Published in final edited form as:

Am J Med Genet A. 2018 May ; 176(5): 1175–1179. doi:10.1002/ajmg.a.38493.

Phenotypic Heterogeneity of ZMPSTE24 Deficiency

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Abstract

A 4 year old girl was referred to the Undiagnosed Diseases Network with a history of short stature, thin and translucent skin, macrocephaly, small hands, and camptodactyly. She had been diagnosed with possible Hallerman-Streiff syndrome. Her evaluation showed that she was mosaic for uniparental isodisomy of chromosome 1, which harbored a pathogenic c.1077dupT variant in *ZMPSTE24* which predicts p.(Leu362fsX18). *ZMPSTE24* is a zinc metalloproteinase that is involved in processing farnesylated proteins and pathogenic *ZMPSTE24* variants cause accumulation of abnormal farnesylated forms of prelamin A. This, in turn, causes a spectrum of disease severity which is based on enzyme activity. The current patient has an intermediate form, which is a genocopy of severe Progeria.

INTRODUCTION

Mutation in the *LMNA* gene is the most common cause of Hutchinson Gilford Progeria Syndrome (HGPS, OMIM # 176670), a disorder of premature aging. This gene encodes prelamin A, which undergoes post translational modification to lamin A, an important protein of the nuclear envelope. Damaging genetic changes that result in progeria cause impaired post translational modification and accumulation of abnormal prelamin A [Gonzalo 2017]. One of the enzymes involved in this pathway is *ZMPSTE24*, and mutations in the *ZMPSTE24* gene that interfere with enzyme function have also been shown to result in impaired post translational modification and accumulation of abnormal prelamin A causing a premature aging phenotype [Denecke et al 2006, Agarawal et al 2003].

Mutations in *ZMPSTE24* have been reported to cause a spectrum of phenotypes characterized by craniofacial, skeletal and skin abnormalities. This disease spectrum results from phenotypic heterogeneity of *ZMPSTE24* mutations which result in varying degrees of enzyme activity [Barrowman et al 2012]. Those with little to no enzyme activity have the most severe of these disorders which is Restrictive Dermopathy (RD, OMIM # 275210). Those with milder deficiency have the less severe disorder of Mandibuloacral Dysplasia with Type B Lipodystrophy (MADB, OMIM # 608612). Those with intermediate activity have an

intermediate disorder which is Atypical HGPS (aHGPS) (see Table). We report here a patient who had the intermediate aHGPS phenotype because of her mosaicism for uniparental isodisomy of chromosome 1, which harbored a *ZMPSTE24* pathogenic variant that was reduced to homozygosity.

CLINICAL REPORT

The patient described here was born at 35 weeks gestation and she was small for gestational age at 1644 g. Her neonatal course was uncomplicated but she was noted to have thin, peeling skin at the time of birth (Supplemental Figure. 1). Her head CT showed wide cranial sutures and a large fontanelle. Her karyotype was normal and her chromosomal microarray showed a 0.5 Mb 22q12.3 duplication that was determined to not be pathogenic. She was seen for further genetics evaluation at the age of 6 months and was noted to have short stature; a large anterior fontanelle and frontal bossing; small, down slanted palpebral fissures, a narrow nasal tip, and micrognathia. Her skin was thin and translucent with alopecia and she had prominent veins (Supplemental Figure. 1). Because her findings were felt to be too severe for HGPS, she was diagnosed as having probable Hallerman-Strieff syndrome. She underwent sequencing of *LMNA*, which was negative.

At 4 years of age she was referred to the Undiagnosed Diseases Network (UDN). She was enrolled at the Vanderbilt clinical site, and her mother consented to the study (IRB protocol NHGRI 15-HG0130) before any study procedures were performed. Her UDN exome sequencing (ES) identified mosaicism for a c.1077dupT pathogenic variant (GenBank NM_005857.4) in the *ZMPSTE24* gene, which predicts a p.(L362fsX18) protein change (Figure. 1 A). Her mother was found to be heterozygous for this mutation and her father did not carry any identified pathogenic variants in this gene. The patient's ES also had significant loss of heterozygosity (LOH) throughout chromosome 1 (Figure. 1 B) and the specific c.1077dupT mutation in *ZMPSTE24* was found in approximately 83% of ES reads. This ratio is in agreement with the great excess of mutant compared to normal alleles that is seen in the Sanger confirmation sequencing (Figure. 1 A). Based on her genotype and the severity of her phenotype she was diagnosed with aHGPS.

Following her UDN evaluation at age 4 years, she was seen again in genetics clinic. She had had a fracture of her left forearm following a fall to the floor in the interim. She continued to have growth failure with a height of 79.1 cm and a weight of 8.8 kg, both less than the 3rd centile. She had decay of her maxillary anterior teeth, but no other dental abnormalities. She had right fifth finger clinodactyly and bilateral third finger camptodactyly. A skeletal survey showed open anterior and posterior fontanelles, acroosteolysis of her distal phalanges, and mild lumbar scoliosis (Supplemental Figure 1). Her clavicles were normally formed and bone mineralization was normal. Laboratory evaluation included a normal creatinine of 0.43 (normal range 0.38–0.54). Her lipid panel showed total cholesterol of 178 (normal range <200), triglycerides of 56 (normal range <150), HDL of 52 (normal range >50) and a calculated LDL of 115 (normal range 1–129). Her blood glucose was normal at 75 (normal range 60–99). She was started on combined treatment with pravastatin and zoledronate at her follow up clinic visit. These FDA approved medications are being used as a part of her routine clinical care.

DISCUSSION

Uniparental isodisomy refers to the inheritance of two identical chromosomes from a single parent, as opposed to heterodisomy in which two homologous chromosomes are inherited from one parent. The extensive LOH found throughout, but limited to, chromosome 1 supports the conclusion that her variant arose from uniparental isodisomy of this chromosome. Isodisomy arises from a non-disjunction event which can occur in meiosis II or later, including post-zygotic changes. Uniparental isodisomy resulting in homozygosity for *LMNA* mutations has previously been demonstrated as a mechanism that causes HGPS [Starke et al 2013, Bai et al 2014]. This is the first reported patient with aHGPS due to *ZMPSTE24* mutation that has been demonstrated to be caused by uniparental isodisomy.

Another unique aspect of this patient is her mosaicism for the uniparental isodisomy which results in an estimated 83% of her reads showing the pathogenic *ZMPSTE24* mutation (Figure 1). The 17% reference sequence allele, which arises from the paternal chromosome, leads to the conclusion that 34% of her cells have typical disomy with a paternal chromosome and maternal chromosome, whereas the remaining 66% of cells carry two maternal chromosomes. There are two possible mechanisms for her mosaicism. In the first the non-disjunction event occurring during meiosis, with subsequent fertilization resulting in a zygote with trisomy of chromosome one, consisting of two maternal chromosomes and one parental chromosome. Two trisomy rescue events would be necessary. One would result in loss of a maternal chromosome resulting in the 34% of typical diploid cells with a maternal and paternal chromosome, and the other would result in loss of the paternal chromosome resulting in the 66% of uniparental iso-disomy cells. In the second mechanism fertilization results in a typical diploid cell with a maternal and paternal chromosome one. Subsequently a non-disjunction event occurs in mitosis during early embryogenesis which results in a cell with trisomy of chromosome 1 with two identical copies of the maternal chromosome and one paternal chromosome. Trisomy rescue by loss of the paternal chromosome results in retention of two identical maternal chromosome ones remaining resulting in the 66% of uniparental iso-disomy cells.

Homozygous p.(L362fsX18) has been reported in multiple patients with RD who usually died within the first week of life (Table). It has previously been demonstrated that the severity of disease with *ZMPSTE24* mutations inversely correlates with the residual enzyme activity and this protein change has been demonstrated *in vitro* to result in a form of the enzyme that completely lacks activity [Barrowman et al 2012]. The 34% of her cells that are estimated to be heterozygous for a normal allele should have adequate enzymatic function as evidenced by her heterozygous mother's normal phenotype. It is likely that residual enzyme activity in these cells resulted in her survival, albeit with a severe phenotype.

The enzymatic pathway of lamin A synthesis involves attachment of a farnesyl group to prelamin A, which is necessary for cleavage by the *ZMPSTE24* enzyme. This makes inhibition of the farnesylation step a logical target for treatment. The substrate for these enzymatic reactions, farnesyl pyrophosphate, is an intermediate in cholesterol biosynthesis [Yang et al 2010]. Several steps of the synthesis proceeding the generation of farnesyl pyrophosphate are inhibited by statins and bisphosphonates. There are both *in vitro* and *in*

vivo data from mouse models that combined treatment with statins and bisphosphonates can ameliorate the phenotype seen in *Zmpste24*^{-/-} mice [Varela et al 2008]. There is a report of a patient who was treated with pamidronate, and bone loss accelerated following withdrawal of this medication. No other improvement in clinical outcomes, particularly in the acroosteolysis or cortical bone density, was noted [Cunningham 2010]. It was based on these results, the skeletal findings, and the history of fracture in the patient reported here, that she was started on treatment with a statin and a bisphosphonate.

In conclusion, we report a 4 year old girl with a severe aHGPS phenotype who is mosaic for a *ZMPSTE24* c.1077dupT mutation which predicts p.(Leu326 fsX18), which typically causes the lethal RD phenotype. Interestingly, the present patient is predicted to have a pathogenic mutation in most cells. We conclude that her mosaicism resulted from uniparental isodisomy. Pathogenic *ZMPSTE24* variants can cause accumulation of farnesylated forms of prelamin A, which, in turn, causes MADB, which is a genocopy of severe Progeria. Given the data demonstrating potential benefit of statins and bisphosphonates the patient described here was started on a trial of pravastatin and zoledronate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful to the patient and her family for participating in the UDN. This work was supported in part by the NIH Common Fund, NIH/NHGRI grant UO1HG007674 [JAP, JHN and RH]

Consortia: Collaborators of the Undiagnosed Diseases Network [UDN] include Christopher J. Adams, David R. Adams, Mercedes E. Alejandro, Patrick Allard, Euan A. Ashley, Mashid S. Azamian, Carlos A. Bacino, Ashok Balasubramanyam, Hayk Barseghyan, Alan H. Beggs, Hugo J. Bellen, Jonathan A. Bernstein, David P. Bick, Camille L. Birch, Braden E. Boone, Bret L. Bostwick, Lauren C. Briere, Donna M. Brown, Matthew Brush, Elizabeth A. Burke, Lindsay C. Burrage, Katherine R. Chao, Shan Chen, Gary D. Clark, Cynthia M. Cooper, William J. Craigen, Mariska Davids, Jyoti G. Dayal, Esteban C. Dell'Angelica, Shweta U. Dhar, Katrina M. Dipple, Laurel A. Donnell-Fink, Naghmeh Dorrani, Daniel C. Dorset, David D. Draper, Annika M. Dries, David J. Eckstein, Lisa T. Emrick, Christine M. Eng, Cecilia Esteves, Tyra Estwick, Paul G. Fisher, Trevor S. Frisby, Kate Frost, William A. Gahl, Valerie Gartner, Rena A. Godfrey, Mitchell Goheen, Gretchen A. Golas, David B. Goldstein, Mary G. Gordon, Sarah E. Gould, Jean-Philippe F. Gourdine, Brett H. Graham, Catherine A. Groden, Andrea L. Gropman, Mary E. Hackbarth, Melissa Haendel, Neil A. Hanchard, Lori H. Handley, Isabel Hardee, Matthew R. Herzog, Ingrid A. Holm, Ellen M. Howerton, Howard J. Jacob, Mahim Jain, Yong-hui Jiang, Jean M. Johnston, Angela L. Jones, Alanna E. Koehler, David M. Koeller, Isaac S. Kohane, Jennefer N. Kohler, Donna M. Krasnewich, Elizabeth L. Krieg, Joel B. Krier, Jennifer E. Kyle, Seema R. Lalani, Lea Latham, Yvonne L. Latour, C. Christopher Lau, Jozef Lazar, Brendan H. Lee, Hane Lee Paul R. Lee, Shawn E. Levy, Denise J. Levy, Richard A. Lewis, Adam P. Liebendorfer, Sharyn A. Lincoln, Joseph Loscalzo, Richard L. Maas, Ellen F. Macnamara, Calum A. MacRae, Valerie V. Maduro, May Christine V. Malicdan, Laura A. Mamounas, Teri A. Manolio, Thomas C. Markello, Paul Mazur, Alexandra J. McCarty, Allyn McConkie-Rosell, Alexa T. McCray, Thomas O. Metz, Matthew Might, Paolo M. Moretti, John J. Mulvihill, Jennifer L. Murphy, Donna M. Muzny, Michele E. Nehrebecky, Stan F. Nelson, J. Scott Newberry, Sarah K. Nicholas, Donna Novacic, Jordan S. Orange, J. Carl Pallais, Christina GS. Palmer, Jeanette C. Papp, Loren DM. Pena, Jennifer E. Posey, John H. Postlethwait, Lorraine Potocki, Barbara N. Pusey, Rachel B. Ramoni, Lance H. Rodan, Jill A. Rosenfeld, Sarah Sadozai, Susan L. Samson, Katherine E. Schaffer, Kelly Schoch, Molly C. Schroeder, Daryl A. Scott, Prashant Sharma, Vandana Shashi, Edwin K. Silverman, Janet S. Sinsheimer, Ariane G. Soldatos, Rebecca C. Spillmann, Kimberly Splinter, Joan M. Stoler, Nicholas Stong, Kimberly A. Strong, Jennifer A. Sullivan, David A. Sweetser, Sara P. Thomas, Cynthia J. Tifft, Nathaniel J. Tolman, Camilo Toro, Alyssa A. Tran, Tiina K. Urv, Zaheer M. Valivullah, Eric Vilain, Tiphane P. Vogel, Daryl M. Waggott, Colleen E. Wahl, Nicole M. Walley, Chris A. Walsh, Michael F. Wangler, Mike Warburton, Patricia A. Ward, Katrina M. Waters, Bobbie-Jo M. Webb-Robertson, Alec A. Weech, Monte

Westerfield, Matthew T. Wheeler, Anastasia L. Wise, Lynne A. Wolfe, Elizabeth A. Worthey, Shinya Yamamoto, Yaping Yang, Guoyun Yu, Jing Zhang and Patricia A. Zornio.

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Figure 1.

A. Sanger sequencing of *ZMPSTE24* showing normal and c.1077dupT p.(L362fs18X) pathogenic variant indicated by the blue arrow.

B. Quantitation of heterozygosity (blue) vs. homozygosity (yellow) for different chromosomes derived from whole exome sequencing reads. Note high homozygosity for chromosome 1 which includes *ZMPSTE24*.

Table

Comparison of clinical features of patients with MADB or aHGPS phenotype and Restrictive Dermopathy due to homozygous c.1077dupT mutation

	MADB or aHGPS phenotype	RD with homozygous c.1077dupT p.(L362fs18X) mutation	Current patient
Premature birth	8/11 (73%)	11/12 (92%)	Yes
Growth failure	11/11 (100%)	N/A	Yes
Delayed closure of fontanelle	8/11 (73%)	9/12 (75%)	Yes
Dysmorphic features: small and narrow nose, micrognathia	10/11 (91%)	N/A	Yes
Dysmorphic features: microtia, down slanting palpebral fissures, microstomia	N/A	11/12 (92%)	No
Clavicle hypoplasia	9/11 (82%)	4/12 (33%)	No
Acroostolysis	8/11 (73%)	0/12 (0%)	Yes
Joint contractures	8/11 (73%)	9/12 (75%)	No
Thin, translucent skin	9/11 (82%)	11/12 (92%)	Yes
Type B Lipodystrophy	9/11 (82%)	0/12 (0%)	Yes
Renal disease	2/11 (18%)	N/A	No
Neonatal Death	0/11 (0%)	9/12 (75%)	No

MADB: mandibuloacral dysplasia with type B lipodystrophy, aHGPS: atypical Hutchinson Gilford Progeria Syndrome, RD: lethal restrictive dermopathy