Mandibuloacral Dysplasia Caused by LMNA Mutations and Uniparental Disomy

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Mandibuloacral dysplasia (MAD) is a rare autosomal recessive disorder characterized by postnatal growth retardation, craniofacial anomalies, skeletal malformations, and mottled cutaneous pigmentation [1, 2]. Hutchinson-Gilford Progeria Syndrome (HGPS) is characterized by the clinical features of accelerated aging in childhood. Both MAD and HGPS can be caused by mutations in the LMNA gene. In this study, we describe a 2-year-old boy with overlapping features of MAD and HGPS. Mutation analysis of the LMNA gene revealed a homozygous missense change, p.M540T, while only the mother carries the mutation. Uniparental disomy (UPD) analysis for chromosome 1 showed the presence of maternal UPD. Markers in the 1q21.3–q22 region flanking the LMNA locus were isodisomic, while markers in the short arm and distal 1q region were heterodisomic. These results suggest that nondisjunction in maternal meiosis followed by loss of the paternal chromosome 1 during trisomy rescue might result in the UPD1 and homozygosity for the p.M540T mutation observed in this patient.

1. Introduction

Mandibuloacral dysplasia (MAD) is a rare autosomal recessive disorder characterized by postnatal growth retardation, craniofacial anomalies, skeletal malformations, and mottled cutaneous pigmentation [1, 2]. Hutchinson-Gilford Progeria Syndrome (HGPS) is an autosomal dominant disorder demonstrating varying symptoms including short stature, hair loss, joint degeneration, and atherosclerosis [3]. Pathogenic mutations in the LMNA gene on chromosome 1q22 and encoding the Lamin A/C protein have been reported in both MAD and HGPS. To date, the majority of cases of MAD are caused by missense mutations in exons 8–10 of the LMNA gene [4, 5] that codes for the LAP2 and emerin-binding domain of the Lamin A/C protein.

Recently, we encountered a two-year-old boy with overlapping features of MAD and HGPS. LMNA sequence analysis was performed to determine the genetic cause of his clinical phenotype. With the aim of identifying the molecular etiology of this boy’s phenotype, a comprehensive study was performed on the patient and parents.

2. Materials and Methods

2.1. LMNA Sequence Analysis. The 12 coding exons plus exon-intron boundaries of the LMNA gene were amplified by polymerase chain reaction (PCR). The purified PCR products were sequenced in both directions using ABI Big Dye terminator mix (Life Technologies, Foster City, CA). Data were analyzed using Mutation Surveyor 3.20 software (SoftGenetics, LLC, PA).

2.2. LMNA Deletion Analysis by Real-Time Quantitative-PCR. Real-time quantitative-PCR (RT-qPCR) was performed using 3 different primer pairs specific to exon 10 of the LMNA gene and detected using Power SYBR Green (Life Technologies) following manufacturer instructions. The relative copy
number was calculated based on the standard curve method and compared to PMP22 gene, which was used as an internal control. A ratio of 0.8–1.2 was indicative of no deletion/duplication.

2.3. Microsatellite Analysis. Genotyping of microsatellite markers on chromosomes 1, 6, and 15 was performed on the patient and both parental samples. Microsatellite markers were amplified and separated on an ABI PRISM 3130xl Genetic Analyzer (Life Technologies). The PCR fragments were analyzed using ABI PRISM GeneScan and Genotyper software (Life Technologies).

This study was approved by the University of Chicago Institutional Review Board (IRB protocol number 11-0151).

3. Results

3.1. Clinical Phenotype. The patient is a two-year-old boy from a nonconsanguineous family of Chinese descent. At 3 months of age, he started presenting with progressive hair loss. Thickening of the skin on his knees developed at 6 months of age followed by progressive joint contractures and hyperpigmentation with sclerosis of the skin. By 1 year of age, his weight was reduced to below the 3rd percentile; he also developed stiffness and blunting of the fingertips. Osteoporosis was noted on radiographs. At 18 months of age, his head circumference, height, and weight were 50th, 25th, and below the 3rd percentiles, respectively. He was cognitively normal with physical restrictions related to joint contractures. He had striking alopecia, prominent scalp veins, limited jaw mobility, and dental crowding. His hands were small and contracted with bulbous distal tips and purplish discoloration over the extensor surfaces. Contractures were present in all major joints. His skin was diffusely thick. At 2 years of age, radiographs showed striking acroosteolysis in the clavicles, hands and feet, wormian bones, and osteopenia. His phenotype shared features of both MAD and HGPS (Figure 1). Molecular genetic testing was requested to make the molecular
diagnosis. Over time, the patient suffered continued growth failure with progressive skin thickening and stiffness that was partially relieved by topical pimecrolimus. He had a pathological fracture of his radius at the age of 3. Progressive acro-osteolysis of the jaw resulted in premature dental loss. Stamina has decreased.

3.2. Molecular Analysis. DNA sequencing revealed a homozygous c.1619T>C, p.M540T mutation in exon 10 of the LMNA gene in this patient (Figure 2(a)). Subsequent analysis of the parental samples revealed that the mother was a heterozygous carrier of the same mutation but the father was not (Figures 2(b) and 2(c)). This result was confirmed by repeat PCR/sequence analysis using different sets of PCR primers to rule out the possibility of an SNP interfering with PCR amplification. Nonpaternity was excluded by genotyping of 13 microsatellite markers across chromosomes 6 and 15 (data not shown). The presence of a deletion of one copy of the LMNA gene in the patient (which would make the p.M540T mutation appear homozygous) and the patient’s father was investigated by RT-qPCR of exon 10 of the LMNA gene and two copies of the gene were identified (data not shown).

In order to investigate whether uniparental disomy (UPD) involving chromosome 1 may be present in this patient, microsatellite analysis was performed using markers spanning chromosome 1, with increased density in the 1q22 region, where the LMNA gene resides. Analysis of 11 informative microsatellite markers showed that the genotype of the patient matched that of the mother with complete absence of the paternal chromosome 1, indicating maternal UPD (Figure 3(a)). Furthermore, the microsatellite data demonstrated that the proband has a minimal region of isodisomy between markers D1S498 and D1S3792, a 27.2 Mb segment in the 1q21.3–q22 region where LMNA is located, with the rest of chromosome 1 being heterodisomic (Figure 3(b)).

4. Discussion

MAD is a rare, autosomal recessive disorder with clinical manifestation involving skin, skeleton, and adipose tissue.
The pathogenesis of this rare disorder remains incompletely understood. The majority of MAD patients are caused by point mutations in the LMNA gene [6–8]. Patients with overlapping features of MAD and HGPS have also been reported with mutations in the LMNA gene [9–12]. In this study, we report a patient with MAD with clinical features, with some overlapping features of HGPS, who presented with a homozygous p.M540T mutation in the LMNA gene. This mutation has recently been identified in the compound heterozygous state with another missense mutation in a patient with HGPS in whom atypical pathological findings on fibroblast were observed [13]. The p.M540T mutation affects a conserved region within the C-terminal globular domain of A-type lamins and affects a highly evolutionarily conserved amino acid residue. The observation of this mutation in the homozygous state is the likely cause of the disease phenotype in this patient.

Subsequent analysis of the patient’s parents demonstrated only the patient’s mother to be a carrier of the p.M540T mutation and the presence of maternal UPD for chromosome 1 as the cause of the homozygosity in the patient. Previous studies have reported UPD as one of the causes leading to the homozygous mutations in several autosomal recessive disorders [14–17]. In fact, UPD involving the LMNA gene was identified in some of the first molecularly characterized patients with HGPS [18]. Our patient demonstrated isodisomy for the region encompassing the LMNA gene, flanked by heterodisomy. We speculate that during maternal meiosis two recombination events, proximal and distal to the LMNA gene, followed by nondisjunction resulted in a gamete with two copies of chromosome 1 both containing the p.M540T mutation. The further loss of paternal chromosome 1 through trisomy rescue after fertilization led to homozygosity of the p.M540T mutation in the patient (Figure 3(b)).

In conclusion, we have identified a patient with MAD and some overlapping features of HGPS in whom a homozygous p.M540T mutation in the LMNA gene was identified. The homozygosity of the LMNA mutation in this patient was due to maternal UPD of chromosome 1. While UPD involving the LMNA gene has previously been identified in patients with HGPS, our patient represents the first case of UPD1 concomitant with LMNA mutation in MAD. This observation adds to the growing list of autosomal recessive conditions where UPD contributes to the clinical phenotype.

Figure 3: Uniparental disomy analysis of chromosome 1 and schematic representation of the generation of the homozygous p.M540T mutation. (a) Markers around the region of the LMNA gene in 1q22 show maternal isodisomy. Allele sizes for each marker are indicated. Informative markers for maternal UPD are denoted with an asterisk (*). Based on the results, one recombination event could have occurred proximal to D1S89 at 1p31.1 and a second recombination event could have occurred proximal to D1S213 at 1q41 resulting in maternal isodisomy for the 1q21–q22 region where the LMNA resides. Due to the uninformative nature of markers D1S2747, D1S2696, D1S2635, and D1S249 in the mother, it is unclear whether these regions are isodisomic or heterodisomic. The uninformative markers are indicated with question marks. (b) Schematic representation of the generation of the homozygous p.M540T mutation in the patient by the process of recombination and nondisjunction in maternal meiosis followed by trisomy rescue. Nondisjunction is shown as occurring in meiosis II in this figure, but it could also have occurred in meiosis I; the microsatellite markers used could not distinguish between these two possibilities. The p.M540T mutation is indicated by the red bar on one of the maternal chromosome 1’s. Paternal chromosome 1 is indicated by the blue colored. LMNA gene is indicated by the red bar.
Abbreviations

MAD: Mandibuloacral dysplasia
HGPS: Hutchinson-Gilford Progeria Syndrome
UPD: Uniparental disomy.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution

Dr. Shaochun Bai designed and performed the study, drafted the initial paper, and reviewed the final paper as submitted. Mr. Anthony Lozada performed the sequence in the study. Dr. Marilyn C. Jones performed the clinical evaluation of the patient. Dr. Harry C. Dietz was involved in the initial identification of the mutation in this patient. Ms. Melissa Dempsey helped with the revision of the manuscript. Dr. Soma Das helped in designing the study, reviewing, revising and approving the final paper as submitted.

References
