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Biallelic Loss of Function Variants in *SENP7* Cause Immunodeficiency with Neurologic and Muscular Phenotypes

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Author Contribution Statement

ESK and NR wrote the manuscript. JC, IT, EF, NSL, YDS, NRi, VM, MW, and SK coordinated samples, enrolled the patients, established clinical records, and sequencing data collection. . MNB analyzed the genome sequencing results that identified the potential variant. All authors revised and edited the manuscript.

Disclosure of Conflicts of Interest

MNB is the founder of Codified Genomics, LLC. The remaining authors declare no competing interests.

Study approval

The patient and family in Family 1 were enrolled into a study approved by the Institutional Review Board (IRB) at Children's Mercy—Kansas City and conducted in accordance with the Declaration of Helsinki. Written informed consents were obtained from the parents. For Family 2, signed parental consent for publication was obtained in accordance with Hadassah Hebrew University Hospital policy. The patient and family in Family 3 were enrolled in a study approved by the Institutional Review Board (IRB) at the Technical University Munch and conducted in accordance with the Declaration of Helsinki.

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Abstract

To evaluate a novel candidate disease gene, we engaged international collaborators and identified rare, biallelic, specifically homozygous, loss of function variants in *SENP7* in four children from three unrelated families presenting with neurodevelopmental abnormalities, dysmorphism, and immunodeficiency. Their clinical presentations were characterized by hypogammaglobulinemia, intermittent neutropenia, and ultimately death in infancy for all four patients. SENP7 is a sentrin-specific protease involved in posttranslational modification of proteins essential for cell regulation, via a process referred to as deSUMOylation. We propose that deficiency of deSUMOylation may represent a novel mechanism of primary immunodeficiency.

Keywords

genome sequencing; exome sequencing; immunodeficiency; inborn error of immunity; SUMOylation; deSUMOylation

Primary immunodeficiencies, or inborn errors of immunity (IEI), are an increasingly appreciated heterogeneous group of diseases that predispose infants and children to infection, as well as autoimmune disorders and malignancies.[1] Early identification of these disorders is imperative as there can be significant associated morbidity and mortality. With the advent of massively parallel sequencing, novel IEIs are being discovered annually.[1]. The identification of novel genetic causes of IEIs can simultaneously facilitate an increase in our collective understanding of the underlying mechanisms and pathways of the immune system. In other words, discovery of a novel IEI gene in an affected patient can potentially enable us to work “backwards” to then uncover a new cellular pathway essential to human immunology.

Immune regulation requires well-orchestrated protein regulation. Posttranslational modification of proteins through the attachment of a small ubiquitin-like modifier (SUMO) protein, a process referred to as SUMOylation, can modulate the function and localization of the target protein, affecting many cellular systems including transcription and DNA binding, repair and replication.[2–7] In particular, SUMO proteins have been widely implicated in the development and maintenance of the host immune system.[8] Cell harmony is maintained by balancing SUMOylation with the reverse process, SUMO deconjugation (deSUMOylation), whereby SUMO is removed from a substrate through the action of one of six sentrin-specific proteases (SENPs 1–3 and 5–7).[9–11] DeSUMOylation by SENPs has been shown to likewise be essential for cell development and activity.[12]

The actions of SENPs have wide-ranging essential effects on cellular activities, perhaps most well-demonstrated thus far in neuronal and hematologic developmental processes. Neuronal differentiation is associated with a net SUMO deconjugation balance, with an overall decrease in SUMOylation seen in during rodent brain development.[4] Additionally, several SENPs have been shown to be increased in subsets of cancer.[11] SENP5 in particular is required for a number of deSUMOylation processes, and its impairment has

a significant impact on both neuronal and neutrophil differentiation.[4] Di Bacco et al showed that knockdown of SENP5 resulted in decreased cell proliferation and abnormal nuclear morphology, consistent with an essential role in mitosis and cytokinesis that has been demonstrated by other groups.[2,10,11] More recently, SENP5 has been demonstrated to play a role in the neutrophil differentiation of leukemic cells, with inhibition of SENP5 expression in AML cell lines resulting in significantly attenuated neutrophil differentiation.[13]

SENP7 encodes a specialized chain-editing enzyme with ubiquitous expression in human tissues[14–16], and promotes stable heterochromatin structure during mitosis.[17] SENP7-mediated deSUMOylation is necessary for sarcomere organization, and deficiency of SENP7 has been shown to result in incompetent chromatin conformation.[18] SENP7 has been shown to be a key regulator of neuronal differentiation, DNA damage detection, and homologous recombination repair.[4,12,14] More recently, Senp7 has been reported to be a regulator of lipid homeostasis in mice.[19] In the innate immune system, SENP7 has a role in both the activation process of the NLRP3 inflammasome and of STING.[20,21] In the adaptive immune system, SENP7 is responsible for PTEN degradation in response to oxidative stress, thus maintaining the metabolic fitness and effector function of CD8+ cells in the tumor microenvironment.[22]

Recently, *SENP7* was implicated in human disease in a single consanguineous family with four affected infants born to unaffected parents.[23] The clinical presentation of those affected infants included congenital arthrogryposis, developmental delay, neutropenia, recurrent infections, respiratory failure, and death in early infancy (under 4 months of age).[23] Exome sequencing determined that all four affected siblings shared a homozygous stop-gain mutation in *SENP7* (c.1474C>T; p.Gln492*), thus, *SENP7* was suggested as a potential candidate disease gene.[23]

Herein we report a multisystemic disorder caused by biallelic- that is homozygous, or compound heterozygous- loss of function mutations in gene encoding SENP7, encompassing hypogammaglobulinemia, neutropenia, recurrent infection, neurologic features, and uniform early fatality. We describe four infants from three unrelated families, all of whom died prior to their first birthday, in whom we identified unique germline autosomal recessive stop-gain mutations in *SENP7*. Our three affected families share phenotypic overlap with the family described by Samra et al[23], and the mechanism in all cases was a loss of function of the SENP7 protein. Taken together, these findings support a novel gene-disease association and indicate that biallelic loss of function mutations in *SENP7* cause a previously unrecognized inborn error of immunity with syndromic features. Furthermore, identification of this IEI implicates deSUMOylation as an essential process in normal development of the human immune system.

Methods

Written informed consent was provided by the parents for all three families. Illumina (HiSeq2000) whole genome sequencing (WGS) was performed on the proband, affected sibling and their parents as previously described.[24] Reads were aligned to the human reference genome (hg19) and variants called by the DRAGEN platform (v2.1). Variants were annotated by CASSANDRA[25] and prioritized based on inheritance, predicted pathogenicity

of the variant and known gene function. We established an international collaboration via Genematcher[26] and located two additional unrelated, affected patients with similar genotype and phenotype (Figure 1B; Table I). Singleton exome sequencing was performed on patient F2-II-1, followed by Sanger sequencing of both parents to confirm heterozygosity in the parents (Supplemental Methods). Patient-parent trio exome sequencing (WES) was performed within a national framework for patients with ultra-rare disorders for individual F3-II-1 using Twist Human Exome 2.0 Plus kits with comprehensive exome and mitochondrial DNA spike-ins. Sequencing was performed on a NovaSeq6000 platform (Illumina). (Supplemental Methods).

Results

Genome-wide sequencing (WGS or WES) was performed on each patient and their parents, by three separate institutions following their own protocols.[24] In all patients, homozygous stop-gain (truncating) variants were identified in the gene *SENP7* (Figure 1A and 1B). *SENP7* was independently considered a strong candidate disease gene by each group owing to its transcript function, expression in affected organ systems, and the intolerance of the gene to homozygous loss of function variants in the population.[27] *SENP7* contains fewer loss of function variants than expected by chance in a healthy population and no other reports of homozygous LoF (loss of function) mutations in this gene exist in the literature or in Genematcher.[26,27]

Clinical review of the patients' records showed strong, overlapping phenotypes, as well as significant phenotypic overlap with the family described by Samra et al (Table I).[23] All patients were born to consanguineous parents of diverse ethnicities (Figure 1A, Table I). Pregnancy was uncomplicated for the majority of families, with the exception of premature birth at 32 weeks' gestational age for the sibling in Family 1. The other three affected children were born at term, with two requiring cesarean section for non-reassuring fetal heart rate tracings. All four infants required admission to the neonatal intensive care unit (NICU) at birth for respiratory failure necessitating endotracheal intubation. All four were found to have hypogammaglobinemia and suffered from recurrent infections despite receiving intravenous immunoglobulin (IVIG) replacement. There was no report of quantitative immunoglobulin levels in Samra et al's family[23], thus it is presently not clear if hypo/agammaglobulinemia is a universally shared finding for all patients with loss of function mutations in *SENP7* (Table I, Supplemental Table 2). Three of the four infants (Families 1 and 2) were also noted to have varying levels of neutropenia that were clinically refractory to treatment with granulocyte colony stimulating factor (G-CSF). Likewise, two of the three affected infants described by Samra et al also displayed congenital neutropenia that was not clinically affected by receiving G-CSF (Table 1).[23] In addition to the immunologic and hematologic abnormalities, all patients displayed a severe neurologic phenotype manifested by limb hypertonia (4/4 infants, Table I), arthrogryposis of the upper extremities (2/4), seizures (3/4), global developmental delay (4/4), and failure to thrive necessitating place of a surgical feeding tube (4/4). Despite cardiorespiratory support, broad-spectrum antibiotics, G-CSF (2/4), and immunoglobulin replacement therapy (3/4), all patients died between the ages of 5 and 9.5 months. Detailed clinical courses are provided for each of the four patients in the Supplemental Material.

Discussion

We describe four patients from three unrelated families found to have homozygous loss of function mutations in *SENP7*, manifesting clinically as a universally fatal inborn error of immunity with multisystemic features. A homozygous stop-gain variant in *SENP7* was recently independently identified as a potential disease candidate in a single consanguineous family with strikingly overlapping features to the three affected families presented here, most notably neurodevelopmental abnormalities, neutropenia, immunodeficiency, and without exception, death in infancy.[23] Collectively, these data suggest that biallelic loss of function mutations in *SENP7* cause a previously unrecognized inborn error of immunity with syndromic features.

Identification of this IEI implicates the process of deSUMOylation as essential for the normal development of the human immune system. DeSUMOylation, in which the small ubiquitin-like modifier (SUMO) protein is removed from a substrate, is necessary for cell homeostasis, and is facilitated by SENPs.[9–12] The known wide-ranging essential effects of SENPs on cellular activities have previously been best demonstrated *in vitro* in the neuronal and hematological developmental processes[4], and notably, our patients were the most clinically affected in these two systems. All patients displayed hypogammaglobulinemia, but despite treatment with antibiotics and immunoglobulin replacement therapy, all of the patients died in infancy. Similarly, the affected infants in the family reported by Samra et al also died in infancy despite treatment with antibiotics (3/3) and G-CSF (2/3).[23] Overlapping phenotypic features between the seven described patients in total included respiratory failure shortly after birth, limb hypertonia, failure to thrive, and dysmorphic facies.[23]

SENP7 has been demonstrated to be a regulator of DNA repair and mitosis and is required for homologous recombination, resistance to DNA damaging agents, and chromatin relaxation in DNA damage response.[14] Mutations in DNA repair genes (e.g., Artemis, DNA ligase IV) have been shown to result in severe combined immunodeficiency (SCID).[28,29] The established role of SENP7 as a known modulator of DNA repair[14] postulates a reasonable mechanism for the hypogammaglobulinemia observed in all four of the patients presented here.

All four patients clinically were severely affected by viral disease (Supplemental Table 2). SENP7 acts to suppress viral replication through regulation of CHD3, IRF3 and KAP1.[21] Both IRF3 and CHD3 are involved in HSV-1 repression, and *Senp7* KO mice have impaired viral DNA sensing and were more susceptible to herpes simplex virus (HSV-1) infection.[21] This posits a plausible mechanism for the severe viral infections in our described patients.

In summary, we describe a novel IEI caused by loss of function mutations in *SENP7*, leading to pleotropic immune defects, and we present these three families as early examples of human disease caused by deSUMOylation defects. Given the many essential roles that deSUMOylation plays in cell homeostasis[12], the severe multisystemic disease observed in our patients with loss of function mutations in *SENP7* is reckonable. More studies of the wide-ranging effects of SENP7 knockdown in both cell lines and animal models will be

necessary to comprehensively delineate its role in immune system function, in the context of its wide-ranging interactions in various cell activities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Sequencing data supporting the findings of this study are available upon reasonable request. CASSANDRA is available from https://www.hgsc.bcm.edu/software.

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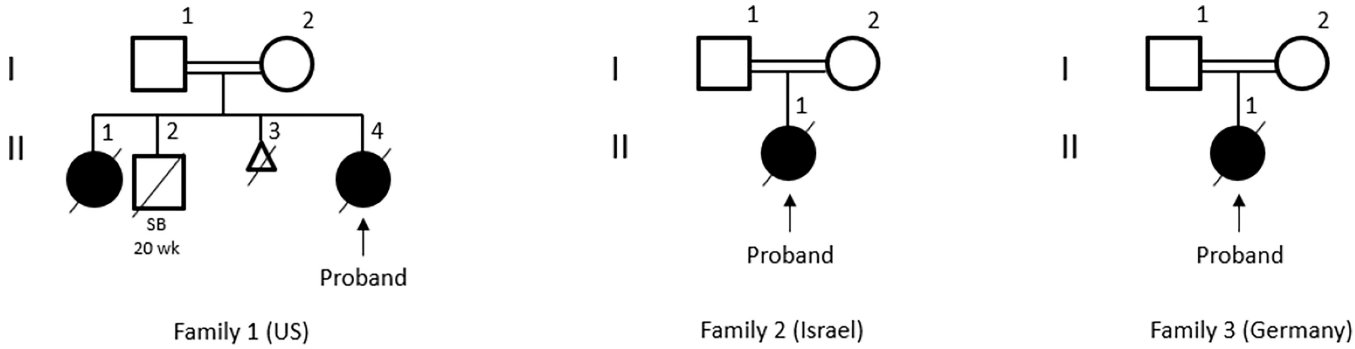

Family	Gene	Genomic location (hg19)	Transcript	HGVS cDNA	HGVS Protein	MAF	Zygosity
1	*SENP7*	chr3:101050886G>A	NM_020654.5	c.2641C>T	p.Q881X	0	Homozygous
2	*SENP7*	chr3:101086772C>A	NM_020654.5	c.880G>T	p.E294X	0	Homozygous
3	*SENP7*	chr3:101086679G>A	NM_020654.5	c.973C>T	p.Q325X	0	Homozygous
Samra et al	*SENP7*	Not provided	Not provided	c.1474C>T	p.Q492X	Not provided	Homozygous

Figure 1.

A) Family pedigrees; B) Variant information

MAF: minor allele frequency

Table 1.

Features of 4 patients with homozygous loss of function mutations in *SENP7* and 3 previously reported patients from the Samra et al 2023 family[23]

	Patient (F1-II-4)	Sibling (F1-II-1)	Patient (F2-II-1)	Patient (F3-II-1)	Samra et al patient III-4	Samra et al patient III-3	Samra et al patient III-7
Demographics							
Gestational age (weeks)	37	32	37+3	38	34	34	42
Sex	F	F	F	F	M	F	M
Race/Ethnicity	Guatemalan	Guatemalan	Arab	Turkish	Unk	Unk	Unk
Pregnancy	n/a	PPROM ****	n/a	n/a	n/a	n/a	n/a
Method of delivery	C/S * for NRFHT **	Unk	C/S	C/S * for NRFHT **	C/S * for breech and fetal distress	C/S * for breech and fetal distress	NSVD
NICU admission (y/n)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clinical Features -immunologic							
Congenital/neonatal neutropenia	Yes	Yes	Yes (neonatal)	No	Yes (neonatal)	No	Yes
Hypogammaglobulinemia	Yes	Yes	Yes	Yes	Unk	Unk	Unk
Recurrent infections	Yes	Yes	Yes	Yes	Yes	No	Yes
Infection/Immune-related therapies attempted	Antibiotics, GCSF ***	Antibiotics, GCSF ***, IVIG/ SCIG *****	Antibiotics, IVIG/ SCIG *****	Antibiotics, antiviral therapy, IVIG/ SCIG *****	Antibiotics, GCSF ***	No	Antibiotics
Clinical Features- nonimmune							
Cardiac arrest	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Respiratory failure	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Microcephaly	No	Yes	No	No	No	No	Yes
Limb hypertonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Seizures	No	Yes	Yes	Yes	Unk	Unk	Unk
Neuroimaging	MRI brain 1mo: prominent extra-axial fluid spaces, otherwise normal	MRI brain 5mo: normal	CT head: hydrocephalus, Dandy Walker Malformation	MRI brain 9mo: normal	MRI brain neonatal: delayed myelination, symmetric white matter hyperintensities in basal ganglia and periventricular	Unk	Unk
Clinically significant cardiac defects	No(PFO)	No	No (2 ASDs)	No	No	No (bicuspid aortic valve)	No
Microretrognathia	Yes	Unk	No	Yes	No	Yes	Yes
Single palmar crease	Yes	No	Yes	No	No	No	Yes
Low set ears	No	Yes	Yes	Yes	No	No	Yes

	Patient (F1-II-4)	Sibling (F1-II-1)	Patient (F2-II-1)	Patient (F3-II-1)	Samra et al patient III-4	Samra et al patient III-3	Samra et al patient III-7
Camptodactyly of fingers	Yes	No	Yes	No	Unk	Unk	Unk
Hypoplastic thumbs	Yes	No	Yes (left)	No	Unk	Unk	Unk
Arthrogryposis	No	Yes- upper extremities	Yes- upper extremities	Unk	Yes-upper extremities	Yes-upper and lower extremities	Yes-upper and lower extremities
Hypothyroidism	Yes	Yes	Yes (subclinical)	No	Unk	Unk	Unk
Failure to thrive	Yes	Yes	Yes	Yes	Yes	Yes	Yes
G tube for feeding	Yes	Yes	Yes	Yes (J-tube)	No	Nasogastric tube	Nasogastric tube
Death in infancy	Yes (5mo)	Yes (8.5mo)	Yes (9.5mo)	Yes (9mo)	Yes (<4mo)	Yes (<4mo)	Yes (<4mo)

* C/S = Cesarian section

** NRFHT = non-reassuring fetal heart rate tracing

*** GCSF = granulocyte colony stimulating factor

**** PPROM = preterm premature rupture of membranes

***** IVIG = intravenous immunoglobulin, SCIG = subcutaneous immunoglobulin