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Microcephalic Osteodysplastic Primordial Dwarfism type I with biallelic mutations in the *RNU4ATAC* gene

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Abstract

Microcephalic osteodysplastic primordial dwarfism type I (MOPD I) is a rare autosomal recessive developmental disorder characterized by extreme intrauterine growth retardation, severe microcephaly, central nervous system abnormalities, dysmorphic facial features, skin abnormalities, skeletal changes, limb deformations, and early death. Recently, mutations in the *RNU4ATAC* gene, which encodes U4atac, a small nuclear RNA that is a crucial component of the minor spliceosome, were found to cause MOPD I. MOPD I is the first disease known to be associated with a defect in small nuclear RNAs. We describe here the clinical and molecular data for 17 cases of MOPD I, including 15 previously unreported cases, all carrying biallelic mutations in the *RNU4ATAC* gene.

Keywords

Microcephalic osteodysplastic primordial dwarfism type I; MOPD I; RNU4ATAC; small nuclear RNA; Taybi Linder syndrome; U4atac

Introduction

Microcephalic osteodysplastic primordial dwarfism type I (MOPD I), or Taybi-Linder syndrome (OMIM 210710), is a rare autosomal recessive disorder characterized by extreme intrauterine growth retardation, microcephaly, central nervous system abnormalities, dysmorphic facial features, skin abnormalities, skeletal changes, limb deformations, and

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early death. Originally reported in 1967 (1), the syndrome was characterized again by Majewski as MOPD types I and III (2, 3). It was subsequently suggested that types I and III were part of the same clinical spectrum with subtle variations among brain anomalies and radiographic changes (4) ; the two types have generally been combined since that time. Only 31 individuals with MOPD I/III from 25 families worldwide were reported in the literature through to 2010 (1–20).

The genetic cause for MOPD type I/III (hereafter referred to in this report as MOPD I) was recently identified (21, 22). Two separate groups found biallelic mutations in the *RNU4ATAC* gene, which produces U4atac, a small nuclear RNA that is a crucial component of the minor spliceosome (23), in 6 previously reported and 22 newly described cases of MOPD type I. Herein, we describe the phenotype of 15 previously unreported cases primarily from a founder population in Ohio and provide a brief review and update of 2 previously reported cases (7, 18). Samples from many of these individuals were used in the mapping and subsequent cloning and characterization of the *RNU4ATAC* gene, and all are known to carry biallelic mutations in *RNU4ATAC* (21).

Materials and Methods

Between 1999 and 2010, fourteen cases of MOPD I from 9 nuclear families were identified in the Ohio Amish population (21, 24), a highly consanguineous founder population of approximately 40,000 individuals located in two regions in Ohio and genetically distinct from the Amish in Lancaster County, Pennsylvania. The parents in all 9 nuclear families are related both to each other and to the parents of the other families in multiple ways. The molecular characterization and genotyping of 7 affected individuals and 13 parents is described elsewhere (21). All individuals provided informed consent for an IRB-approved research study and were asked to donate a sample for genetic research.

A review of cases previously reported in the literature was performed using PubMed and the search terms “Taybi-Linder” “Microcephalic Primordial Dwarfism” “MOPD” “Primordial dwarfism” were used. Phenotypic and genotypic data, when available, were abstracted and summarized (supplementary table 1).

Results

The phenotypic features of the 14 Ohio Amish cases (cases 1–14) are summarized in Table 1. The Amish MOPD I phenotype is very similar to what has been previously described in the literature. It consists of severe intrauterine growth retardation (mean birthweight −5.8 SD, range −3.3 to −7.9 SD adjusted for gestational age (25)), microcephaly (mean occipital frontal circumference (OFC) −7.0 SD, range −4.0 to −9.5 SD), ridged cranial sutures, absent or very sparse hair, dry aged-appearing skin, facial dysmorphism, multiple joint contractures and dislocations, abnormal positioning of hands and feet, brachydactyly, severe developmental brain anomalies and an average life expectancy of 8.5 months (range 2.5 – 18 months). The facial features common to all include prominent occiput, sloping forehead, prominent eyes, prominent nose with downturned tip, and small posteriorly rotated ears (Figure 1). Brain and skeletal imaging were available on three and two cases, respectively, as this type of medical care is not customarily sought out by the Amish for lethal conditions such as MOPD I. Post-natal imaging of the brain was performed in case 10 and case 12; case 13 had a high resolution prenatal ultrasound at 30 weeks including a description of the brain. All 3 cases had agenesis or complete absence of the corpus callosum, lissencephaly or other gyral anomalies, and generalized paucity and abnormal appearance of the brain parenchyma. Other findings in case 12 included hypoplasia of the frontal horns, schizencephaly, abnormal circle of Willis and cisterna magna and an abnormal cerebellum. Obstructive hydrocephalus

occurred postnatally and required a ventriculo-peritoneal shunt. Cases 4 and 10 had skeletal surveys. Case 4 had platyspondyly, horizontal acetabular roofs, and dysplastic acetabule (Supplemental Figure 1). Case 10 had bowed humeri, proximal radioulnar synostosis, widening of distal metaphyses, bowed or hypoplastic phalanges, and normal ossification centers and vertebral bodies. The majority of the Amish cases did not survive past 1 year of age. One patient (case 13; Figure 1, left panel) is currently alive at 12.5 months. All of the Amish cases were homozygous for the 51G>A mutation in the 5'stem loop of U4atac with a single founder haplotype in all alleles.

Three non-Amish cases were utilized in our search for the *RNU4ATAC* gene from Australia (case 15) and Germany (cases 16 and 17) and were also found to have biallelic mutations in this gene. These cases are described as family 5, 6 and 7, respectively in the report by He, et al (21). Case 15, previously reported by Haan, et al (7) is a male of Maltese ancestry. Although the original report described the parents as non-consanguineous, it was determined subsequently that they are 4th cousins. The clinical features of this case are similar to those of the Amish cases, as described in Table 1. This child died at age 33 days. He was homozygous for the 51G>A mutation seen in all Amish cases as well as several other cases reported elsewhere (22). As previously reported (21), the case of Maltese ancestry and all Amish patients studied to date share a short haplotype around the *RNU4ATAC* gene. Analysis of adjacent regions are needed to determine if patients with widely different ethnicities share a single haplotype; such studies are underway.

Case 16 was a female child born to healthy non-consanguineous German parents at 38 weeks by Cesarean section. Her length and weight at birth were greater than three standard deviations below the mean and her OFC was 28cm (−4 SD). At age 33 months she presented with microcephaly and short stature [OFC 37.5cm (−8.6 SD), a length of 75cm (−5.4 SD), and a weight of 6.5 kg (−4.5 SD)]. Craniofacial findings included a flat occiput, microretrognathia but normal sized eyes and nose (Figure 2). She had ulnar deviation of both hands and flat feet with a rounded dorsum. MRI of the brain showed pachygyria, partial agenesis of the corpus callosum and agenesis of the vermis cerebellaris (Figure 3). She had moderate motor and mental development (sitting and crawling at 30 months and walking at 33 months). She walked by the age of 4, was talking at age 6 with normal speech and was toilet trained by the age of 7.5 years. At 9 years she weighed 13 kg (−2SD), had a height of 107cm (−4.6 SD) and an OFC of 39cm (−9.7 SD). This child is homozygous for a 55G>A mutation in the 5' stem loop.

Case 17, originally reported by Klinge, et al is the longest surviving case of MOPD I in the literature. Detailed clinical findings through age three are discussed in the original report (18). Subsequent evaluations of this child at ages 6.25 and 12.25 years have been performed.

At the age of $12^{3}/_{12}$ years, his height was 90 cm (−8.7 SD), his weight was 13.4 kg (−4.5 SD) and he had an OFC of 41 cm (−8.4 SD). Clinical examination revealed severe microcephaly and short stature, small, widely spaced, grayish teeth, but no enamel defects. His hair was grey-mottled. Subluxations of hips, knees and ankles were present and did not allow him to stand (Supplemental figure 2). The dorsa of the feet were edematous and the toenails small and hyperconvex. He had a very friendly personality and was able to understand simple commands although he was not able to verbalize. For communication he used a talker. He attended a school for the mentally handicapped. Frequent infections were present. Clinical examination revealed a severe scoliosis, extension deficits in elbows, radial deviation of hands and cellulite-like skin changes at the abdomen. He died during preparation of this manuscript at age 12.75 years from complications of pneumonia. This child was found to be a compound heterozygote for a 30G>A mutation in the 5'stem loop and a 111G>A mutation on the 3'stem loop.

In addition to the 28 cases of MOPD I shown to be caused by mutations in *RNU4ATAC*22 cases have been reported in the literature as consistent with a clinical diagnosis of MOPD I and are consistent with the *RNU4ATAC* phenotype (Table 2). The average birthweight and OFC of these infants was −4.9 SD and −7.1 SD adjusted for gestational age (25) which is very similar to that seen in the Amish cases. The average life expectancy of these 28 cases was 18.3 months (range 0–6.5 years). Characteristic features reported in the majority of these cases are consistent with those in our cases. Malformations beyond the central nervous system are not typically present except for cryptorchidism in affected males.

Three cases reported as MOPD I share some of the facial and musculoskeletal features but differ in significant ways such as arachnodactyly, large ears, corneal clouding and hirsutism (9); generalized renal tubular leakage with persistent hyponatremia, hypokalemia, hypocalcemia, and hypophosphatemia, and normal scalp hair (13); and osteoporosis, multiple fractures, hepatosplenomegaly, cholestasis without evidence of storage disease, focal renal medullary dysplasia, and normal scalp hair (14). The probable presence of varied metabolic abnormalities in these three reports does not appear to be consistent with the previously observed phenotypes of MOPD I.Genotyping of these cases for mutations in *RNU4ATAC* and other microcephalic primordial dwarfism (MPD) genes will be helpful in clarifying the true extent of the MOPD I phenotype.

Discussion

MOPD I is one of several autosomal recessive syndromes falling into the category of MPD, all of which show severe pre- and post-natal growth retardation and marked microcephaly. Features that set MOPD I apart from other MPD syndromes include the severe brain anomalies, notably neuronal migration defects, as well as sparse hair and dry skin, joint contractures and dislocations, absence of metabolic/endocrine dysfunction, and multiple skeletal anomalies. Although some features seem to be common to most if not all *RNU4ATAC*-mutation positive cases, there is still some phenotypic variability within this group, as demonstrated by the type and severity of brain and skeletal anomalies, degree of motor and speech delay, and wide range of survival. Although it is too early to speculate about genotype-phenotype correlations at this time, one interesting observation within *RNU4ATAC*-positive cases is the difference in survival between those carrying two copies of the 51G>A mutation (mean survival = 10.4 months) vs. those with zero or one copies of the 51G>A mutation (mean survival 78.75 months) Using the log-rank test for differences in survival curves, this difference was significant (p-value = 0.02). Possible explanations for phenotypic variability in MOPD I include functional differences between mutations, tissue specific effects, and genetic variability in downstream target genes. Although no discernible functional differences in splicing of a U12-dependent intron between the various *RNU4ATAC* mutants were observed in *in vivo* experiments performed in Chinese hamster ovary cells (21), these results may not be reflective of splicing in all tissues. Additionally, although fibroblast cultures from MOPD I cases were used to measure splicing of downstream target genes, only cultures from 51G>A homozygotes were used for these experiments (21, 22). Approximately 800 U12-type introns are present in the human genome (26) typically in proteins in the categories of DNA replication/repair, transcription, RNA processing, and translation (27). Further functional studies of mutant *RNU4ATAC* alleles in multiple tissues, as well as characterization of all target genes affected by *RNU4ATAC* mutations will likely shed light on these questions.

The exact mechanisms by which decreased levels of spliceosomal complex RNAs might lead to the MOPD I phenotype remain unclear. Clues may be found by looking at other diseases caused by defects of the minor spliceosome. Although MOPD I is the first disease known to be associated with a defect in small nuclear RNA, it joins two other disorders with

defects in spliceosomal function – autosomal dominant retinitis pigmentosa and spinal muscular atrophy (SMA). Autosomal dominant retinitis pigmentosa is most commonly caused by a defect in rhodopsin. However, several subtypes have been shown to result from mutations in spliceosomal proteins added to both major and minor snRNPs in the Cajal bodies. The retina requires a high level of RNA splicing activity for optimal physiological function and rhodopsin molecules must be replenished each morning just before waking. Degeneration of the retinal pigment epithelium is hypothesized as a cumulative effect due to inefficient mRNA splicing (28). SMA is associated with a deficiency of survival motor neuron (SMN) and the phenotype is dependent on the level of deficiency of SMN (MIM 253300, 253550, 253400, 271150). The SMN complex identifies snRNAs in the cytoplasm, assembles protein heptameric rings onto the snRNAs to form core snRNPs, and accompanies the core snRNPs to the Cajal bodies in the nucleus. Decreased SMN levels preferentially lower U11, U12, and U4atac snRNPs by 30–60% in several tissues including murine brain, spinal cord, and heart (29) and resulted in quantitative splicing changes resulting in both up and down regulation of genes. In addition, lymphoblasts from an individual with SMA type I showed accumulation of the U4atac/U6atac/U5 tri-snRNP in Cajal bodies and a 25 fold reduction of active tri-snRNP and differential splicing inhibition of U12-type introns (30). The differential activity of the minor spliceosome in SMA may be pertinent to the MOPD I phenotype given the involvement of the central nervous system in both conditions.

Over the past 5 years, the genetic cause of several other microcephalic primordial dwarfism syndromes has been reported. Seckel syndrome, microcephalic osteodysplastic primordial dwarfism type II, and Meier-Gorlin syndrome are due to abnormalities in DNA damage response (31, 32), centrosomal function (33–35), and licensing of DNA replication origins (36–38), all of which result in impaired cellular proliferation. Therefore it is likely that disruptions to such global cellular functions such as cellular proliferation, differentiation and growth play a part in MOPD I as well. Transcriptome analysis will be an essential next step and may clarify if the phenotype in MOPD I is due to global aberrant splicing of multiple genes containing U12-dependent introns or rather, a more targeted effect on a small number of key regulatory genes, or both. Of interest, a recent study by Pessa, et al measured the effects on downstream splicing of U12-type intron-containing genes in a U6atac snRNA mutant *Drosophila* line using microarray expression profiling (39). This showed both up and down-regulation of numerous genes, while the expression of many genes was not affected at all. Interestingly, a number of the downstream effects on gene expression could be attributed to aberrant splicing of one gene, *prohibitin*which encodes a mitochondrial membrane protein important in mitochondrial morphology and protein degradation. Transcriptome analysis in fibroblast cultures from MOPD I cases and normal controls is currently underway and we hope that this will shed light on the mechanisms by which these mutations lead to such a severe phenotype.

In conclusion, we report 15 new cases and 2 previously reported cases of MOPD I, all known to carry germline biallelic mutations in the *RNU4ATAC* gene which encodes U4atac, a small nuclear ribonucleoprotein that is part of the minor spliceosome. Given the variability of clinical presentation and severity as well as the significant phenotypic overlap between MOPD I and several other inherited syndromes, establishing the correct clinical diagnosis within this group of disorders has been challenging in the past. It is likely that genotyping of additional cases carrying a diagnosis of MOPD I or other MPD syndromes will result in a re-assessment of the clinical criteria for each condition and a broadening of phenotype(s) to include milder and perhaps atypical cases. We anticipate that the availability of genetic testing for MOPD I and other primordial dwarfism syndromes will also allow clinicians to offer more reliable prognostic and recurrence risk information to families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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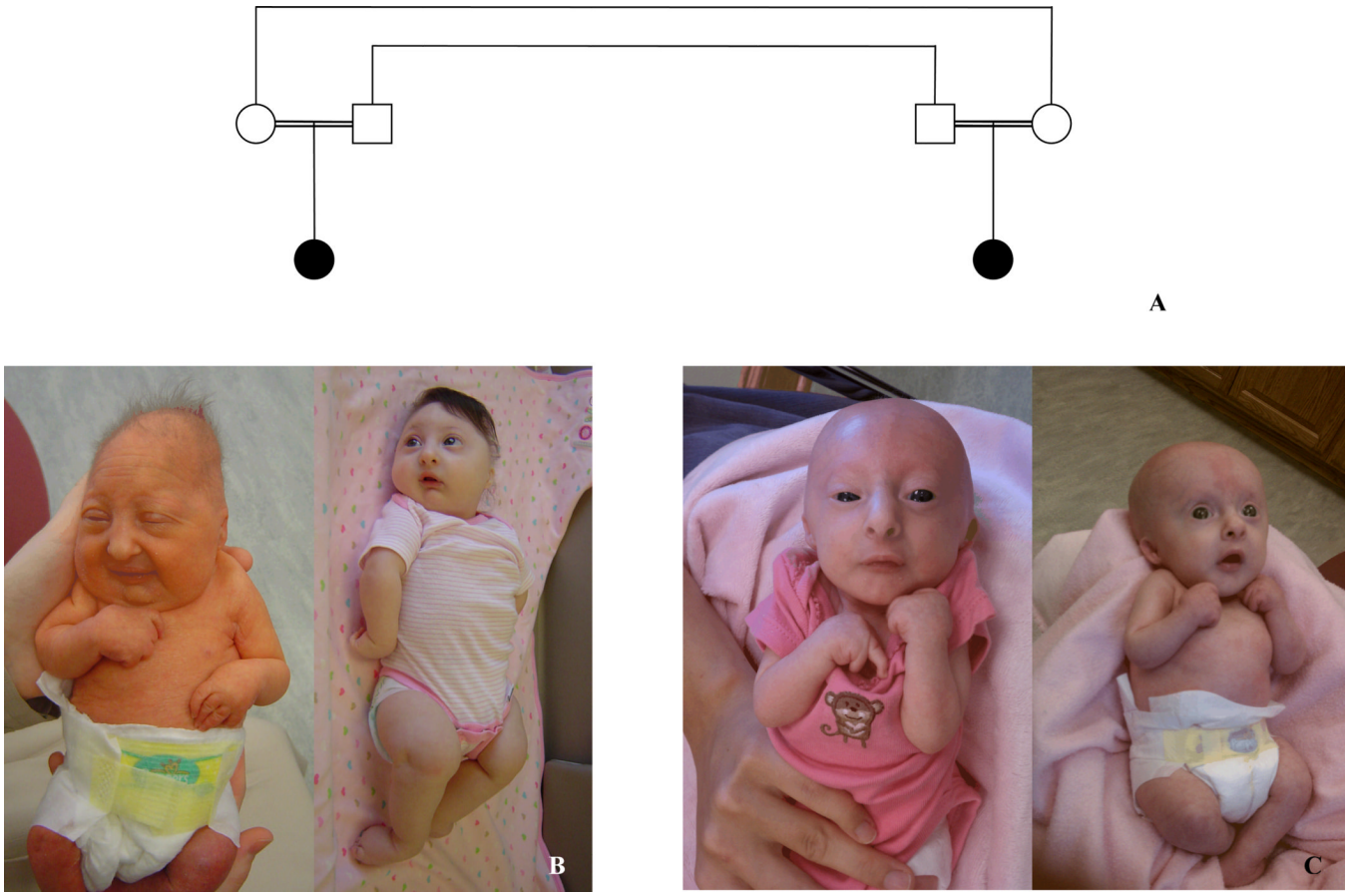

Figure 1.

Two Amish children (cases 13 and 14, Table 1) with MOPD. A. Cases 13 and 14 are related in multiple ways, but their closest degree of relationship is double-first cousin. B. Case 13 at 2 weeks (left panel) and 10.5 months (right panel). Note typical facial features with sloping forehead, broad nasal bridge with downturned nasal tip, small low-set ears, sparse hair, small chin and multiple joint contractures. C. Case 14 at 4 weeks (left panel) and 6 months (right panel). Note typical facies, absent hair, ulnar deviation of both wrists with contractures. This patient had congenital hydrocephalus.

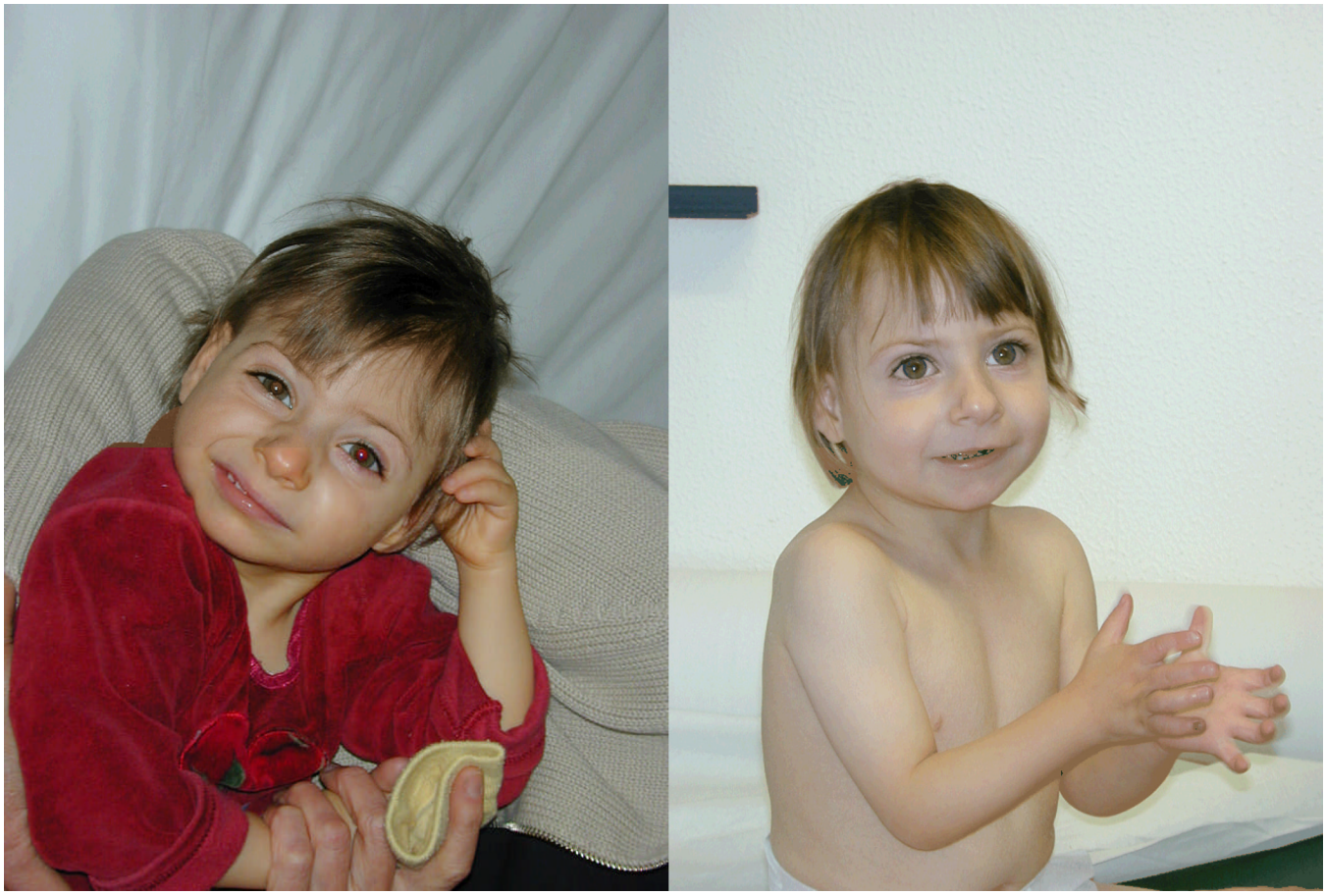

Figure 2.
Case 16 at age 29 months (left) and 33 months (right) with microcephaly and severe growth retardation (height, weight and OFC at 33 months all > −4.5 SD) but relatively mild facial and skeletal features.

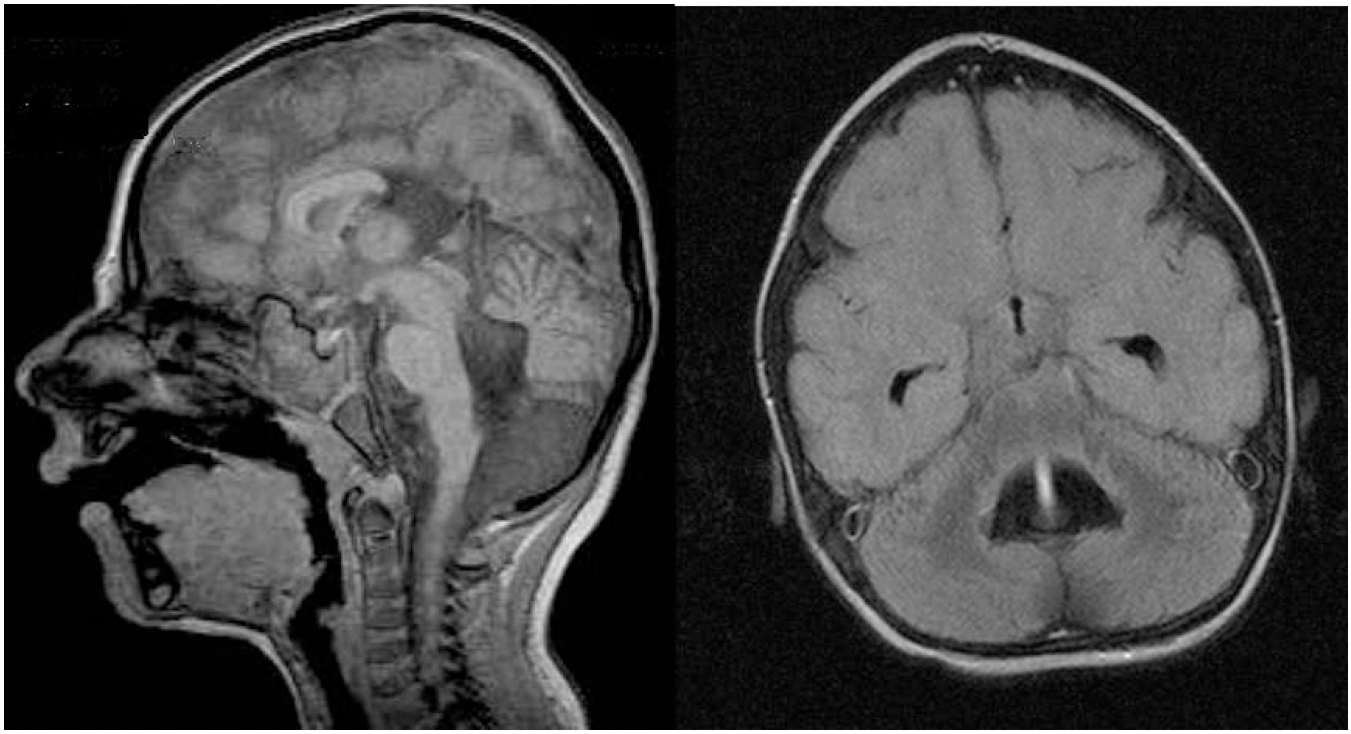

Figure 3.
Brain MRI of case 16. A. Left panel: Sagittal image showing partial agenesis of the corpus callosum and agenesis of the cerebellar vermis. Right panel: Axial image showing pachygyria.

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Table 1

Summary of 17 *RNU4ATAC*-mutation positive cases of MOPD I

Case	Reference	Gender	Ethnicity	Micro-cephaly	Typical brain anomalies	Typical facies	Musculo-skeletal[a]	Radio-graphic findings	Other organ anomalies	Skin/Hair	Age at death	*RNU4ATAC* genotype
1	Present report	F	Amish	+	NE	+	+	NE	NE	NE	18 mo	51G>A;51G>A [b]
2		F	Amish	+	NE	+	+	NE	NE	NE	3.5 mo	51G>A;51G>A [b]
3		F	Amish	+	NE	+	+	NE	NE	+	2.75 mo	51G>A;51G>A
4		F	Amish	+	NE	+	+	+	−	+	10 mo	51G>A;51G>A
5		M	Amish	+	NE	+	+	NE	−	+	9.5 mo	51G>A;51G>A [b]
6		F	Amish	+	NE	+	+	NE	NE	NE	Unknown	51G>A;51G>A
7[c]		Unknown	Amish	NE	NE	NE	NE	NE	NE	NE	Unknown	51G>A;51G>A [b]
8[c]		Unknown	Amish	NE	NE	NE	NE	NE	NE	NE	Unknown	51G>A;51G>A [b]
9		M	Amish	+	+	+	+	+	−	+	10 mo	51G>A;51G>A
10		F	Amish	+	+	+	+	+	−	+	10 mo	51G>A;51G>A
11[c]		F	Amish	NE	NE	NE	NE	NE	NE	NE	4.5 mo	51G>A;51G>A [b]
12		F	Amish	+	+	+	+	NE	−	+	8.5 mo	51G>A;51G>A
13		F	Amish	+	+	+	+	+	NE	+	Alive at 12 mo	51G>A;51G>A
14		F	Amish	+	NE	+	+	NE	Hydrocephaly	+	8 mo	51G>A;51G>A
15	Haan, et al 1989	M	Maltese	+	+	+	+	+	Bilateral cryptorchidism	+	1 month	51G>A;51G>A
16	Present report	F	German	+	+	+	−	NE	−	−	Alive at 9 years	55G>A;55G>A
17	Klinge, et al 2002	M	German	+	+	+	+	+	Bilateral cryptorchidism; Acute lymphocytic leukemia diagnosed at age 2	+	12.75 yrs	30G>A;111G>A

NE = Not evaluated; '+' = present; '-' = absent

[a] Musculoskeletal features on clinical examination only (e.g. joint contractures, joint dislocation, etc.)

[b] Genotype inferred from parental and sibling genotypes

[c] Cases reported by family as affected.