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Does It Run in Your Family? Inherited Truncating *PSMD12* Variants Broaden the Phenotypic Spectrum of Stankiewicz-Isidor Syndrome

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ABSTRACT

Alteration in the ubiquitin-proteasome system results in human disorders with neurological and/or autoinflammatory presentation. Haploinsufficiency of *PSMD12*, which encodes a subunit of the core component of the proteasome, causes Stankiewicz-Isidor syndrome (STISS), characterized by intellectual disability, autism spectrum disorder, craniofacial dysmorphisms, with or without other congenital anomalies, and autoinflammation. We described six patients (four adults) from two unrelated families carrying a known p.(Arg289*) or a novel p.(Tyr111*) *PSMD12* variant. Portraying a completely penetrant condition with inter- and intra-familiar clinical variability, all individuals presented with developmental delay, intellectual disability, craniofacial, and skeletal anomalies. Novel findings in our cohort included unilateral ectopic fingernail, cholesteatoma, oligodontia, and the occurrence of an ovarian teratoma. Most subjects had acne, short stature, and developed obesity since late childhood. Eating behavior was reported. Good sociality and behavioral concern emerged as well. None presented clinical manifestations of autoinflammation and the detected IFN-I signature perturbations were not specific. Together with a complete literature review, we expanded the clinical spectrum of STISS, highlighting the relevance of inherited variants, and discussing challenges in diagnosis and management. We finally consider the intriguing role of *PSMD12* in human development and propose to index "onychoheterotopia" among the Human Phenotype Ontology terms.

1 | Introduction

High-throughput technologies significantly contributed to improve the diagnostics of neurodevelopmental disorders (NDDs). Proband-parent trios sequenced by exome (ES) or genome (GS) followed by filtering for *de novo*, X-linked or biallelic variants has proven to be a powerful strategy in the diagnostic pathway of these conditions (Martin et al. 2018; Sahin and Sur 2015). With more than 4000 genes associated with NDDs, most pathogenic variants occur *de novo*, involve exons, and, in half cases, disrupt the gene function (Deciphering Developmental Disorders Study 2017). Among familial NDDs, the most frequent models of inheritance are either X-linked or autosomal recessive, with rare inherited autosomal dominant (IAD) NDDs. Generally, the

interpretation of molecular data in IAD NDDs is challenging, due to incomplete penetrance, clinical variability with mild manifestations, and parental mosaicism.

The disruption of genes—such as *UBE3A*, *UBE3B*, *HUWE1*, *USP7*, *USP9X*, and *PSMD12*—interacting in the ubiquitin-proteasome system (UPS) pathway for the regulation of cellular homeostasis through degradation of intracellular ubiquitin-conjugated proteins results in a host of heterogenous NDDs (Ebstein et al. 2021) (Supporting Information, Figure 1). *PSMD12* (OMIM *604450) encodes for a regulator component of the 26S proteasome complex, which is a marker of ubiquitination targeting proteins intended for degradation. Heterozygous loss-of-function *PSMD12* variants and *PSMD12* deletions are associated with "Stankiewicz-Isidor syndrome" (STISS) (OMIM #617516), characterized by delayed psychomotor development, intellectual disability (ID), autism spectrum disorder (ASD), behavior anomalies, craniofacial dysmorphisms, and variable congenital anomalies (Küry et al. 2017). In some cases, the disruption of *PSMD12* function has been related to autoinflammation and a type I interferon (IFN-I) signature (Isidor et al. 2022; Yan et al. 2022).

We report six individuals including four adults from two unrelated families exhibiting a syndromic NDD, with a known (c.865C>T; p.(Arg289*)) or a novel (c.333T>G; p.(Tyr111*)) nonsense variant in *PSMD12*. Together with the complete literature review, we stress the inheritance of *PSMD12* variants and expand the STISS spectrum phenotype by: (a) describing different medical histories, (b) reporting novel clinical signs, (c) documenting heterogenous IFN-I alterations without clinical signs of inflammation, and (d) highlighting complete penetrance with inter- and intra-familial clinical variability of this condition. Accounting onycoheterotopia among congenital anomalies in *PSMD12*-related spectrum, we finally propose to index the term among the ontology of human phenotypic abnormalities.

2 | Methods

2.1 | Patients' Enrollment and Clinical Evaluation

Patients have been referred and evaluated at the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy.

2.2 | Molecular Analysis

Sample collection and processing; data analysis, variant filtering, prioritization, and interpretation were performed as summarized in the Supporting Information (See Data S1). Confirmation and segregation analysis of variants were performed by Sanger sequencing.

2.3 | Quantification of the Interferon Score (IS)

Sample collection, processing, and analysis were performed as summarized in the Supporting Information (See Data S1).

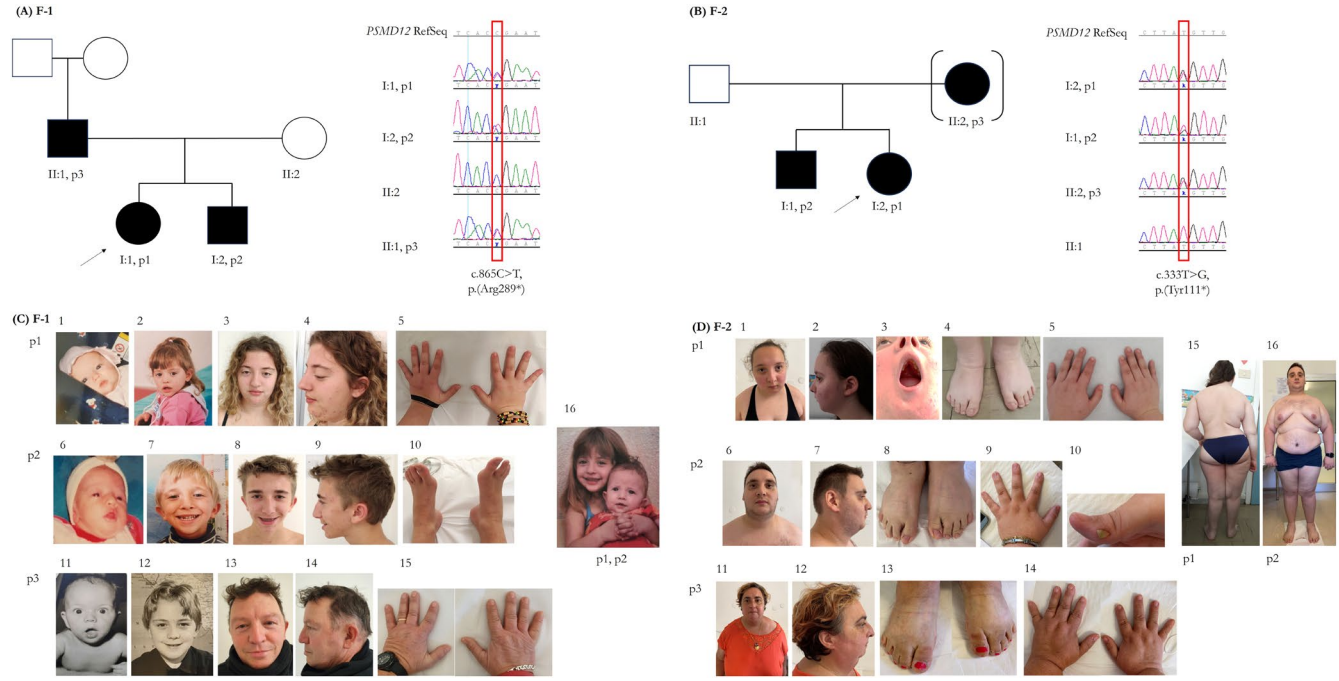

FIGURE 1 | Pedigrees and clinical pictures of affected individuals from both families. (A) Pedigrees and electropherograms of F-1; (B) Pedigrees and electropherograms of F-2; genotypes for *PSMD12* are indicated in the pedigree. Variants showed in the electropherograms correspond to: c.865C>T, p.(Arg289*) and c.333T>G, p.(Tyr111*); *PSMD12* gene (NM_002816.3); (C) Photos of the affected individuals from F-1: 1. p1, newborn; 2. p1, child; 3. p1, adolescence; 4. p1, adolescence; 5. p1 hands; 6. p2, newborn; 7. p2, child; 8. p2, adolescence; 9. p2, adolescence; 10. p2 feet; 11. p3, newborn; 12. p3, child; 13. p3, adult; 14. p3, adult; 15. p3 hands; 16: p1 and p2, childhood. (D) Photos of the affected individuals from F-2: 1. p1, child; 2. p1, child; 3. p1 oral cavity and palate; 4. p1 feet; 5. p1 hands; 6. p2, adult; 7. p2, adult; 8. p2 feet; 9. p2 hands; 10. p2 right thumb with ectopic fingernail; 11. p3, adult; 12. p3, adult; 13. p3 feet; 14. p3 hands; 15. p1 back; 16: p2 front. (F-1 for Family 1; F-2 for Family 2; p for probands).

2.4 | Literature Review

We searched MEDLINE (PubMed) with the keywords UPS, NDD, or STISS in combination with germline *PSMD12*. Articles written in English and published until July 2024 were included. Only cases with a confirmed molecular diagnosis were included.

3 | Results

3.1 | Molecular Findings

Quartet (parents and two affected siblings) family 1 (F1) WES analysis identified the heterozygous nonsense variant c.865C>T, p.(Arg289*) in *PSMD12* (NM_002816.3), in both siblings (F1p1 and F1p2) and their father (F1p3). The variant is predicted to have a stop-gain effect, has a null frequency in gnomAD and in 1000 Genomes. It is classified as damaging by *in silico* prediction software (PaPI score: 0.988; DANN score: 0.998), it has already been reported as pathogenic in the HGMD database and described in the literature (Yan et al. 2022). Paternal grandparental DNA samples were tested by Sanger sequencing: the variant resulted to be *de novo* in F1p3.

Quartet (parents and two affected siblings) family 2 (F2) WES analysis identified the heterozygous nonsense variant c.333T>G, p.(Tyr111*) in *PSMD12* (NM_002816.3), in both siblings (F2p1 and F2p2) and their mother (F2p3). Resulting in the creation of a premature termination codon, the variant is predicted to have a stop-gain effect. It is a novel variant, not reported in databases of healthy individuals and gene mutations, classified as damaging by in silico prediction software (PaPI score: 0.964; DANN score: 0.991). Maternal grandparental DNA samples were not available for testing. There was no evidence of somatic mosaicism in the exome and Sanger sequencing data in either F1p3 or F2p3.

Both variants were considered pathogenic according to the ACMG guidelines (Richards et al. 2015).

3.2 | Clinical Reports

F1 is a non-consanguineous family of northeast Italian ancestry with two siblings affected by mild ID (pedigree in Figure 1A). The older daughter (F1p1) presented neonatal mild hypotonia with feeding difficulties, global developmental delay, recurrent otitis media with effusion managed with tympanoplasty and a surgically removed ovarian mature teratoma at the age of 17 years. At the age of 18, she was first referred to the clinical geneticist because of a mild ID (IQ = 65) without behavioral concerns, short stature (height at −2,3SD), and obesity (BMI 33.5 kg/m^2). She showed diffuse acne and stretch marks. Facial appearance evolved during growth: as an adolescent, she exhibited brachycephaly, hypertelorism, posteriorly rotated and oval ears, and micrognathia (Figure 1C). She had puffy hands with mild brachydactyly (Figure 1C), bilateral thinned distal radial epiphysis without a proper Madelung deformity at X-rays, and oligodontia. Ultrasound examination documented hepatic steatosis with pancreatic fatty involution. Her younger brother (F1p2) had a history of intrauterine growth restriction (IUGR) and was prematurely delivered at 36 + 4 weeks of gestation because of maternal preeclampsia, being born small for gestational age. He presented a global developmental delay with prevalent speech delay and received a diagnosis of mild ID (IQ = 65), deserving of school support. Facial appearance evolved during growth (Figure 1C). At the age of 15, he showed normal growth parameters, diffuse acne, mild hypertelorism and low-set, posteriorly rotated ears, arched palate, malocclusion with reverse bite, and bilateral *pes cavus* (Figure 1C). Despite a common immaturity in their behavior, both siblings reported a globally good social life. Brain MRI, echocardiography, and X-Ray bone age were normal in both probands (F1p1 and F1p2). Reverse phenotyping evaluation pointed out learning difficulties with a poor educational outcome in the siblings' father (F1p3). F1p3 was overweight, with a tendency to gain weight since adolescence, and presented a final height of 160 cm. Upon clinical examination, he showed a shy behavior, mild dysmorphisms with broad forehead, mild frontal bossing, and brachydactyly (Figure 1C). IFN-I alteration was measured for F1p2 (positive IS value of 9.5). F1p1 and F1p3 showed negative IS calculations.

F2 is a non-consanguineous family (pedigree in Figure 1B). The index case (F2p1) was a 12-year-old girl, born at 31 weeks of gestation after a pregnancy complicated by gestational diabetes and suspicion of spina bifida at ultrasound evaluation. She was admitted to neonatal intensive care unit for a severe respiratory distress. At birth, she showed cleft palate, which was surgically corrected. Echocardiography pointed out an interventricular defect. Upon evaluation, she had a severe, global developmental delay with moderate ID (QI < 40), a severe adaptive behavior with apathy. The girl had also convergent strabismus resistant to surgical treatments and untreated unilateral hearing loss associated with cholesteatoma. At the physical evaluation she appeared obese (Figure 1D). She had a broad forehead, small, low-set ears, hypertelorism with upslanted, narrow palpebral fissures, wide nasal bridge, micro-retrognathia, microstomia with narrow palate and crowded teeth (Figure 1D). She exhibited kyphoscoliosis, hand brachydactyly, tapering fingers, flat feet with 2–3 and 4–5 syndactyly and an advanced bone age at hand X-rays. She had also diffused acne and bilateral axillary acanthosis nigricans.

Her brother (F2p2) was evaluated at 22 years of age. He was born at 38 weeks of gestation, requiring incubator for low birth weight. The parents reported a history of global developmental delay with learning difficulties, mild ID with behavior concern characterized by fluctuating temper with irritability and aggression alternating to apathy. His weight was under the 3rd centile until the age of seven, when he progressively started gaining weight and became obese in late childhood, with central fat distribution and a BMI > 44 kg/m^2. Behavioral eating disorder was also noted. Furthermore, he presented strabismus, ocular hypertelorism with palpebral upslanting, ogival, narrow palate, and wide uvula (Figure 1D). He had flat, wide feet with 2–3 and 4–5 syndactyly, kyphoscoliosis, and *genu valgum* (Figure 1D). He also showed congenital unilateral, ectopic, supernumerary fingernail, appearing as a triangular, hard nail, growing from a linear base located in the external surface of the right thumb, resistant to various attempts of surgical eradication (Figure 1D). The siblings' mother (F2p3) was an adopted 49-year-old woman. She reported a history of delayed speech development, learning difficulties, needing daily support and

help in everyday activities. She had recurrent and unexplained, spontaneous abortions at the first trimester. She presented mild palpebral upslanting, low-set columella and narrow palate, *genu valgum*, wide feet with 2–3 and 4–5 syndactyly (Figure 1D). She had a short stature (152 cm), appeared obese (BMI > 40 kg/m^2) and presented a cardiac murmur. Weak IFN-I alteration was measured for F2p3 (IS value of 4.4), whereas F2p1 and F2p2 displayed negative IS values.

3.3 | Literature Review

Six papers reporting *PSMD12* patients have been selected from the literature by PubMed research. Five articles in English language have been finally included in the study, whose data have been summarized together with those related to our patients (Table S1).

4 | Discussion

4.1 | Syndromic NDDs With Autosomal Dominant Inheritance

Autosomal dominant inheritance of pathogenetic variants is quite unusual in large cohorts of NDDs patients analyzed by trio WES (Gao et al. 2019). For instance, only a single occurrence of IAD has been reported by analyzing 87 families with NDDs (Álvarez-Mora et al. 2022). In particular, series of IAD NDDs included Snijders Blok-Campeau syndrome related to *CHD3* gene, *ZNF292*-, and *TLK2*- related disorders (Mirzaa et al. 2020; Reijnders et al. 2018; Van Der Spek et al. 2022). Sometimes, pathogenetic variants may be inherited by a healthy or mildly affected parent, who is a somatic mosaic for the variant (Chérot et al. 2018). Asymptomatic parents may also transmit a pathogenic variant in case of monogenic intellectual disability associated with autosomal dominant gene with incomplete penetrance (de Masfrand et al. 2024).

In most patients affected by STISS, *PSMD12* pathogenic variants occurred *de novo* (Isidor et al. 2022; Khalil et al. 2018; Küry et al. 2017) (see Table 1). However, two families were described, both with a variant transmitter father who was mildly affected (Khalil et al. 2018; Yan et al. 2022). We described here two additional families with maternal as well as paternal inheritance of a novel or a known *PSMD12* truncating variant. In both cases, we experienced the referral of a single index proband, the female affected sibling. As part of the genetic evaluation, detailed family history is collected and further clinical evaluation may be indicated. In particular, the attribution of the disease phenotype to parents is crucial for variant interpretation in trio WES analysis. Since the possibility of variable expressivity with minimal exhibiting signs in autosomal dominant inheritance, we highlighted the opportunity of probands' first-degree relatives and grandparents assessment too.

4.2 | Clinical Presentation and Novel Findings

We describe six patients affected by STISS presenting with global developmental delay, ID (1 moderate, 5 mild), craniofacial dysmorphisms, skeletal anomalies, and new clinical features expanding the already reported disease manifestations (Table 1).

Despite the gestalt is not specific, hypertelorism, small, low-set ears, and micro-(retro)gnathia were frequent dysmorphisms. In contrast, upslanting of the palpebral fissures and low hanging columella in F2 were unreported craniofacial anomalies. Moreover, palate defects, including the second case of cleft palate, narrow palate, and broad uvula were recurrent features, whereas dental crowding, and related malocclusion, seem a novel finding together with oligodontia (F1p1). In addition, we reported for the first time unilateral cholesteatoma (F2p1).

Skeletal findings were reported in almost half of the patients with STISS (Isidor et al. 2022; Khalil et al. 2018; Küry et al. 2017). The most frequent findings were 2–3 toe syndactyly, kyphoscoliosis, and flat feet. Our patients presented 2–3 toe syndactyly, sometimes together with 4–5 toe syndactyly. Previous studies reported syndactyly only in association with 17q24 contiguous gene deletions (Hancarova et al. 2018; Küry et al. 2017; Naud et al. 2017). However, skeletal and craniofacial abnormalities have been already reported in STISS due to point mutations in *PSMD12*.

We described the first case of congenital, persistent onychoheterotopia in F2p2. No similar anomalies were noted neither in other fingers, toes or extradigital locations, nor in his relatives. Congenital ectopic nail or onychoheterotopia is an extremely rare condition of undetermined pathogenesis (Ferrari, Mazzarello, and Barbi 2021; Riaz, Rashid, and Khachemoune 2011). It is generally sporadic, rarely it recurred in some families, and only in a minority of cases it has been associated with other malformations, such as Pierre Robin sequence or skeletal anomalies (Ferrari, Mazzarello, and Barbi 2021; Franceschini et al. 2001; Miura 1978; Roger et al. 1986). Terms as “onychoheterotopia” or “ectopic nail” have not yet been included in clinical databases, such as the Human Phenotype Ontology (HPO), which provides a standardized vocabulary of phenotypic abnormalities encountered in human disease (Human Phenotype Ontology n.d.). At the best of our knowledge, this is the first evidence of ectopic, supernumerary fingernail in a monogenic syndrome. Interestingly, thumb agenesis and hypoplasia, various preaxial hand anomalies, and unilateral polydactyly were rarely described (Isidor et al. 2022; Khalil et al. 2018; Küry et al. 2017). Onychoheterotopia could be a whip shape of polydactyly, expanding the reported preaxial anomalies (Küry et al. 2017). Overall, *PSMD12* haploinsufficiency may alter epithelial and epithelial–mesenchymal interactions during embryogenesis leading to variable manifestation, such as onychoheterotopia and cholesteatoma. We also hypothesize a potential role of UPS dysfunction in the molecular biology of this poorly understood and seriously destructive epithelial lesion of the temporal bone.

F1p1 is the first described patient affected by a tumor, having had a mature ovarian teratoma during childhood. No alternative germline pathogenic variant associated with tumor susceptibility emerged by WES. Molecular investigation on tumoral tissue was not carried out after surgery, which occurred before the diagnosis of STISS. Mature teratomas are the most common type of ovarian tumors in children, and their embryology, pathology, and genetic basis still remain poorly understood (Łuczak

TABLE 1 | Novel clinical findings in the reported patients.

Clinical category	Unreported clinical findings with HPO term	Novel clinical findings
Prenatal findings	Oligohydramnios HP:0001562	
Dysmorphisms	Upslanted palpebral fissure HP:0000582; Low hanging columella HP:0009765	
Craniofacial abnormalities	Narrow palate HP:0000189; Broad uvula HP:0010809; Cholesteatoma HP:0009797	
Growth	Short stature HP:0004322	
Congenital anomalies	Renal cortical hyperechogenicity HP:0033132; 4–5 toe cutaneous syndactyly HP:6000503; Brachydactyly HP:0001156	Unilateral ectopic, sopranumerary fingernail/Onychoheterotopia
X-rays skeletal findings	Hypoplastic distal radial epiphyses HP:0006386; Advanced ossification of carpal bones HP:0004233	
Odontostomatological presentation	Oligodontia HP:0000677; Dental crowding HP:0000678; Dental malocclusion HP:0000689; Anterior open-bite malocclusion HP:0009102	
Behavior abnormalities	Abnormal eating behavior HP:0100738; Apathy HP:0000741	
Medical comorbidities	Recurrent otitis media HP:0000403; Hepatic steatosis HP:0001397; Pancreatic steatosis HP:0033757; Recurrent Miscarriage HP:0005268	
Cancer	Ovarian teratoma HP:0012226	

Note: Table shows novel clinical findings in our patients grouped into clinical categories (first column) classified by existing HPO terms (Human Phenotype Ontology n.d.) (second column) or described only (third column).

and Bagłaj 2018). So far, no evidence of cancer in patients with STISS emerged. However, the dysregulation of the ubiquitin system is known as a risk mechanism for tumor development (Fhu and Ali 2021). *PSMD12* knockdown resulted in inhibition of cell growth and migration in cytological experiments, and a genome-wide CRISPR-Cas9 knockout confirmed that *PSMD12* is a crucial gene for breast cancer cell growth (Du et al. 2020). Somatic variants in the *PSMD12* gene may be involved in the promotion of cellular growth, migration and the inhibition of apoptosis during cancer genesis, targeting modulators of the proteasome system as potential therapeutic molecules (Aliabadi et al. 2021; Shen et al. 2013). In F1p1 the etiology of the teratoma is still unclear, and an association with germline truncating *PSMD12* is worth mentioning in the light of second hit hypothesis in teratoma tissue, even without ruling out alternative possible causes.

Most of our patients (5/6) showed short stature, also reported as severe in a Chinese patient affected by STISS found to be heterozygous for c.601C>T, p.(Arg201*) variant in *PSMD12* (Xu et al. 2023). IUGR was also found in F1p2 and F2p2, finally accounting for 33.9% (19/56) of STISS patients (Isidor et al. 2022; Khalil et al. 2018; Küry et al. 2017; Yan et al. 2022). Antenatally, F1p2 had also oligohydramnios. In contrast, congenital anomalies are not frequent findings. In our cohort, perimembranous interventricular septal defect (1/6), elongated kidneys with unilateral pyelectasia and contralateral renal hyperechoic spot (1/6), and cryptorchidism (1/6) were described during postnatal investigations. Visceral anomalies are rarely reported and heterogeneous, involving mostly heart or kidney, and having a mild impact on health (Isidor et al. 2022; Küry et al. 2017). No major brain anomalies have been reported, except for a single case with periventricular nodular heterotopia, mild ventriculomegaly and decreased white matter (Khalil et al. 2018). Most of the patients reported neonatal concerns, related to prematurity, low birth weight or feeding difficulties (Isidor et al. 2022; Khalil et al. 2018; Küry et al. 2017). Indeed, multiple prenatal findings were reported only in those 17q24 microdeletions encompassing *PSMD12*. Naud and colleagues described a fetus with craniofacial dysmorphisms including retrognathia, talipes equinovarus, and syndactyly, without major visceral malformation, harboring a 2.5 Mb deletion including *PSMD12*, which was proposed as a candidate gene to explain most of the phenotype (Naud et al. 2017).

Describing a cohort including four adults, we pointed out some age-related features. Most of our patients (5/6) presented a progressive tendency to overweight and obesity since late childhood after having presented low weight during early childhood and even in case of low birth weight and prenatal growth restriction. F2p2 had an eating behavioral disorder. None of our patients had a diagnosis of ASD: in F1, they all exhibited a good sociality, even if the father was quite shy, while in F2 behavior anomalies varied from apathy to alternation of apathy and irritability. F2p1 had refractory strabismus and untreated unilateral hearing loss, which may have contributed to worsen her developmental outcomes.

None of our patients presented clinically evident manifestations of autoinflammation. However, we highlight that diffuse, early-onset, and unexplained acne was present in 4 out of 6 individuals and that F1p1 had an unexplained hepatic and pancreatic steatosis. Although still under medical investigation, fatty involution may be the consequence of a long-lasting (auto)-inflammatory process. We performed reverse phenotyping investigations on IFN-I signaling in all the individuals demonstrating a weak IFN-I signaling perturbation only in two cases (F1p2; F2p3) and a basal inflammatory response. Heterogeneous inflammatory response in different patients from the same family without any clinical manifestation suggests that IFN-I signaling should not be considered as a specific biomarker of STISS, limiting its adoption for variant interpretation, genotype–phenotype correlation, and prognosis.

Finally, F2p3 is the first affected mother transmitting STISS to her offspring. She also had unexplained, recurrent, early miscarriages without difficulty to conceive. Lethality as the extreme manifestation of the STISS spectrum, second hit hypothesis, or higher mutational burden of damaging variants are hypotheses requiring further investigations.

4.3 | Molecular Considerations

The molecular basis of STISS is not completely understood. Being a highly conserved gene, with a high haploinsufficiency score (HI index = 5.57%) and predicted to be extremely intolerant to heterozygous loss-of-function variants (pLI = 1.0), *PSMD12* has been associated with STISS in case of haploinsufficiency (Isidor et al. 2022; Khalil et al. 2018; Küry et al. 2017; Yan et al. 2022). Up to now, microdeletions completely involving *PSMD12*, small intragenic deletions, nonsense, and frameshift variants in *PSMD12* have been reported as pathogenic (Table 1). Exceptionally, a missense variant, c.1105T>C, p.(Trp369Arg), in *PSMD12* has been related to STISS with craniosynostosis (Timberlake et al. 2023). In vivo studies of the c.865C>T, p.(Arg289*), found in F1, supported the haploinsufficiency due to spontaneous degradation of the truncated protein (Yan et al. 2022). We enriched the group of pathogenic variants in *PSMD12*, reporting a novel truncating variant, which affects the amino acid 111, located before the functional domain (Richards et al. 2015).

5 | Conclusion

Inherited *PSMD12* pathogenetic variants occur in STISS, impacting on genetic counseling and prenatal diagnosis. *PSMD12* haploinsufficiency is characterized by complete penetrance and variable expressivity, from mild NDD, good sociality, and minor craniofacial features to severe developmental delay with sensorial defects, craniofacial features requiring surgical correction, and congenital anomalies. Therefore, in the era of high-throughput sequencing analysis, we remarked the role of an accurate clinical evaluation of family members and the possibility of variant inheritance as possible tools for undiagnosed NDDs. UPS pathway seems involved in epithelial–mesenchymal interactions during human development. Onychoheterotopia, cholesteatoma, and oligodontia expand the spectrum of congenital anomalies. IUGR, short stature, and age-related tendency to obesity may be part of growth history. Eating disorder may be accounted for within the STISS behavioral phenotype. We advocate to index "onychoheterotopia" in the human ontology of phenotypic abnormalities (Human Phenotype Ontology n.d.). Reporting a co-occurrence of ovarian teratoma, we question the role of second hit hypothesis in cancer promotion and in variable expressivity. IFN-I signaling does not clearly correlate with clinical manifestations of autoinflammation.

Author Contributions

Agnese Feresin: conceptualization of the study; clinical evaluation of patients; collection of clinical data; literature review; drafting of manuscript. Beatrice Spedicati: clinical evaluation of patients; collection of clinical data; drafting of manuscript. Stefania Zampieri; Anna Morgan: molecular data evaluation and interpretation; editing of manuscript. Andrea Magnolato: clinical evaluation of patients. Alessandra Tesser; Alberto Tommasini: experiments; editing of manuscript. Maria Teresa Bonati: clinical evaluation of patients; editing of manuscript. Giorgia Girotto: molecular data evaluation and interpretation; editing of manuscript; funding. Flavio Faletra: conceptualization of project; supervision of project; clinical evaluation of patients; editing of manuscript. All authors agree with the final version of the manuscript.

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Ethics Statement

Written informed consent was obtained from all participants or their legal guardians. The study was conducted in accordance with the tenets of the Helsinki Declaration and was approved by the Ethics Committee of the Institute for Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy. Written informed consent has been obtained from the patients to publish this paper.

Conflicts of Interest

Author declare no conflict of interest. At the moment of submission, AF is external consultant for Menarini Silicon Biosystems S.p.A. working on the cbNIPT project.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Aliabadi, F., B. Sohrabi, E. Mostafavi, H. Pazoki-Toroudi, and T. J. Webster. 2021. "Ubiquitin–Proteasome System and the Role of Its

Inhibitors in Cancer Therapy." *Open Biology* 11, no. 4: 200390. https://doi.org/10.1098/rsob.200390.

Álvarez-Mora, M. I., A. Sánchez, L. Rodríguez-Revenga, et al. 2022. "Diagnostic Yield of Next-Generation Sequencing in 87 Families With Neurodevelopmental Disorders." *Orphanet Journal of Rare Diseases* 17: 60. https://doi.org/10.1186/s13023-022-02213-z.

Chérot, E., B. Keren, C. Dubourg, et al. 2018. "Using Medical Exome Sequencing to Identify the Causes of Neurodevelopmental Disorders: Experience of 2 Clinical Units and 216 Patients." *Clinical Genetics* 93, no. 3: 567–576. https://doi.org/10.1111/cge.13102.

de Masfrand, S., B. Cogné, M. Nizon, et al. 2024. "Penetrance, Variable Expressivity and Monogenic Neurodevelopmental Disorders." *European Journal of Medical Genetics* 69: 104932. https://doi.org/10.1016/j.ejmg.2024.104932.

Deciphering Developmental Disorders Study. 2017. "Prevalence and Architecture of de Novo Mutations in Developmental Disorders." *Nature* 542, no. 7642: 433–438. https://doi.org/10.1038/nature21062.

Du, X., X. Shen, L. Dai, F. Bi, H. Zhang, and C. Lu. 2020. "PSMD12 Promotes Breast Cancer Growth via Inhibiting the Expression of Pro-Apoptotic Genes." *Biochemical and Biophysical Research Communications* 526, no. 2: 368–374. https://doi.org/10.1016/j.bbrc.2020.03.095.

Ebstein, F., S. Küry, J. J. Papendorf, and E. Krüger. 2021. "Neurodevelopmental Disorders (NDD) Caused by Genomic Alterations of the Ubiquitin-Proteasome System (UPS): The Possible Contribution of Immune Dysregulation to Disease Pathogenesis." *Frontiers in Molecular Neuroscience* 14: 733012. https://doi.org/10.3389/fnmol.2021.733012.

Ferrari, M., V. Mazzarello, and E. Barbi. 2021. "Onychoheterotopia in Children." *Dermatology Reports* 13, no. 2: 9068. https://doi.org/10.4081/dr.2021.9068.

Fhu, C. W., and A. Ali. 2021. "Dysregulation of the Ubiquitin Proteasome System in Human Malignancies: A Window for Therapeutic Intervention." *Cancers* 13, no. 7: 1513. https://doi.org/10.3390/cancers13071513.

Franceschini, P., D. Licata, A. Guala, G. Di Cara, and D. Franceschini. 2001. "Peculiar Facial Appearance and Generalized Brachydactyly in a Patient With Congenital Onychodysplasia of the Index Fingers (Iso-Kikuchi Syndrome)." *American Journal of Medical Genetics* 98, no. 4: 330–335. https://doi.org/10.1002/1096-8628(20010201)98:4<330::aid-ajmg1104>3.0.co;2-d.

Gao, C., X. Wang, S. Mei, et al. 2019. "Diagnostic Yields of Trio-WES Accompanied by CNVseq for Rare Neurodevelopmental Disorders." *Frontiers in Genetics* 10: 485. https://doi.org/10.3389/fgene.2019.00485.

Hancarova, M., M. Malikova, M. Kotrova, J. Drabova, M. Trkova, and Z. Sedlacek. 2018. "Association of 17q24.2-q24.3 Deletions With Recognizable Phenotype and Short Telomeres." *American Journal of Medical Genetics. Part A* 176, no. 6: 1438–1442. https://doi.org/10.1002/ajmg.a.38711.

Human Phenotype Ontology. n.d. Accessed July 29, 2024. https://hpo.jax.org/.

Isidor, B., F. Ebstein, A. Hurst, et al. 2022. "Stankiewicz-Isidor Syndrome: Expanding the Clinical and Molecular Phenotype." *Genetics in Medicine* 24, no. 1: 179–191. https://doi.org/10.1016/j.gim.2021.09.005.

Khalil, R., C. Kenny, R. S. Hill, et al. 2018. "PSMD12 Haploinsufficiency in a Neurodevelopmental Disorder With Autistic Features." *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 177, no. 8: 736–745. https://doi.org/10.1002/ajmg.b.32688.

Küry, S., T. Besnard, F. Ebstein, et al. 2017. "De Novo Disruption of the Proteasome Regulatory Subunit PSMD12 Causes a Syndromic Neurodevelopmental Disorder." *American Journal of Human Genetics* 100, no. 2: 352–363. https://doi.org/10.1016/j.ajhg.2017.01.003.

Łuczak, J., and M. Bagłaj. 2018. "Ovarian Teratoma in Children: A Plea for Collaborative Clinical Study." *Journal of Ovarian Research* 11: 75. https://doi.org/10.1186/s13048-018-0448-2.

Martin, H. C., W. D. Jones, R. McIntyre, et al. 2018. "Quantifying the Contribution of Recessive Coding Variation to Developmental Disorders." *Science* 362, no. 6419: 1161–1164. https://doi.org/10.1126/science.aar6731.

Mirzaa, G., J. X. Chong, A. Piton, et al. 2020. "De Novo and Inherited Variants in ZNF292 Underlie a Neurodevelopmental Disorder With Features of Autism Spectrum Disorder." *Genetics in Medicine* 22, no. 3: 538–546. https://doi.org/10.1038/s41436-019-0693-9.

Miura, T. 1978. "Two Families With Congenital Nail Anomalies: Nail Formation in Ectopic Areas." *Journal of Hand Surgery* 3, no. 4: 348–351. https://doi.org/10.1016/s0363-5023(78)80035-5.

Naud, M.-E., L. Tosca, J. Martinovic, et al. 2017. "Prenatal Diagnosis of a 2.5 Mb De Novo 17q24.1q24.2 Deletion Encompassing KPNA2 and PSMD12 Genes in a Fetus With Craniofacial Dysmorphism, Equinovarus Feet, and Syndactyly." *Case Reports in Genetics* 2017: 1–5. https://doi.org/10.1155/2017/7803136.

Reijnders, M. R. F., K. A. Miller, M. Alvi, et al. 2018. "De Novo and Inherited Loss-Of-Function Variants in TLK2: Clinical and Genotype-Phenotype Evaluation of a Distinct Neurodevelopmental Disorder." *American Journal of Human Genetics* 102, no. 6: 1195–1203. https://doi.org/10.1016/j.ajhg.2018.04.014.

Riaz, F., R. M. Rashid, and A. Khachemoune. 2011. "Onychoheterotopia: Pathogenesis, Presentation, and Management of Ectopic Nail." *Journal of the American Academy of Dermatology* 64, no. 1: 161–166. https://doi.org/10.1016/j.jaad.2009.11.018.

Richards, S., N. Aziz, S. Bale, et al. 2015. "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genetics in Medicine* 17, no. 5: 405–424. https://doi.org/10.1038/gim.2015.30.

Roger, H., P. Souteyrand, J. P. Collin, G. Vanneuville, and P. Teinturier. 1986. "Onychoheterotopia With Polyonychia Associated With Pierre Robin Syndrome: Apropos of a New Case. (Trial of Classifying Nail Ectopia)." *Annales De Dermatologie et De Venereologie* 113, no. 3: 235–242.

Sahin, M., and M. Sur. 2015. "Genes, Circuits, and Precision Therapies for Autism and Related Neurodevelopmental Disorders." *Science* 350, no. 6263: aab3897. https://doi.org/10.1126/science.aab3897.

Shen, M., S. Schmitt, D. Buac, and Q. P. Dou. 2013. "Targeting the Ubiquitin–Proteasome System for Cancer Therapy." *Expert Opinion on Therapeutic Targets* 17, no. 9: 1091–1108. https://doi.org/10.1517/14728222.2013.815728.

Timberlake, A. T., S. McGee, G. Allington, et al. 2023. "De Novo Variants Implicate Chromatin Modification, Transcriptional Regulation, and Retinoic Acid Signaling in Syndromic Craniosynostosis." *American Journal of Human Genetics* 110, no. 5: 846–862. https://doi.org/10.1016/j.ajhg.2023.03.017.

Van der Spek, J., J. Den Hoed, L. Snijders, et al. 2022. "Inherited Variants in CHD3 Show Variable Expressivity in Snijders Blok-Campeau Syndrome." *Genetics in Medicine* 24, no. 6: 1283–1296. https://doi.org/10.1016/j.gim.2022.02.014.

Xu, L., Y. Wang, Q. Zhang, et al. 2023. "[Clinical Characteristics and Genetic Analysis of a Patient With STISS Syndrome due to Variant of PSMD12 Gene]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi = Zhonghua Yixue Yichuanxue Zazhi = Chinese." *Journal of Medical Genetics* 40, no. 3: 349–353. https://doi.org/10.3760/cma.j.cn511374-20220207-00097.

Yan, K., J. Zhang, P. Y. Lee, et al. 2022. "Haploinsufficiency of PSMD12 Causes Proteasome Dysfunction and Subclinical Autoinflammation." *Arthritis and Rheumatology* 74, no. 6: 1083–1090. https://doi.org/10.1002/art.42070.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.