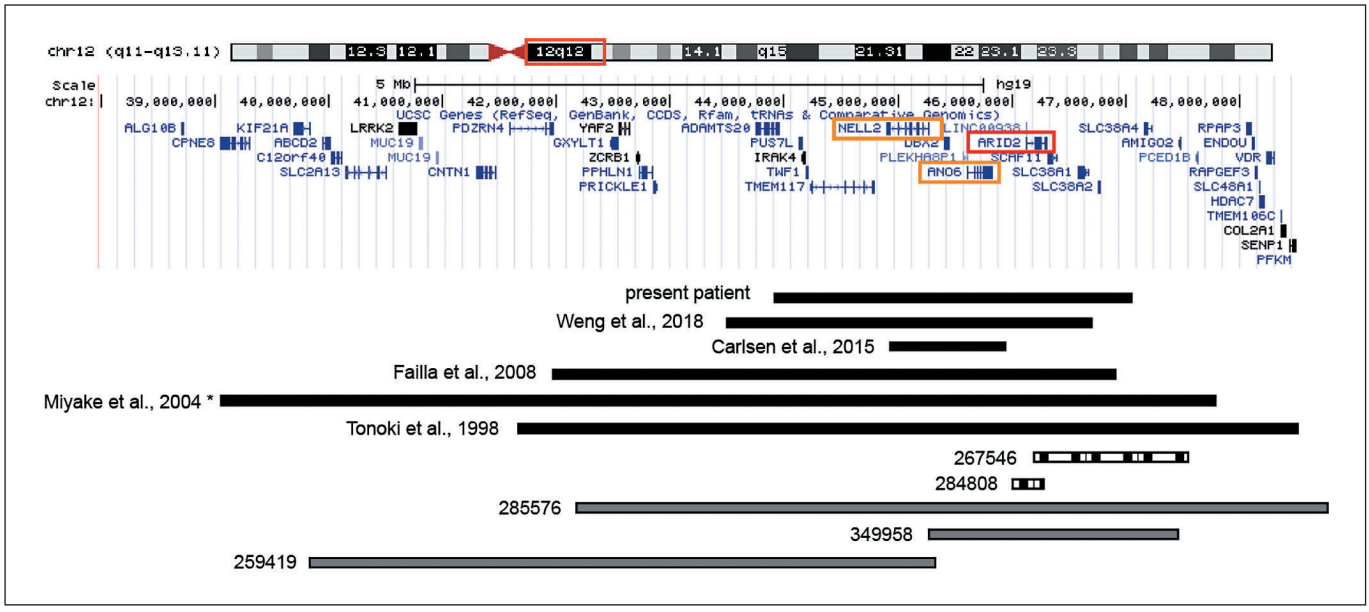

Fig. 2. Schematic illustration of gross proximal deletions at 12q described in the literature and present case. Black bars: published cases, lined bars: published DECIPHER cases, grey bars: unpublished DECIPHER cases.

other patients. Moreover, congenital atrial septal defect was present in one patient reported by Weng et al. [2018], and a dilated aortic root and a slightly thickened ventricular septum were detected in one patient at age 21 month reported by Carlsen et al. [2015].

The deletion spans 12 protein coding genes, of which 4, *TWF1*, *TMEM117*, *NELL2*, and *ARID2*, have haploinsufficiency scores below 25% and are thereby likely to cause loss of function [Huang et al., 2010]. Moreover, 3 of the genes within the deleted region, *ANO6*, *IRAK4*, and *ARID2*, have previously been associated with known clinical conditions (OMIM morbid). *ANO6* is associated with deficient platelet coagulation activity named Scott syndrome [Suzuki et al., 2010], which is a recessive condition. *IRAK4* is involved in the functioning of immune system [Picard et al., 2003]. The symptoms in our patient do not match the phenotypes described for these disorders.

The minimal critical region and candidate genes for deletions at 12q12 were debated in at least 4 papers describing 4 patients with overlapping deletions (Fig. 2) [Miyake et al., 2004; Failla et al., 2008; Carlsen et al., 2015; Weng et al., 2018]. Miyake et al. [2004] suggested *YAF2* and *AMIGO2* as possible candidates for the phenotypic condition in their 2 patients. The hypothesis of *YAF2* to be associated with the growth retardation was also supported by Failla et al. [2008]. Additionally, they suggested *PRICKLE1* to cause learning disability.

Weng et al. [2018] as well as Carlsen et al. [2015] pointed out the importance of *NELL2* in the physiology of the nervous system and possible association with growth retardation. A recent study showed the importance of *NELL2* in appetite behaviour in rats and reduced food intake after the downregulation of *NELL2* expression in the hypothalamus [Jeong et al., 2017]. Overall, only feeding difficulties were annotated in the patients with deletion 12q without any specific mention about essentially reduced appetite. Moreover, the patient reported by Carlsen et al. [2015], who carries a deletion involving *NELL2*, does not show severe growth retardation. Therefore, we presume that *NELL2* is unlikely to have a major impact on the growth retardation described in this cohort.

ARID2 has not been considered as a strong candidate gene for the cohort of patients with 12q proximal gross deletions before. However, *ARID2* is the only overlapping gene in the 4 previously reported cases to be associated with the disorder [Bramswig et al., 2017; Van Paemel et al., 2017; Gazdagh et al., 2019]. *ARID2* was not deleted in the patient described by Carlsen et al. [2015] (Fig. 2). Interestingly, that patient neither presented with moderate nor severe growth retardation (Table 1); his growth parameters were even normalised by the age of 10, and he has an increased head circumference.

Table 2. Clinical features of individuals with *ARID2* variants

	Present patient	Decipher 267546[a]	Decipher 284808[a]	Van Paemel et al., 2017	Shang et al., 2015			
					1	2	3	4
Genetic abnormality	3.1-Mb deletion (*ARID2*, entire gene)	1.39-Mb deletion (*ARID2*, exons 4–21)	246-kb deletion (*ARID2*, exons 1–16)	105-kb deletion (*ARID2*, exons 3–5)	c.2536delG; p.Val846Leufs*3	c.1028T>A; p.Leu343*	c.4441delC; p.His1481Ilefs*4	c.4318C>T; p.Q1440*
Age/gender	5 ys 3 m/M	23 ys/F	4.5 ys/M	3 ys 11m/F	15 ys/F	8 ys/F	6 ys/F	8 ys/F
Height/weight, SD	–3/–2.2	–1/NA	–3.6/NA	–3.3/–4	–2/NA	–1/–1	–1/–2	–1/–2
Length/weight at birth, SD	–2/–1	NA/–2	NA/–4	–2.2/–1.4	NA/–2	NA/–1	NA/–1	NA/–1
Head circumference, SD	–1	–0.5	–0.05	–2.0	NA	NA	NA	NA
Hypotonia	+	+	NA	+	+	NA	–	+
Behaviour	Autism (atypical)	Anxiety	Sleep disturbance	ADHD/noise sensitivity	ADHD/anxiety	ADHD/ aggressive	Water affinity/ noise sensitivity	ADHD/tics
Delayed motor development	Mild (oral), dyspraxia	NA	+	+	+	+	+	+
Cognitive delay	+	NA	NA	+	+	+	+	+
Speech delay	++ (expressive)	NA	+	+	+	NA	+	NA
Intellectual disability	Border line	Moderate learning difficulties	NA	NA	+	NA	NA	NA
Head	Broad/high forehead/ scafocephaly	Broad forehead	Broad forehead	High forehead	Frontal bossing	Frontal bossing	Frontal bossing	Frontal bossing
Face	Long	Long	–	Coarse	NA	Coarse	Coarse	NA
Large/low-set ears	+/–	NA/+	–/+	NA/–	+	NA/+	+/+	+
Hypertelorism	–	–	–	–	NA	NA	+	NA
Strabismus	Slight	NA	NA	+	NA	NA	NA	NA
Palpebral fissures	Horizontal	Down-slanting	Horizontal	Down-slanting	Down-slanting	Down-slanting	Down-slanting	Down-slanting
Flat/broad nasal bridge	Broad	–	–	–	NA	–	–/+	NA
Abnormal nose shape	–	Long	–	Broad tip	NA	NA	NA	NA
Anteverted nares	–	–	–	–	NA	–	–	NA
Long philtrum	+	+	+	Prominent	NA	Flat	Flat	NA
Mouth size/chin	Micrognathia	Micrognathia	Micrognathia	Retrognathia	Micrognathia	Retrognathia	Micrognathia	Micrognathia
Mouth shape	Normal	Thin upper lip	Thin upper lip	Normal	NA	Wide	Thin upper lip	NA
Cleft/high-arched palate	+ (high)	+	NA	–	NA	+	NA	NA
Widely set nipples	+	NA	NA	NA	NA	NA	NA	NA
Small hands/feet	–/–	Arachnodactyly	NA	NA	NA	NA	NA	NA
Hypoplastic nails	+ (toes)	+ (toes)	+ (toes)	+	NA	NA	NA	NA
5th finger clinodactyly	–	NA	NA	NA	NA	NA	NA	NA
Cardiac malformations	NA	NA	NA	NA	NA	+ (ASD)	NA	NA
Feeding difficulties	+	NA	+, laryngomalacia	+, oromotor dysfunction	+	+	+	+
Other	Small pectus excavatum			Clubfoot unilateral, bilateral hip dysplasia				

ARID2 encodes an AT-rich interactive domain (ARID)-containing DNA-binding protein required for the stabilisation of SWI/SNF chromatin remodelling complex SWI/SNF-B (PBAF), which regulates embryonic cell patterning and cell cycle control [Xu et al., 2012; You et al., 2013; Cabot et al., 2017]. It has been associated with short stature, intellectual disability, and specific dysmorphic features [Shang et al., 2015; Gazdagh et al., 2019]. However, only a few patients with *ARID2* deficiency have been described. Common clinical symptoms for these cases are short stature and global developmental delay with cognitive impairment [Shang et al., 2015; Bramswig et al., 2017; Van Paemel et al., 2017; Gazdagh et al., 2019]. They also share dysmorphic features such as a coarse face with prominent forehead, broad nose, and down-slanting palpebral fissures (Table 2). Micrognathia, abnormal philtrum and posteriorly rotated low-set ears were present in most of the patients. Moreover, a majority of the patients present with hypotonia, feeding difficulties, and various behavioural abnormalities.

Table 2 (continued)

	Bramswig et al., 2017		DDD 267395[a]	DDD 275526[a]	DDD 263830[a]	DDD 265539[a]	DDD 272339[a]
	1	2					
Genetic abnormality	c.3411_3412delAG; p.Gly1139Serfs*20	c.156delC; p.Arg53Glufs*5	c.1158dup; p.(Asn387*)	c.399C>G; p.(Tyr133*)	c.4444C>T; p.(Gln1482*)	c.4687_4690dup; p.(Thr1564Lysfs*5)	c.2645_2646insCT; p.(Val883Leufs*10)
Age/gender	7 ys/M	4 ys/M	2 ys/M	6 ys 10 m/M	8 ys 3 m/M	3 ys 11 m/M	18 ys/M
Height/weight, SD	−2.14/NA	−2.2/NA	−2/−1	−2/−1	−1.37/+0.94	−2/NA	+0.74/+1.5
Length/weight at birth, SD	−1.6/−1.6	−0.7/+2.1	NA/−0.53	NA/−1	NA/+0.16	NA/−2.2	NA/−1.16
Head circumference, SD	+0.68	−0.4	+0.3	+2	+0.65	NA	+0.04
Hypotonia	+	+	+	NA	NA	NA	NA
Behaviour	Inability to sit alone	+	"Routine driven"/ rigid/anxiety	"Routine driven"/ noise sensitivity	Rigid/anxiety	NA	Quiet
Delayed motor development	+	+	+	+	+	+	–
Cognitive delay	+	+	+	+	+	+	+
Speech delay	+	+	+	++	++	+	++
Intellectual disability	Severe	++	Moderate	Moderate	+	+	+
Head	High forehead	Large forehead/ frontal bossing	Plagiocephaly	Broad forehead	NA	High/broad forehead	NA
Face	Coarse	Coarse/triangular	Non-coarse	Coarse	NA	Coarse	Coarse
Large/low-set ears	−/+	–	Protruding	NA/+	NA/NA	Posteriorly rotated	NA
Hypertelorism	+	–	–	NA	NA	NA	NA
Strabismus	–	–	NA	+	NA	NA	NA
Palpebral fissures	Narrow	Horizontal, narrow	NA	Down-slanting	NA	NA	NA
Flat/broad nasal bridge	+/–	+	NA	NA	NA	+/+	NA
Abnormal nose shape	Broad, short	Broad, short	NA	NA	NA	Broad tip	Broad tip
Anteverted nares	+	+	NA	NA	NA	+	NA
Long philtrum	+/prominent	Prominent	NA	NA	NA	Broad	NA
Mouth size/chin	Large/–	Large/–	NA	NA	Micrognathia	NA	Micrognathia
Mouth shape	Thin upper, full lower lips	Thin upper lip, thick lower lip	Thin upper lip vermilion; downturned corners	NA	NA	NA	Thick lower lip vermilion
Cleft/high-arched palate	–	–	NA	NA	NA	NA	NA
Widely set nipples	NA	NA	NA	NA	NA	NA	NA
Small hands/feet	+/+	NA	NA	NA	Short toes	NA	NA
Hypoplastic nails	+	+	NA	+ (toes)	+ (fingers)	small nails 2nd toes	NA
5th finger clinodactyly	NA	+	NA	NA	NA	+	NA
Cardiac malformations	NA	NA	NA	NA	NA	NA	NA
Feeding difficulties	+	–	NA	NA	NA	+, poor swallow	NA
Other	Dandy-Walker anomaly, abnormal corpus callosum		Constipations, frequent infections, myotonic dystrophy	Dysmorphic corpus callosum, delayed myelination	Webbed neck, Wormian bones	Myopia, hypermetropia	Low anterior hairline, thick eyebrows, pes cavus, joint hypermobility, myopia

[a] Adapted from Gazdagh et al., 2019. Deleted exons were deducted according to array breakpoints using USCG Genome Browser (GRCh37/h19). *ARID2* SNVs correspond to NM_152641.3 transcript. ADHD, attention deficit hyperactivity disorder; ASD, atrial septal defect; DDD, deciphering developmental disorders; m, months; NA, not assessed; ys, years. +, present; –, absent.

Both cohorts with *ARID2* SNVs and with whole gene deletions (del12q) share distinct facial dysmorphic features such as prominent forehead, low-set ears, broad nose, long/prominent philtrum, and small mouth. Small hands and feet are much more common in patients with del12q whereas down-slanting palpebral fissures were only present in 2 cases. Coarse face was not typical for the del12q group, whereas widely spaced nipples were not annotated for the *ARID2* SNVs group. Hypotonia and feeding difficulties are features annotated for most of the pa-

Fig. 3. ARID2 protein structure (adapted from UniProtKB Q68CP9) and distribution of pathogenic variants across the protein. Functional regions: ARID: AT-rich DNA interaction domain, LXXLL: nuclear receptor recognition motif, RFX: winged-helix-DNA-binding domain, ZNF: C2H2 zinc finger region. Position of SNVs reported by Shang et al. [2015], Bramswig et al. [2017], and Gazdagh et al. [2019] are marked with arrows. Intragenic deletions reported by Van Paemel et al. [2017] and Gazdagh et al. [2019] are indicated with red lines and deleted exons are annotated.

tients in both groups. Developmental delay was observed in all patients.

Severe growth retardation (<–3SD) was not present neither in the *ARID2* SNVs cohort nor in the patient from Carlsen et al. [2015] who had an intact *ARID2*. Furthermore, one patient with an intragenic deletion in *ARID2* (DECIPHER 267546) did not show severe growth retardation. Instead these patients were growing in the range of –1 SD to –2.2 SD.

ARID2 deficiency is also correlated with Coffin-Siris syndrome (CSS; MIM 617808) pointing out global developmental delay, short stature, and coarse facial features [Bramswig et al., 2017; Van Paemel et al., 2017]. CSS is caused by pathogenic variants in different components of the SWI/SNF-BAF complex, including ARID1A and ARID1B [Santen et al., 2013]. Since ARID2 is a component of the PBAF subunit of the SWI/SNF complex, coexpression of *ARID2* with *ARID1A* and other components of the BAF complex suggests a phenotypic overlap such as intellectual disability for CSS and *ARID2* deficiency [Lessard et al., 2007; Bramswig et al., 2017; Van Paemel et al., 2017]. However, typical CSS features like hypertrichosis, sparse scalp hair, long eyelashes, and bushy eyebrows are present neither in the *ARID2* SNVs nor in the del12q group.

ARID2-containing SWI/SNF-PBAF protein complex regulates tissue-specific gene expression. Depletion of ARID2 affects expression of the anabolic growth factor *BMP4* and the growth factor receptor *FGFR2* being critical for osteoblast differentiation, particularly pre-osteoblast commitment [Xu et al., 2012]. The same study demonstrated a negative effect of *ARID2* depletion on the mineralisation phenotype in maturing osteoblasts. These facts might explain the growth abnormality and craniofacial features in patients carrying heterozygous variants in *ARID2*. Complete *ARID2* knockout mice display severe cardiac defects with reduced proliferation of cardiomyocytes and embryonic lethality [He et al., 2014]. Implication of ARID2 in the cardiac system development could explain observed heart defects in some patients (Tables 1, 2). There are no described cases with homozygous depletion of *ARID2* in humans.

Remarkably, all described SNVs in *ARID2* (frameshift and nonsense) have a deleterious effect. The variant c.3411_3412delAG (p.Gly1139Serfs*20) was even hypothesised to be attended by nonsense-mediated RNA decay (NMD) leading to haploinsufficiency of *ARID2* [Bramswig et al., 2017]. A similar mechanism for a deleterious effect may be speculated for other SNVs. However, detailed analysis of the NMD phenomenon for any *ARID2* SNV was not performed.

In fact, the different grade of growth retardation in the 2 groups of patients may indicate different effects of SNVs or intragenic deletions and gross deletions on ARID2 functional implication in the pathogenesis. Analysis of the location of SNVs and deletions in correlation with ARID2 structure may shed new light to the prediction of possible functional effects of these genetic variants. ARID2 is an 1835 aa protein containing 4 distinguished functional regions (Fig. 3). Three highly conservative DNA-binding domains (ARID, RFX, and ZNF) together with a nuclear receptor recognition motif (LXXLL) medi-

ate transcriptional activation of selected genes [Emery et al., 1996; Savkur and Burris, 2004; Patsialou et al., 2005].

Most SNVs located between the LXXLL and ZNF regions are predicted to cause a loss of the ZNF domain. The exceptions are the p.Arg53Glufs*5 variant located in the ARID domain and p.Tyr133* located just after the ARID domain. These patients together with the patient carrying the p.Gly1139Serfs*20 variant, with a hypothesised NMD effect, show growth retardation just below –2 SD, which is more severe compared to patients with other *ARID2* SNVs [Bramswig et al., 2017]. Most published cases with intragenic deletions within *ARID2*, span either only the ARID domain (exons 3–5 deleted) or ARID together with LXXLL and RFX regions (exons 1–16 deleted) [Van Paemel et al., 2017; Gazdagh et al., 2019]. However, DECIPHER patient 267546 does not have a severe growth retardation, though all 4 functional regions are deleted (exons 4–21 deleted). Very little is known about the growth parameters for this patient during the first and second decades of her life. Also, we do not know whether she received a hormonal therapy in a view of a short stature. Growth parameters presented in Table 2 correspond to 23 years, whereas all other patients have been examined on younger age. We admit that growth is a complex and dynamic trait which is influenced by both genetic and environmental factors. Thus, for a stronger comparative and correlative analysis, growth and developmental parameters would have to be compared for every patient at the same age. Some of the included patients were shown to carry other genetic variants, both CNVs and SNVs, unrelated to the 12q11q13 region. These variants were interpreted as likely benign based on their functional score and/or mode of inheritance [Shang et al., 2015; Bramswig et al., 2017; Gazdagh et al., 2019]. However, we cannot completely exclude possible functional impact of these or other genetic variants on growth or development.

Taken together our observations corroborate that gross deletions at 12q11q13 represent a distinct clinical subgroup of genetic abnormalities. Described deletions span different genes, and some clinical variations are the same or differ in between patients. Growth retardation (<–2 SD) is present in 5 out of 6 patients suggesting a critical region for this clinical feature with *ARID2* as a possible candidate gene. The present study is the first attempt to draw a connection between gross deletions at 12q12q13 and *ARID2* deficiency. Comparative analysis of phenotypes for both *ARID2* SNVs and del12q groups indicates craniofacial, skeletal and central nervous system abnormalities with high similarity between the 2 cohorts. However, a growth retardation <–2 SD seems to be present mainly in patients with gross deletions, partially or completely spanning the *ARID2* gene. Further characterisation of the effect of above-described genetic variants on *ARID2* expression and protein structure would bring us a better understanding of pathogenesis in patients carrying proximal 12q11q13 deletions.

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Statement of Ethics

This study was approved by the ethics committee. Written parental consent was obtained.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.S. compiled the study. C.S.Z. and N.P. examined and described the patient. M.S. and A.C.T. analysed genetic testing results. M.S., A.C.T., and C.S.Z. wrote the manuscript.

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