

1q24 deletion syndrome. Two cases and new insights into genotype-phenotype correlations

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Declarations

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Abstract

1q24q25 deletions cause a distinctive phenotype including proportionate short stature, microcephaly, brachydactyly, dysmorphic facial features and intellectual disability. We present a mother and son who have a 672kb microdeletion at 1q24q25. They have the typical skeletal features previously described but do not have any associated intellectual disability. We compare the genes within our patients' deletion to those in the deletions of previously reported cases. This indicates two genes that may be implicated in the intellectual disability usually associated with this deletion syndrome; *PIGC* and *C1orf105*. In addition, our cases provide supporting evidence to recent published work suggesting that the skeletal features may be linked to the microRNAs *miR199* and *miR214*, encoded within intron 14 of the Dynamin-3 gene.

Keywords

1q24 deletion

Short stature

Brachydactyly

Dysmorphology

PIGC

DNM3

Intellectual disability

Cognitive impairment

INTRODUCTION

Microdeletions on the long arm of Chromosome 1 are relatively uncommon. In recent years, a consistent phenotype has emerged in association with 1q24q25 deletions. All patients reported to date have had mild to moderate intellectual disability. The skeletal features reported include prenatal onset growth retardation, which persists as significant postnatal short stature of up to -5SD, microcephaly up to -4SD, small hands and feet with brachydactyly and in particular, fifth finger clinobrachydactyly. Of those investigated, several also had delayed bone age [Chatron et al., 2015].

The reported dysmorphic facial features include micrognathia, small, low set ears with absent or hypoplastic lobes, a short nose with a broad bridge and bulbous tip, full eye lids or partial ptosis, a tented upper lip and a small chin. A few patients have been reported to have a broad neck, hypertelorism, a cleft lip / palate or high palate [Burkardt et al.2011, Chatron et al. 2015].

Other features, less frequently described include renal, cardiac and genital malformations, craniosynostosis and single palmar creases. Some patients had feeding difficulties secondary to hypotonia, requiring a gastrostomy. Two patients were reported to have seizures and one had an Arnold-Chiari malformation [Chatron et al. 2015].

Burkardt et al. (2011) reported the first cohort of patients and defined a 1.9MB critical region, which they proposed accounted for the phenotype. They suggested

the gene *CENPL* may be associated with the skeletal features and the gene *DNM3* may be associated with the intellectual disability [Burkardt et al., 2011].

Chatron et al. (2015) collected a larger cohort of 18 patients and the phenotype was further defined. Three distinct types of deletion were characterized. A proximal deletion of 2.5MB encompassing 20 genes was more commonly associated with cardiac and renal malformations. An intermediate deletion of 490Kb, which was the most common imbalance seen, encompassed the genes *DNM3*, *C1orf105*, *PIGC*, *DNM3OS* and 3 microRNAs *miR199*, *miR214* and *miR3120*. A larger, distal deletion of 2.7Mb encompassing 27 genes was also seen [Chatron et al. 2015].

Chatron et al's (2015) 'intermediate deletion', which is part of Burkardt et al's previously described critical region seems to be the region most consistently linked with the phenotype. As such, the likely critical region was further narrowed to the 490Kb region between 1:171970575-172460683 (hg19) [Chatron et al., 2015] (Figure 1).

Ashraf et al reported two further patients with typical features but smaller deletions, one of which contained only three genes. This further narrowed the critical region for the skeletal features. It was suggested that the skeletal features may be linked specifically to intron 14 of *DNM3*, which has an antisense transcript encoding two microRNAs; *miR199* & *miR214* [Ashraf et al., 2015]. Indeed, a previous patient had been described, whose deletion did not include *DNM3* or *miR199* & *miR214* and this patient had no skeletal features [Della Monica et al., 2007].

An additional patient was described in 2016 with a large 11.35 Mb deletion encompassing both the proximal and intermediate deletion. As expected, the patient's features overlapped those described in association with each of these regions, but he also had profound sensorineural hearing loss, which is less frequently reported. In addition, the patient responded to treatment with growth hormone [Lam & Morris 2016]. None of the previously reported patients has shown a significant response to growth hormone [Burkardt et al., 2011, Ashraf et al., 2015]

CLINICAL REPORT

We present two patients; an 18 month old boy (Patient A) and his mother (Patient B).

Patient A

Patient A is an 18 month old male, the only child of patient B. His parents are non-consanguineous. His mother's pregnancy was uncomplicated, but a growth scan at 38+4 weeks showed his femurs to be on the 5th centile for length. He was born by forceps delivery weighing 2.59Kg at 38+6 weeks (2-9th centile). His head circumference was 33.9cm (9th-25th centile). No length was recorded at this time.

Over his first year of life, his height fell significantly below the 0.4th centile. He was referred for a Paediatric Endocrinology assessment. He underwent basic investigations including renal, liver, thyroid function, erythrocyte sedimentation rate, C-reactive protein and a coeliac screen, which were all normal. His full blood count revealed mildly elevated lymphocytes and platelets, consistent with a concurrent viral

illness. His adjusted calcium was slightly elevated at 2.64mmol/L (normal range: 2.20-2.60 mmol/L), however on repeat testing 2 months later this was normal (2.52 mmol/L). IGF-1 was low at 2.6nmol/L (normal range: 3.1-27.3nmol/L).

There were no concerns about his development and his milestones were appropriate. He smiled at 6 weeks, sat at 6 months, development his first words at 14 months and walked at 19 months.

On examination at 18 months, he had a small chin with a tall, broad forehead and high hairline. His ears were posteriorly rotated. He had mild brachydactyly with single palmar creases bilaterally. He had proportionate short stature. At a decimal age of 1.12 years his height was 62.8cm (-5.4SDS below the mean). His weight was 6.74kg (-4.8SDS below the mean) and his head circumference was 48.3cm (just above 50th centile).

His parents consented to genetic investigations and an array-CGH was performed. This showed an abnormal male array profile with a heterozygous deletion of chromosome 1 at 1q24.3: arr[hg19]1q24.3(171609483_172281412)x1.

The minimum deletion size was 672kb from base pair 171,609,483 to base pair 172,281,412 (Hg19); maximum size of 821kb, from base pair 171,502,074 to base pair 172,323,065. The minimal region includes the genes *MYOC*, *VAMP4*, *METTL13*, exons 1-16 of *DNM3* and *miR199*, *miR214* and *miR3120* (Ensembl transcript 001, NM 001136127). The maximal deletion also includes exons 29-34 of *PRRC2C*. This microdeletion was considered to account for his phenotype.

His ongoing management will include monitoring by the Paediatric Endocrinologists and the team may consider a trial of growth hormone treatment when he is 4 years old.

Patient B

Patient B is a 40 year old female. She was born at term weighing 2.95kg (9-25th centile). Her development was normal and she met her milestones appropriately; she smiled at 4 weeks, sat at 6 months, walked at 15 months and developed her first words at 18 months. Her growth was reportedly normal until the age of 3 years, at which point it plateaued. At 10 years, her height was reported to be more than -3SDS below the mean and she was treated with growth hormone for 5 years. There was some reported initial response to growth hormone, but this diminished over the following years. By 15 years of age her height remained more than -3SD below the mean. No specific cause for her proportionate short stature was ever identified. She is of above average intelligence; she achieved a BSc, MSc and PGDip and now works in a skilled profession.

Her parents and siblings were of normal stature; her father's height was 167cm (9th centile) and her mother's height was 162cm (25-50th centile). Her brother's height was reported to be 190cm (91st-98th centile) and her sister's height was reported to be 167cm (50-75th centile). There was no history of short stature in the wider family.

At the age of 38y, after the birth of her son (Patient A), she planned to use the contraceptive implant. As part of her assessment for this, a DEXA scan was arranged and this was reported to show low bone density. She was referred for further investigations of possible osteoporosis. On review, it was found that her bone density was in fact normal but that her total skeletal volume was low. Her skeletal X-rays were reviewed and showed a reduced radial to humeral ratio and dysplasia of the olecranon and proximal tibia. There was some bowing of the distal radius and a suggestion of a possible Madelung deformity at the wrist. Based on these radiological findings, a possible diagnosis of Leri Weil dyschondrosteosis was proposed. Sequencing of the *SHOX* gene along with MLPA was therefore arranged; the results were normal.

Simultaneously, her son (Patient A) was referred for investigation into his short stature. His array CGH identified a 1q24 deletion, which was confirmed to be maternally inherited by array CGH. Patients A and B were reviewed together in the skeletal dysplasia clinic.

On examination, her head circumference was 55.8cm (50th centile), height 139.7cm (7cm below 0.4th centile; -3.1SDS). She was not disproportionate. She had a small chin with low set posteriorly rotated ears. Her feet were broad and her toes were short. She had prominent ulnar styloids, mild brachydactyly and 5th finger clinodactyly bilaterally (Figure 2).

In light of her son's genetic test result, it became evident that her short stature and clinical features were consistent with the 1q24 deletion. For completeness, her

parents were offered testing for the 1q24 deletion using array CGH, and this confirmed that the deletion occurred de novo in Patient B.

METHOD

Array CGH testing was performed on extracted DNA using an Agilent ISCA 60k oligoarray (Agilent Technologies, Santa Clara, CA) according to the manufacturer's recommendations. Data was analysed using Agilent Cytogenomics software (Version 3.0.6.6). Promega Human Genomic DNA was used as a reference (Promega, Madison, WI).

DISCUSSION

We have described a mother and son with significant short stature, minor facial dysmorphism and digital anomalies with a 672kb 1q24 microdeletion. We have demonstrated that they both have skeletal features typical of deletions in this region. Notably, Patient B has no intellectual disability and works in a skilled profession. Similarly, there is no evidence of developmental delay or intellectual disability in Patient A. Intellectual disability has consistently been reported in association with 1q24 deletions. All known patients reported to date have had mild to moderate intellectual disability. Our patients' deletion includes the genes *MYOC*, *VAMP4*, *METTL13* and *DNM3*. This suggests that haploinsufficiency of these genes is not responsible for the intellectual disability associated with deletions in this region.

Chatron *et al*'s cohort of 13 patients with 'intermediate' deletions, including a critical 490Kb region at 1;171,970,575-172,466,683 all exhibited mild to moderate intellectual disability. The genes included in this region are *DNM3*, *C1orf105*, *PIGC*, *DNM3OS*, and *miR199*, *miR214* and *miR320*. The deletion in our patients overlaps this region, but does not include the genes *PIGC* or *C1orf105*. This implicates these two genes as possible candidates in the intellectual disability associated with 1q24 deletions.

There is no published evidence suggesting a role for *C1orf105*, and no reports of an association with intellectual disability. *PIGC* encodes the PIGC protein, which is part of an enzyme complex involved in the biosynthesis of the Glycosylphosphatidylinositol (GPI) protein anchor. The other proteins in the complex include PIGA, PIGC, PIGH, PIGP, PIGQ, DPM2 and PIGY. GPI anchor proteins tether other proteins, such as enzymes and receptors to the cell membrane [Pagnamenta et al., 2017]. They are expressed ubiquitously throughout the body and correct functioning is critical for embryological development [Edvardson et al., 2017].

Homozygous and compound heterozygous mutations in *PIGC* have recently been described to cause severe intellectual disability, global developmental delay and seizures [Edvardson et al., 2017]. Homozygous variants in other members of the PIG family have previously been implicated in intellectual disability [Ilkovsky et al., 2015]. Genes encoding the other proteins interacting in these pathways are therefore also likely to be plausible candidates for intellectual disability.

As yet, no variants in *PIGC* have been described in the Deciphering Developmental Disorders study, although biallelic variants in other members of the PIG family are recorded [DDD study, Pagnamenta et al., 2017]. The phenotype reported in association is broad, but global developmental delay and intellectual disability are consistent findings.

GPI anchor biogenesis defects are usually inherited in an autosomal recessive way [Pagnamenta et al., 2017], and there is no published evidence to suggest that haploinsufficiency in a GPI-anchor biosynthesis protein is clinically significant. However, recent work using autozygosity mapping and whole exome sequencing has indicated that biallelic alterations in *PIGC* may be embryonic lethal [Shamseldin et al., 2015]. As such, it is plausible that haploinsufficiency of *PIGC* could have an effect on intellectual development.

The above hypothesis would not explain the 5 patients reported by Chatron et al whose deletion did not include *PIGC*, but who had intellectual disability. However, all of these patients had much larger deletions of at least 6MB. As such, there may be other relevant genes within their deletions, which also contribute to an intellectual disability phenotype.

With regards to the skeletal phenotype, our cases provide further evidence supporting the significance of *DNM3* and / or *miR199-214* in the skeletal features, as suggested by Ashraf et al. [2015]. There has been no published evidence to suggest a role for *DMN3* in skeletal development. However, mouse studies support a potential role for *miRNA199-214* in skeletal development [Watanabe et al., 2008].

Functional studies have also indicated involvement of both *miR199* and *miR214* in bone formation [Ashraf et al., 2015]. There is emerging evidence to suggest that *miR214* is involved in regulating the Wnt/B catenin signaling pathway in the development of human osteosarcoma. This could provide a plausible hypothesis for a role in skeletal development [Zhu et al., 2017]. There is little published evidence on the role of *mi3120*, but this also remains a possible contributor to the phenotype.

Previous authors have suggested a role for the gene *LHX4* in the associated growth retardation [Nishimura et al., 2010, Lam et al., 2016]. However, this gene is not deleted in our patients, which reduces the likelihood of this gene being central to the skeletal phenotype.

In summary, we suggest that the intellectual disability described in 1q24 deletion syndrome may be associated with the genes *C1orf105* or *PIGC*. Our case adds further evidence to support possible role of the microRNAs encoded within the *DNM3* gene in the associated skeletal phenotype. It is likely that whole genome sequencing will provide further clarification of the genetic alterations responsible for the phenotype within the 1q24q25 region. In addition, ongoing phenotyping of patients with overlapping deletions in this region may continue to solidify specific genotype-phenotype correlations. Delineation of the important genetic factors involved, will aid more precise genetic counseling for the families involved.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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FIGURE LEGENDS

Figure 1: Cytogenetic location of deletion in patients A and B (in red), the 1.9MB critical region reported by Burkardt et al (in blue) and Chatron et al's intermediate region (in green), with reference to the position of relevant genes. *Adapted from Ensembl 2018.*

Figure 2: Clinical Photographs of Hands and Feet of Patient B demonstrating brachydactyly.

Supplementary Figure: Array CGH profile of deletion found in Patients A & B.