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RESEARCH REVIEW

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# Genotype–phenotype correlation in Phelan-McDermid syndrome: A comprehensive review of chromosome 22q13 deleted genes

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## Abstract

Phelan-McDermid syndrome (PMS, OMIM #606232), also known as chromosome 22q13 deletion syndrome, is a rare genetic disorder characterized by intellectual disability, hypotonia, delayed or absent speech, motor impairment, autism spectrum disorder, behavioral anomalies, and minor aspecific dysmorphic features. Haploinsufficiency of *SHANK3*, due to intragenic deletions or point mutations, is sufficient to cause many neurobehavioral features of PMS. However, several additional genes located within larger 22q13 deletions can contribute to the great inter-individual variability observed in the PMS phenotype. This review summarizes the phenotypic contributions predicted for 213 genes distributed along the largest 22q13.2-q13.33 terminal deletion detected in our sample of 63 PMS patients by array-CGH analysis, spanning 9.08 Mb. Genes have been grouped into four categories: (1) genes causing human diseases with an autosomal dominant mechanism, or (2) with an autosomal recessive mechanism; (3) morphogenetically relevant genes, either involved in human diseases with additive co-dominant, polygenic, and/or multifactorial mechanisms, or implicated in animal models but not yet documented in human pathology; (4) protein coding genes either functionally nonrelevant, with unknown function, or pathogenic through mechanisms other than haploinsufficiency; piRNAs, noncoding RNAs, miRNAs, novel transcripts and pseudogenes. Our aim is to understand genotype–phenotype correlations in PMS patients and to provide clinicians with a conceptual framework to promote evidence-based genetic work-ups, clinical assessments, and therapeutic interventions.

**KEYWORDS**
autism, chromosome 22q13.3 deletion syndrome, Phelan-McDermid syndrome, *SHANK3*

## 1 | INTRODUCTION

Phelan-McDermid syndrome is a rare genetic disorder characterized by global developmental delay, severe deficits in or lack of expressive language, moderate to profound intellectual disability (ID), behavioral manifestations frequently including autism, muscle hypotonia, deficits in motor coordination, seizures, abnormal brain MRI and minor dysmorphic features. Malformations and comorbidities found in sizable minorities of PMS patients include genito-urinary abnormalities, heart defects, gastrointestinal (GI) symptoms, endocrine-metabolic

disorders, and immune dysfunctions (Phelan & McDermid, 2012; Soorya et al., 2013; Kolevzon et al., 2014) (Table 1). To date, more than 1500 patients with PMS are enrolled in the "Phelan-McDermid Syndrome International Registry" of the PMS Foundation and over 2500 individuals have self-identified as PMS patients world-wide (https://www.pmsf.org/international/). However, PMS is underdiagnosed and its exact prevalence is unknown.

PMS can be caused by: (a) terminal chromosome 22q13 deletions, usually de novo, but in about 20% of cases one parent carries a balanced translocation, enhancing the risk of recurrent PMS; (b) intragenic *SHANK3* deletions; (c) unbalanced translocations or other chromosomal rearrangements, yielding the formation of a ring chr. 22; (d) disruptive point mutations in the *SHANK3* gene (Dhar et al., 2010; Phelan & Betancur, 2011; De Rubeis et al., 2018).

*SHANK3* is the strongest candidate gene, as loss or inactivation of one *SHANK3* allele is sufficient to determine PMS (Bonaglia et al., 2011; Phelan & McDermid, 2012). *SHANK3* contains 24 exons spanning approximately 58.5 kb. It is expressed in all brain regions, heart, spleen, kidney, uterus, lung, and GI epithelium (Lim et al., 1999), as well as in the neuromuscular junction, in the dendrites of sympathetic postganglionic neurons and myenteric neurons, and in thymocytes (Redecker et al., 2006; Raab et al., 2010). Multiple intragenic promoters and alternatively spliced exons yield various mRNA and protein isoforms, differently expressed in different cell types, subcellular localizations, stages of development and brain regions. *SHANK3* encodes a scaffolding protein located in the postsynaptic density (PSD), endowed with six domains connecting the actin cytoskeleton to different membrane and cytoplasmic proteins, such as AMPA,

**TABLE 1** Major clinical features associated with Phelan-McDermid syndrome (Kohlenberg et al., 2020; Kolevzon et al., 2014; Phelan et al., 2011; Sarasua et al., 2011; Sarasua et al., 2014a; Soorya et al., 2013)

| | |
|---|---|
| Central nervous system: behavioral and neurological manifestations | Global developmental delay; absence of expressive language (50%) or speech delay (100%); moderate-to-profound intellectual disability (about 87%); ASD (26%–84%); aggressive behavior (28%); impulsiviness (47%); biting (self or others) (46%); abnormal reflexes (48%); elevated pain threshold (77%); seizures (febrile and/or nonfebrile) (14%–41%); sleep disturbance (41%–46%); abnormal brain MRI (7%–75%) (arachnoid cyst, delayed myelination, generalized white matter atrophy, unspecific white matter hyperintensities or gliosis, thinning or hypoplasia of the corpus callosum, ventriculomegaly, focal cortical atrophy, frontal lobe hypoplasia, enlarged cisterna magna, cerebellar vermis hypoplasia); neurologic, motor and cognitive regression in early childhood (18%); regression during adolescence within 1–3 years oafter the onset of psychiatric illness (66%–84%); catatonia (53%); probable progressive neurodegeneration. |
| Central and peripheral musculoskeletal signs and symptoms | Generalized hypotonia (weak cry, poor head control, feeding difficulties, etc.) (29%–100%); delayed motor milestones; inability to walk; ataxia; muscle weakness; dynamic and static balance deficits; decreased upper limb strength; gross and fine motor coordination deficits; broad-based and unsteady gait; oral motor dysfunction; bladder dysfunction; scoliosis; hyperextensible joints (25%–61%); lax ligaments (65%). |
| Cardiovascular system | Heart defects, including tricuspid valve regurgitation, aortic regurgitation, patent ductus arteriosus, total anomalous venous return, atrial septal defect, and so on (3% to >25%). |
| Genitourinary system | Renal abnormalities or malformations, including vesicoureteral reflux, increased kidney size, dilated renal pelvis, renal cysts or polycystic kidney, hydronephrosis, horseshoe kidney, renal agenesis or dysplastic kidneys, duplicate kidney, and so on (17%–38%); urinary tract infections (8%). |
| Gastrointestinal system | Gastroesophageal reflux (42%–44%); constipation and/or diarrhea (38%–41%); cyclic vomiting, feeding difficulties and pica. |
| Endocrine-metabolic system | Hypothyroidism (3%–6%); precocious or delayed puberty (0%–12%); impaired hepatic function and autoimmune hepatitis and liver failure (rare). |
| Sensory organs (hearing and vision) | Cortical auditory and visual impairment (extensive use of peripheral vision, difficulty in processing cluttered images, problems with depth perception, difficulty discerning spoken words from background noise); hyperopia and myopia, blindness and optic nerve hypoplasia (rare). |
| Dysmorphic features | Bulbous nose (47%–80%); ears anomalies (27%–86%); long eyelashes (37%–93%); large fleshy hands (33%–68%); epicanthal folds (30%–73%); periorbital fullness (25%–60%); thin and dysplastic toenails (3%–78%); pointed chin (22%–62%); dolichocephaly (0%–86%); high arched palate (25%–47%); 2/3 toe syndactyly (9%–48%); ptosis (3%–57%); strabismus (26%); full cheeks (25%); sacral dimple (13%–37%); hypertelorism (13%–36%); deep-set eyes (6%–31%); macrocephaly (7%–31%); wide nasal bridge (16%); microcephaly (6%–14%). |
| Body growth | Short stature/delayed growth (0%–13%); tall stature/accelereted growth (3%–18%). |
| Miscellaneous | Lymphedema (22%–29%); dental problems (malocclusion, wide-spaced teeth, crowding); recurring upper respiratory tract infections (8%–53%); decreased skin perspiration with tendency to overheat (60%); skin rashes (39%); immune deficiency (12%). |

Abbreviations: ASD, autism spectrum disorder; MRI, magnetic resonance imaging.

NMDA, and mGluR receptors, as well as PSD-95. Through these protein–protein interactions, Shank3 fosters synapse formation and plasticity, regulates dendritic spine morphology, and promotes the trafficking, anchoring, and correct clustering of glutamate receptors and adhesion molecules in the glutamatergic synapse (Verpelli et al., 2012). In addition to its postsynaptic roles, Shank3 is also expressed presynaptically across development, early in the growth cone of unpolarized hippocampal neurons and later in the axons of polarized neurons, where it modulates presynaptic NMDA receptor levels at axon terminals (Halbedl et al., 2016).

Genotype–phenotype correlations in PMS are complex. Many PMS features are related to the haploinsufficiency of *SHANK3*, but most neurological and behavioral symptoms are also present in patients carrying interstitial 22q13 deletions not involving *SHANK3* (Disciglio et al., 2014; Sarasua et al., 2014a; Simenson et al., 2014). *SHANK3* mutations have been associated with a wide array of clinical phenotypes, including autism spectrum disorder (ASD), intellectual disability (ID), and schizophrenia, where they explain 0.69%, ≤2.12%, and 0.6%–2.16% of patients, respectively (Mitz et al., 2018). The size of PMS-causing deletions can be extremely variable, ranging from 0.22 to 9.22 Mb, due to the absence of recurrent breakpoints (Sarasua et al., 2014a) and may be positively associated with phenotypic severity, despite great interindividual variability and conflicting results (Sarasua et al., 2011; Soorya et al., 2013; Sarasua et al., 2014a; Sarasua et al., 2014b). Therefore, in-depth knowledge of the genes located in the deleted region represents the first step necessary to carry out clinically meaningful genotype–phenotype correlations in PMS patients.

This review has been undertaken to achieve both scientific and clinical aims, namely: (a) to analyze the functional role and the pathogenic potential of all genes distributed along the largest terminal 22q13 region found deleted in PMS, providing a foundation for future genotype–phenotype correlations in deletion carriers; (b) to prompt clinicians to request targeted gene sequencing of the nondeleted allele, in the presence of autosomal recessive clinical phenotypes superimposed to more typical PMS symptoms; (c) to promote individually tailored medical diagnostic and follow-up protocols for PMS patients with different deletion sizes.

## 2 | MATERIALS AND METHODS

The purpose of this analysis is to describe the function and clinical role of all genes spanning the largest 22q13.2-q13.33 terminal deletion detected by array-CGH (Human Genome CGH 1x1M Microarray, Agilent) in our sample of 63 PMS patients (Antonio M. Persico, Arianna Ricciardello and Coll., manuscript in preparation). The genomic DNA segment hereby analyzed is 9.08 Mb long (hg19/42,139,543–51,224,252). Information about each gene was retrieved using *Ensemble Biomart tool* (Ensemble Gene 98, hg19/GRCh37). Furthermore, the 22q13 region was studied through the following public databases: 1) *PubMed*; 2) *UCSC Genome Browser*; 3) *OMIM* for the association with human diseases and as reference for defining gene inheritance patterns; 4) *GnomAD* (v2.1.1) to define the "probability of being loss-of-function intolerant" score (PLi), the ratio of observed to expected loss-of-function variants occurring in each gene and its confidence intervals; 5) *GTEx* (v.8) for tissue expression; 6) *UniProtKB/Swiss-prot* for protein information; 7) *GeneCard* (v.4.14); 8) *MalaCard* (v.4.14) for additional information about gene roles in human diseases (only pathologies with scores ≥1 on *MalaCard* are included). Based on all available information, each gene received a "PMS pathogenicity score" depending on evidence of pathogenic roles, as follows: 2 = autosomal dominant; 1 = autosomal recessive; 0.5 = additive, co-dominant with morphogenetic roles in humans and/or animal models, or involved in human multifactorial disorders, or in relevant animal models only; 0 = genes currently devoid of sufficient evidence of pathogenicity in humans and/or in animal models, when haploinsufficient. Data were then manually annotated in Tables 2–4 and in Tables S1–S4, respectively.

## 3 | RESULTS

The largest 22q13.2-q13.33 terminal deletion identified in one of our PMS patients encompassed 213 genes. Based on their human disease-causing mechanism and PMS pathogenicity scores, these genes were classified into four categories. Their primary physiological function and involvement in human pathology are hereby briefly described. Additional information on each gene is available in the Supplementary Materials.

### 3.1 | Category 1: Autosomal dominant disease genes

This category involves three genes, in addition to *SHANK3*, potentially relevant to chr. 22q13 deleted PMS patients due to their implication in human diseases with an autosomal dominant mechanism (Table 2, Figure S1 and Table S1). Evidence of dominant effects is conclusive for *TCF20*, less consistent for *SCO2* and *UPK3A* (see pLI and o/e in Table 2):

1. *$SCO_2$ plays* a critical role in cytochrome c oxidase (COX or complex IV) function in mitochondria (Frye et al., 2016). Pathogenic mutations can produce a severe form of autosomal dominant myopia with partial loss of retinal ganglion cells (Tran-Viet et al., 2013), or autosomal recessive cardiomyopathies and encephalomyopathies (Pronicka et al., 2013). However, heterozygous pathogenic *$SCO_2$* variants often display low penetrance, conceivably due to adjustments of the methylation status of the *$SCO_2$* promoter in the nondeleted allele (Thomford et al., 2018).
2. *UPK3A* is a component of the uroplakins family, expressed on the transitional epithelium covering the urinary tract. *$UPK3A^{-/-}$* mice display vesicoureteral reflux, hydronephrosis and altered renal function. De novo heterozygous missense variants were found associated with renal adysplasia or hypodysplasia in some (Jenkins

**TABLE 2** Genes located in the 22q13 deleted region involved in human autosomal dominant diseases (see also Table S1). [A] Bonafide haploinsufficient/AD genes with high pLI and low o/e; [B] possible AD genes with low pLI and high o/e

| Genes [OMIM n] | Gene description | Coordinates chr 22 (GRCh37/hg19) | Biotype pLI,[a] o/e (C.I.) | Biological function[b] | Associated Diseases[c] - OMIM: Phenotype [MIM n.]; (inheritance) |
|---|---|---|---|---|---|
| [A] *SHANK3 or PROSAP2* [606230] | SH3 and multiple ankyrin repeat domains 3 or proline-rich synapse associated protein 2. | 51,113,070–51,171,640 | Protein coding<br>pLI = 1<br>o/e = 0.039 (0.01–0.12) | (1) Scaffold protein of the postsynaptic density.<br>(2) Structural and functional organization of the dendritic spine and synaptic junction. | (1) Phelan-McDermid syndrome [MIM:606232] (AD);<br>(2) Schizophrenia 15 [MIM:613950] (AD). |
| [A] *TCF20* [603107] | Transcription factor 20. | 42,556,019–42,611,445 | Protein coding<br>pLI = 1<br>o/e = 0.03 (0.01–0.1) | (1) Transcriptional activator that binds to the regulatory region of matrix metalloproteinase-3 (MMP3) and controls stromelysin expression.<br>(2) Co-activator of JUN, SP1, PAX6 and ETS1. | Developmental delay with variable intellectual impairment and behavioral abnormalities [MIM:618430] (AD) |
| [B] *SCO2* [604272] | Cytochrome C Oxidase Assembly Protein. | 50,961,997–50,964,570 | Protein coding<br>pLI = 0<br>o/e = 1.08 (0.65–1.76) | Copper metallochaperone essential for the synthesis and maturation of cytochrome c oxidase subunit II (MT-CO2/COX2). It catalyzes the transfer of reducing equivalents from COX to molecular oxygen and its deficiency causes an increase in reactive oxygen species. | (1) Myopia 6 (MYP6) [MIM:608908] (AD);<br>(2) Cardioencephalo-myopathy, Fatal Infantile, Due To Cytochrome C Oxidase Deficiency 1 [MIM:604377] (AR). |
| [B] *UPK3A* [611559] | Uroplakin 3A. | 45,680,868–45,691,755 | Protein Coding<br>pLI = 0<br>o/e = 1.19 (0.78–1.78) | (1) Regulation of the asymmetric unit membrane-cytoskeleton interaction in terminally differentiated urothelial cells.<br>(2) Formation of urothelial glycocalyx, which may prevent bacterial adherence. | Possible association with congenital anomalies of the kidney and urogenital tract. |

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; o/e, ratio of observed to expected loss-of-function variants occurring in a gene, based on a mutational model that takes into account sequence context, coverage and methylation; C.I., confidence intervals.

[a]pLI: probability that a gene is loss-of-function intolerant, ranging from 0 to 1 (most tolerant to most intolerant, respectively).

[b]Summary of UCSC Genome Browser; Entrez Gene; GeneCards; UniProtKB/Swiss-prot. A more detailed description and tissue expression patterns drawn from the GTEx portal are available in Table S1.

[c]Associated diseases according to GeneCards (Version 4.14: March 11, 2020) and MalaCards (Version 4.14.0.3: March 8, 2020) are available in Table S1.

et al., 2005; Schönfelder et al., 2006), but not all studies (Jiang et al., 2004; Hwang et al., 2014), possibly due to incomplete penetrance and/or low incidence of causal variants.

3. *TCF20* encodes a coactivator of several transcription factors (Rekdal et al., 2000) and is also paralogous to *RAI1*, the critical gene deleted in Smith-Magenis syndrome and duplicated in Potocki-Lupski syndrome. It is highly expressed in the brain and strongly linked to severe neurodevelopmental phenotypes, encompassing cognitive and motor deficits, autistic traits, Attention Deficit/Hyperactivity Disorder (ADHD), craniofacial dysmorphisms, macrocephaly, body overgrowth, muscle hypotonia, seizures, constipation, scoliosis, strabismus, myopia, and keratoconus (Torti et al., 2019). Inactivating SNPs/indels or deletions cause a clinical phenotype similar to Smith-Magenis syndrome (The DDD Study, 2019).

## 3.2 | Category 2: Autosomal recessive disease genes

This class includes 14 genes, known to cause autosomal recessive diseases in humans (Table 3, Figure S1 and Table S2). Further details about these genes, as well as two additional genes, *A4GALT* and *CYP2D6*, critical to P-blood groups and pharmacogenomics, respectively, but not involved in human diseases, are available in the Supplementary Materials and in Table S2.

**TABLE 3** Genes located in the 22q13 deleted region involved in human autosomal recessive diseases (see also Table S2)

| Genes [OMIM n] | Gene description | Coordinates chr 22 (GRCh37/hg19) | Biotype pLI,[a] o/e (C.I.) | Biological function[b] | Associated Diseases[c] - OMIM: Phenotype [MIM n.]; (inheritance) |
|---|---|---|---|---|---|
| *ARSA* [607574] | Arylsulfatase A | 51,061,182–51,066,601 | Protein coding<br>pLI = 0<br>o/e = 0.90<br>(0.62–1.34) | Hydrolyzes cerebroside sulfate to cerebroside and sulfate. | Metachromatic Leukodystrophy [MIM: 250100] (AR).<br>1a. adult form;<br>1b. juvenile form;<br>1c. late infantile form. |
| *CHKB* [612395] | Choline kinase beta or choline/ethanolamine kinase | 51,017,387–51,021,253 | Protein Coding<br>pLI = 0<br>o/e = 0.59<br>(0.39–0.92) | Catalyze the phosphorylation of choline and ethanolamine; it is the first enzyme in the biosynthesis of phosphatidylcholine and phosphatidylethanolamine in all animal cells. | Muscular Dystrophy, Congenital, Megaconial Type [MIM:602541] (AR) |
| *TYMP* [131222] | Thymidine phosphorylase | 50,964,181–50,968,514 | Protein coding<br>pLI = 0<br>o/e = 0.52<br>(0.32–0.92) | Growth promoting activity on endothelial cells, angiogenic activity in vivo and chemotactic activity on endothelial cells in vitro. Catalyzes the reversible phosphorolysis of thymidine; the produced molecules are then utilized as carbon and energy sources or in the rescue of pyrimidine bases for nucleotide synthesis. | Mitochondrial DNA depletion syndrome 1 (MNGIE type) or Mitochondrial Neurogastrointestinal Encephalopathy Syndrome [MIM:603041] (AR). |
| *SBF1* [603560] | SET binding factor 1 | 50,883,431–50,913,464 | Protein coding<br>pLI = 0.999<br>o/e = 0.17<br>(0.12–0.27) | Probable pseudophosphatase. Promotes the exchange of GDP to GTP, converting inactive GDP-bound Rab proteins into their active GTP-bound form. Contains a Guanine nucleotide exchange factor (GEF) domain, necessary for its role in growth and differentiation. | Charcot–Marie–Tooth disease, type 4B3 [MIM:615284] (AR). |
| *TUBGCP6* [610053] | Tubulin gamma complex associated protein 6 | 50,656,118–50,683,400 | Protein coding<br>pLI = 0<br>o/e = 0.74<br>(0.6–0.93) | Involved in mitotic spindle formation, γ-tubulin ring complex (γ-TuRC) assembly and the localization of γ-tubulin to the centrosome. | Microcephaly and chorioretinopathy, autosomal recessive, 1 [MIM: 251270] (AR). |
| *MLC1* [605908] | Modulator of VRAC current 1 | 50,497,820-50,523,781 | Protein coding<br>pLI = 0<br>o/e = 0.74<br>(0.49–1.16) | MLC1 role in ion, water homeostasis in the brain and down-regulation of intracellular pathways involved in the activation and proliferation of astrocytes has been assumed (Brignone et al., 2015); however, the precise function of MLC1 remains still unknown. | Megalencephalic leukoencephalopathy with subcortical cysts [MIM: 604004] (AR). |

(Continues)

**TABLE 3** (Continued)

| Genes [OMIM n] | Gene description | Coordinates chr 22 (GRCh37/hg19) | Biotype pLI,[a] o/e (C.I.) | Biological function[b] | Associated Diseases[c] - OMIM: Phenotype [MIM n.]; (inheritance) |
|---|---|---|---|---|---|
| *ALG12* [607144] | -ALG12 Alpha-1,6-Mannosyl-transferase;<br>-Asparagine-linked glycosylation 12, homolog of;<br>-Dolichyl-*P*-mannose:Man-7-GlcNAc-2-PP-dolichyl-alpha-6-mannosyltransferase | 50,296,854–50,312,106 | Protein coding<br>pLI = 0<br>o/e = 0.66<br>(0.43–1.03) | Catalyzes the addition of the eighth mannose residue in an alpha-1,6 linkage onto the dolichol-PP-oligosaccharide precursor (dolichol-PP-Man(7)GlcNAc(2)) required for protein glycosylation. | Congenital disorder of glycosylation, Type Ig; CDG1G [MIM: 607143] (AR). |
| *TRMU* [610230] | TRNA 5-Methylaminomethyl-2-Thiouridylate Methyltransferase. | 46,731,298–46,753,237 | Protein coding<br>pLI = 0<br>o/e = 1.10<br>(0.79–1.56) | Catalyzes the 2-thiolation of uridine on the wobble positions of tRNA(Lys), tRNA(Glu), and tRNA(Gln), resulting in the formation of 5-taurinomethyl-2-thiouridine moieties. | (1) Deafness, mitochondrial, modifier of [MIM: 580000] (Mitochondrial).<br>(2) Liver failure, transient infantile [MIM:613070] (AR). |
| *CYB5R3* [613213] | Cytochrome B5 Reductase 3 (CB5R). | 43,013,846–43,045,405 | Protein Coding<br>pLI = 0<br>o/e = 0.49<br>(0.29–0.85) | (a) Membrane-bound in mitochondria: desaturation and elongation of fatty acids, cholesterol biosynthesis, hydroxylation of steroid hormones and xenobiotic drugs;<br>(b) Water-soluble in erythrocyte: methemoglobin reduction. | (1) Methemoglobinemia, type I; [MIM: 250800];<br>(2) Methemoglobinemia, type II [MIM: 250800], (AR). |
| *RNU12* [//] | RNA, U12 small nuclear. | 43,011,251–43,011,399 | RNA gene (snRNA) | RNA gene and is affiliated with the snRNA class. | Congenital cerebellar ataxia due to RNU12 mutation. |
| *NDUFA6* [602138] | NADH–Ubiquinone Oxidoreductase 1 Alpha Subcomplex 6. | 42,481,530–42,486,888 | Protein coding<br>pLI = 0<br>o/e = 0.93<br>(0.5–1.71) | Accessory subunit of NADH dehydrogenase (Complex I), the first enzyme of the mitochondrial respiratory chain which catalyzes the transport of two electrons from NADH to coenzyme Q leading to synthesis of ATP. | Mitochondrial complex I deficiency, nuclear type 33 [MIM: 618253], (AR). |
| *NAGA* [104170] | Alpha-*N*-acetylgalactosaminidase. | 42,454,338–42,466,846 | Protein coding<br>pLI = 0<br>o/e = 0.88<br>(0.61–1.3) | Removes terminal alpha-*N*-acetylgalactosamine residues from glycolipids and glycopeptides; it is required for the breakdown of glycolipids. | (1) Kanzaki disease [MIM: 609242], (AR);<br>(2) Schindler disease, type I [MIM: 609241], (AR);<br>(3) Schindler disease, type III [MIM: 609241], (AR). |

**TABLE 3** (Continued)

| Genes [OMIM n] | Gene description | Coordinates chr 22 (GRCh37/hg19) | Biotype pLI,[a] o/e (C.I.) | Biological function[b] | Associated Diseases[c] - OMIM: Phenotype [MIM n.]; (inheritance) |
|---|---|---|---|---|---|
| *TNFRSF13C* [606269] | Tumor necrosis factor (TNF) receptor superfamily member 13C. | 42,321,036–42,322,821 | Protein coding pLI = 0.27 o/e = 0.27 (0.1–1.27) | Enhances B-cell maturation and survival in vitro and is a regulator of the peripheral B-cell population. Promotes the survival of mature B-cells and the B-cell response. | Immunodeficiency, common variable, 4 [MIM: 613494], (AR). |

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CSF, cerebrospinal fluid; o/e: ratio of observed to expected loss-of-function variants occurring in a gene, based on a mutational model that takes into account sequence context, coverage, and methylation; C.I., confidence intervals.

[a]pLI: probability that a gene is loss-of-function intolerant, ranging from 0 to 1 (most tolerant to most intolerant,respectively).

[b]Summary of UCSC Genome Browser; Entrez Gene; GeneCards; UniProtKB/Swiss-prot. A more detailed description and tissue expression patterns drawn from the GTEx portal are available in Table S2.

[c]Associated diseases according to GeneCards (Version 4.14: March 11, 2020) and MalaCards (Version 4.14.0.3: March 8, 2020) are available in Table S2.

1. *ARSA* encodes for arylsulfatase A, a lysosomal enzyme whose deficit causes *metachromatic leukodystrophy* (*MLD*). This metabolic disease is characterized by (a) increased levels of urinary sulfatides leading to demyelinating sensorimotor polyneuropathy; (b) peculiar brain imaging abnormalities (periatrial and frontal horns leukodystrophy with periventricular sparing); (c) cognitive and behavioral regression. The late-infantile, juvenile and adult forms differ both in age at onset and in clinical presentation (Beerepoot et al., 2019).
2. *CHKB* codes for choline kinase beta. Homozygous and compound heterozygous variants cause *Congenital Muscular Dystrophy* (*CMD*), *Megaconial type*. Affected individuals show early onset muscle wasting, motor and speech delay, severe ID, microcephaly, and mitochondrial structural abnormalities at muscle biopsy. Ichthyosis-like skin changes, dilated cardiomyopathy, and other cardiac anomalies have been described in some patients (Mitsuhashi et al., 2011).
3. *TYMP* encodes thymidine phosphorylase, the enzyme that catalyzes the first step of the mitochondrial deoxyribonucleoside catabolic pathway. *TYMP* mutations cause the *mitochondrial neurogastrointestinal encephalomyopathy* (*MNGIE-MTDPS1*), one of the mitochondrial DNA (mtDNA) depletion syndromes (Pacitti et al., 2018). The major clinical features of *MNGIE* are severe gastrointestinal symptoms, peripheral neuropathy, and ocular signs including ophthalmoplegia and, less frequently, myopia and pigmentary retinopathy (Pacitti et al., 2018).
4. *SCO2* (see Category 1, Table 2 and Table S1).
5. *SBF1* is a member of the myotubularin protein family, involved in phosphoinositide-mediated signaling and membrane trafficking. Its mutations cause different forms of autosomal recessive *Charcot–Marie–Tooth Neuropathy* (*CMT4B3*, *AR-CMT2*). Disease onset usually occurs at the end of the first decade, with areflexia, cranial neuropathies, skeletal deformities, polyneuropathy, and extrapyramidal movements (Manole et al., 2017; Flusser et al., 2018).
6. *TUBGCP6* encodes for an integral constituent of the centriole, required for centriole overduplication and microtubular array formation. Homozygous or compound heterozygous mutations interfere with the proliferation and migration of neuroblasts, yielding microcephalic primordial dwarfism, characterized by prominent growth retardation, extreme microcephaly, severe ID, retinopathy, brain MRI malformations and additional neurological deficits (Martin et al., 2014).
7. *MLC1* encodes for a membrane protein similar to voltage-dependent potassium ($K^+$) channel subunits. It is almost exclusively expressed in the central nervous system (CNS), mainly in astroglial processes, where it plays a major role during the process of myelin deposition. Homozygous mutations in *MLC1* lead to the *classic*, *deteriorating form of megalencephalic leucoencephalopathy with subcortical cysts* (*MLC1*), characterized by progressive macrocephaly with mild ID, followed by the onset of progressive pyramidal and extrapyramidal signs, seizures, and severe brain MRI abnormalities. On average, loss of walking without support occurs in early adolescence. Rare *MLC1* missense mutations and

common variants have also been found associated with periodic catatonia (Selch et al., 2007).

8. *ALG12* encodes for an α6-mannosyltransferase; its deficit lead to the accumulation of oligosaccharides linked to lipid carriers in the endoplasmic reticulum. *ALG12* mutations produce a *congenital disorder of glycosylation, Type Ig* (*ALG12-CDG*), typically characterized by recurrent infections, neurodevelopmental delay, ID, muscle hypotonia, progressive microcephaly, failure to thrive, brain MRI alterations, decreased coagulation factors, cardiac defects, facial dysmorphisms and skeletal abnormalities suggestive of pseudodiastrophic dysplasia, strabismus, and retinitis pigmentosa (Esfandiari et al., 2019; Tahata et al., 2019).
9. *TRMU* is responsible for the synthesis of mitochondrial (mt) thiouridylase, necessary for the thiolation of uridine in the mt-tRNA. Homozygous *TRMU* deletions and mutations produce deficiencies in mtDNA-encoded proteins, essential for the respiratory chain, yielding (1) acute reversible infantile-onset liver failure, (2) nonsyndromic and aminoglycoside-induced sensorineural hearing loss, and (3) transient benign infantile myopathy characterized by an acute onset of severe muscle hypotonia, feeding difficulties, and lactic acidosis since neonatal life, at times accompanied by liver failure (Uusimaa et al., 2011; Gaignard et al., 2013).
10. *CYB5R3* encodes for a cytochrome b5 (cb5) reductase, which catalyzes the transfer of reducing equivalents from *NADH* to the hemoprotein of cb5, acting as electron donor to methemoglobin. *CYB5R3* mutations cause a *recessive congenital methemoglobinaemia* (*RCM*), distinguished in *type I* and *type II*. Both forms begin with cyanosis, but type I allows normal life expectations, whereas patients with type II usually do not reach adulthood and display a more severe phenotype, characterized by profound ID, failure to thrive, progressive microcephaly up to, in some cases, hypertonia and opisthotonus (Percy & Lappin 2008).
11. *RNU12* is an RNA gene; homozygous splicing mutations have associated with early onset cerebellar ataxia (Elsaid et al., 2017).
12. *NDUFA6* encodes for an accessory subunit essential for the assembly and activity of complex I (NADH ubiquinone oxidoreductase) of the respiratory chain. Its complete loss-of-function leads to the *mitochondrial complex I deficiency nuclear type 33* (*MC1DN33*) disease. The most important clinical features include generalized hypotonia, developmental delay, neurological regression and deterioration, seizures, and brain MRI abnormalities (Alston et al., 2018). Downregulation of *NDUFA6* gene expression has been linked to age-related decreases in atrial energetic efficiency in human hearts (Emelyanova et al., 2018) and to bipolar disorder I in some (Washizuka et al., 2005), but not all studies (Machado-Vieira et al., 2015).
13. *NAGA* produces a lysosomal exoglycosidase. Its deficiency causes *Schindler disease*, a well-characterized lysosomal storage disease clustered into three forms, *type I* (infantile-onset), *type II* also known as *Kanzaki disease* (adult-onset), and *type III* (Ferreira & Gahl, 2017). The clinical phenotypes of these three forms are described in the Supplementary Materials.
14. *TNFRSF13C* encodes the B cell-activating factor receptor (*BAFFR*) belonging to the *TNF* superfamily. Its homozygous deletion is associated with *common variable immunodeficiency disorder 4* (*CVID4*), characterized by B-cell lymphopenia, low serum levels of immunoglobulins, recurrent infections and lung disease. It is frequently associated with: (a) autoimmune disorders, especially hematologic and gastrointestinal; (b) dermatologic manifestations, like atopic dermatitis and vasculitis; (c) predisposition to develop lymphomas, as well as gastric and breast cancers (Pescador Ruschel & Vaqar, 2020).

### 3.3 | Category 3: Morphogenetic genes

This cluster encompasses 15 genes either (a) involved in multifactorial human diseases with additive mechanism, (b) with demonstrated morphogenetic roles in humans and mice, or (c) involved in animal models of human disease, but not yet found encompassing pathogenic variants in human patients (Table 4, Figure S1 and Table S3).

1. *RABL2B* null mice develop male infertility, polydactyly, and, with age, retinal degeneration, hepatic steatosis, insulin resistance and obesity, associated with decreased capacity for hepatic fatty acid oxidation (Kanie et al., 2017; Yi Lo et al., 2016). Only intronic variants with in silico influences on exon splicing have been reported (Hosseini et al., 2017).
2. *MAPK8IP2* encodes a scaffold protein able to facilitate signal transduction through the MAP kinase pathway, regulating the balance between proliferation and differentiation in a cell-specific manner (Semba et al., 2020). *MAPK8IP2*$^{-/-}$ mice exhibit prominent deficits in locomotor activity and ataxic gait, in addition to defective social interactions and learning (Giza et al., 2010). Even just the hemizygous loss of *MAPK8IP2* causes impaired neuronal maturation (Roessler et al., 2018).
3. *PLXNB2* codes for one of the Plexins (Plxn), large transmembrane receptors for semaphorins (Sema). Plxnb2 plays multiple important roles in the CNS, ranging from neural tube closure (Deng et al., 2007), to the proliferation and migration of cerebellar granule cell precursors, as well as cell specification, differentiation, and migration during corticogenesis, and excitatory synapse formation in the hippocampus (Deng et al., 2007; McDermott et al., 2018). Outside the CNS, *PLXNB2* is expressed in the immature glomeruli and mesenchyme of the developing kidney, where Plxnb2 binds Sema4C and contributes to the branching of the ureteric epithelium. Indeed, Plxnb2$^{-/-}$ mice frequently display morphological abnormalities of the kidney and urinary tract (Perälä et al., 2011).
4. *BRD1* produces a scaffold protein involved in chromatin remodeling through histone *H3K14* acetylation, critical to transcriptional regulation especially in hematopoietic and neural stem cells. Indeed, *BRD1*$^{-/-}$ mice exhibit defective neural tube closure, erythroid failure, and abnormal lenses. Several studies have found an association between *BRD1* gene polymorphisms and

**TABLE 4** Genes with a morphogenetic role, involved in human diseases with additive co-dominant, polygenic and/or multifactorial mechanisms, or implicated in animal models but not yet documented in human pathology (see also Table S3)

| Genes [OMIM n] | Gene description | Coordinates chr 22 (GRCh37/hg19) | Biotype pLI,[a] o/e (C.I.) | Biological function[b] | Associated Diseases[c] (a) OMIM: Phenotype [MIM n.]; (inheritance) (b) GeneCards: (version 4.14: March 11, 2020) |
|---|---|---|---|---|---|
| *RABL2B* [605413] | Member of RAS oncogene family like 2B | 51,205,920–51,222,087 | Protein coding pLI = 0 o/e = 0.89 (0.55–1.5) | GTPase involved in the ciliary entry of intraflagellar transport complexes (IFT-B). It influences the stability and recruitment of IFT-B to the centriole. | a) // b) Oligoasthenoteratozoospermia and Phelan-McDermid Syndrome. |
| *MAPK8IP2, IB2 or JIP2* [607755] | Mitogen-activated protein kinase 8 interacting protein 2. | 51,039,131–51,049,979 | Protein coding pLI = 1 o/e = 0 (0–0.1) | Encodes for a scaffold protein involved in the modulation of MAP kinase pathway proteins, in particular mitogen-activated protein kinase kinases pathway (MAPKKs), extracellular signaling-regulated kinases and c-Jun N-terminal kinases (JNKs). | a) // b) Cervical verrucous carcinoma and isthmus cancer. |
| *PLXNB2* [604293] | Plexin B2 | 50,713,408–50,746,001 | Protein coding pLI = 0.99 o/e = 0.19 (0.13–0.28) | Required for normal differentiation and migration of neuronal cells during brain corticogenesis and for normal embryonic brain development. Plays a role in RHO-A activation and subsequent changes of the actin cytoskeleton. | a) // b) Colloid adenoma and Walker-Warburg Syndrome. |
| *BRD1* [604589] | Bromodomain-containing protein 1. | 50,166,937–50,217,979 | Protein coding pLI = 1 o/e = 0.12 (0.07–0.24) | Component of the MOZ/MORF complex, which has a histone H3 acetyltransferase activity. | a) // b) Schizophrenia and nodular prostate. |
| *CELSR1* [604523] | Cadherin EGF LAG seven-pass G-type receptor 1. | 46,756,731–46,933,067 | Protein coding pLI = 1 o/e = 0.17 (0.12–0.25) | Encodes a member of the flamingo subfamily. Receptor that may have an important role in cell/cell signaling during nervous system formation. | a) Neural tube defects, susceptibility to [MIM: 182940]. b) Hereditary Lymphedema and Neural Tube Defects. |
| *FBLN1* [135820] | Fibulin 1 | 45,898,719–45,997,014 | Protein coding pLI = 0.92 o/e = 0.18 (0.1–0.34) | It may play a role in cell adhesion and migration along protein fibers within the extracellular matrix (ECM). Has been implicated in cellular transformation, tumor invasion, hemostasis and thrombosis. | a) Synpolydactyly, 3/3′4, associated with metacarpal and metatarsal synostoses [MIM:608180] (AD). b) Synpolydactyly 2 and Fbln1-related developmental delay-central nervous system Anomaly-Syndactyly Syndrome |
| *PRR5* [609406] | Proline-rich protein 5 | 45,072,688–45,133,561 | Protein coding pLI = 0.07 o/e = 0.30 (0.16–0.64) | Circadian clock gene that encodes a subunit of the mammalian target of rapamycin complex 2 (mTORC2). Regulates cell growth and survival in response to hormonal signals; plays an important role in modulation of platelet-derived growth factor signaling. | a) // b) Tuberous sclerosis 1 and tuberous sclerosis 2. |

(Continues)

**TABLE 4** (Continued)

| Genes [OMIM n] | Gene description | Coordinates chr 22 (GRCh37/hg19) | Biotype pLI,[a] o/e (C.I.) | Biological function[b] | Associated Diseases[c] (a) OMIM: Phenotype [MIM n.]; (inheritance) (b) GeneCards: (version 4.14: March 11, 2020) |
|---|---|---|---|---|---|
| *PARVB* [608121] | Parvin Beta | 44,420,157–44,565,112 | Protein coding<br>pLI = 0<br>o/e = 0.89<br>(0.63–1.28) | Adapter protein that plays a role in integrin signaling. Involved in the reorganization of the actin cytoskeleton and formation of lamellipodia. Plays a role in cell adhesion, cell spreading, establishment or maintenance of cell polarity, and cell migration. | a) //<br>b) Coronary restenosis and Miyoshi muscular dystrophy. |
| *SAMM50* [612058] | Sorting and assembly machinery component 50, *S. cerevisiae*, homolog of. | 44,351,261–44,392,412 | Protein coding<br>pLI = 0<br>o/e = 0.06<br>(0.41–0.89) | Plays a crucial role in the maintenance of the structure of mitochondrial cristae and the proper assembly of the mitochondrial respiratory chain complexes. Required for the assembly of TOMM40 (translocase of outer mitochondrial membrane 40 homolog) into the TOM complex. | a) //<br>b) Glanders and Melioidosis. |
| *PNPLA3* [609567] | Patatin-like phospholipase domain-containing protein 3. | 44,319,619–44,343,448 | Protein coding<br>pLI = 0<br>o/e = 0.71<br>(0.47–1.1) | Catalyzes coenzyme A (CoA)-dependent acylation of 1-acyl-sn-glycerol 3-phosphate (2-lysophosphatidic acid/LPA) to generate phosphatidic acid (PA), an important metabolic intermediate and precursor for both triglycerides and glycerophospholipids. | a) Fatty liver disease, nonalcoholic, susceptibility to, 1 [MIM:613282] (multifactorial).<br>b) Fatty liver disease and nonalcoholic fatty liver disease. |
| *SULT4A1* [608359] | Sulfotransferase family 4A Member 1. | 44,220,387–44,258,378 | Protein coding<br>pLI = 0.97<br>o/e = 0.07<br>(0.02–0.32) | Brain-specific sulfotransferase that catalyzes the transfer of a sulfonate group from 3′-phosphoadenosine 5′-phosphosulfate (PAPS) to an acceptor group of the substrate. Is believed to be involved in the metabolism of drugs and neurotransmitters in the central nervous sistem (CNS). | a) //<br>b) Anteroseptal Myocardial Infarction and Myeloproliferative Syndrome, Transient. |
| *MPPED1* [602112] | Metallophosphoesterase domain-containing protein 1. | 43,808,020–43,902,800 | Protein coding<br>pLI = 0<br>o/e = 0.44<br>(0.25–0.83) | It has metallophosphoesterase activity (in vitro). | a) //<br>b) Wilms Tumor, Aniridia, Genitourinary Anomalies, Mental Retardation Syndrome and Aniridia 1. |
| *SCUBE1* [611746] | Signal peptide, CUB and EGF-like domain-containing protein 1. | 43,599,229–43,739,394 | Protein coding<br>pLI = 0.96<br>o/e = 0.18<br>(0.11–0.31) | Could function as an adhesive molecule and its matrix bound and soluble fragments may play a critical role in vascular biology. | a) //<br>b) Crimean-Congo Hemorrhagic Fever and Deafness, Autosomal Dominant 31 |

**TABLE 4** (Continued)

| Genes [OMIM n] | Gene description | Coordinates chr 22 (GRCh37/hg19) | Biotype pLI,[a] o/e (C.I.) | Biological function[b] | Associated Diseases[c] (a) OMIM: Phenotype [MIM n.]; (inheritance) (b) GeneCards: (version 4.14: March 11, 2020) |
|---|---|---|---|---|---|
| *BIK* [603392] | BCL-2 interacting killer or BCL2-interacting killer (apoptosis-inducing). | 43,506,754–43,525,718 | Protein coding pLI = 0 o/e = 1.37 (0.74–1.91) | Accelerates programmed cell death through the mitochondrial pathway by recruiting calcium from the endoplasmatic reticulum and in the reshaping of mitochondrial cristae. | a) // b) // |
| *SREBF2* [600481] | Sterol regulatory element binding transcription factor 2. | 42,229,106–42,302,375 | Protein coding pLI = 0.21 o/e = 0.24 (0.15–0.38) | Regulates fatty acid synthesis, cholesterol biosynthesis and homeostasis. Binds the sterol regulatory element 1 (SRE-1) (5′-ATCACCCCAC-3′) found in the flanking region of the LDRL and HMG-CoA synthase genes. | a) // b) Atherosclerosis susceptibility and avascular necrosis. |

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; o/e: ratio of observed to expected loss-of-function variants occurring in a gene, based on a mutational model that takes into account sequence context, coverage and methylation; C.I., confidence intervals.

[a]pLI: probability that a gene is loss-of-function intolerant, ranging from 0 to 1 (most tolerant to most intolerant,respectively).

[b]Summary of UCSC Genome Browser; Entrez Gene; GeneCards; UniProtKB/Swiss-prot. A more detailed description and tissue expression patterns drawn from the GTEx portal are available in Table S3.

[c]Associated diseases according to MalaCards (Version 4.14.0.3: March 8, 2020) are available in Supplementary Table S3.

schizophrenia (SCZ) or bipolar disorder (BPD) (Nyegaard et al., 2010). The *BRD1*$^{+/-}$ mouse has been proposed as an animal model of SCZ (Qvist et al., 2017; Paternoster et al., 2019).

5. *CELSR1* encodes for a cadherin primarily expressed in the embryo and adult brain. It is a key component of the Wnt/planar cell polarity (PCP) pathway, crucial for embryonic neurodevelopment, as well as endothelial cell proliferation and migration. *CELSR1* mutant mice display brain malformations and behavioral dysfunctions (Boucherie et al., 2018). Gain-of-function mutations have been associated with neural tube and congenital heart defects, both in mouse and in humans. The DECIPHER database (https://decipher.sanger.ac.uk/) lists numerous cases linking *CELSR1* with ASD, hyperactivity, delayed speech and ID, as well as primary nonsyndromic lymphedema. Lastly, *CELSR1* plays a pivotal role also in kidney and ureter development, both in rodents and humans (Brzóska et al., 2016).
6. *FBLN1* encodes for fibulin-1, an extracellular matrix glycoprotein which interacts with fibroblast growth factor 8 (FGF8), playing a role in survival and migration of neural crest cells in mouse and vertebrate embryos. Null mouse embryos show cardiac abnormalities, cranial nerve defects and hypoplasia of organs derived from neural crest cells, including thymus, thyroid, aortic arch arteries (Cooley et al., 2008). *FBLN1*$^{-/-}$ mice also display high prenatal mortality, endothelial disruption in small vessels, glomerular abnormalities in the kidney, and delayed lung maturation (Kostka et al., 2001).
7. *PRR5* plays a crucial role for survival, proliferation, and differentiation of neural progenitor cells, as well as energy balance, obesity and hyperphagia. *PRR5* may also represent a predictable tumor suppressor gene in breast cancer. Lastly, a genome-wide association has been demonstrated between *PRR5-ARHGAP8* and BPD with binge eating behavior (McElroy et al., 2018).
8. *PARVB* protein interacts with *ARHGEF6* (Rho guanine nucleotide exchange factor 6), involved in integrin signaling and resulting in the activation of Rho GTPases. Marked hypomethylation of CpG26 in the regulatory region of *PARVB* variant 1 has been described in patients with nonalcoholic fatty liver disease (NAFLD). Overexpression of *PARVB* promotes apoptosis and is expected to foster liver fibrosis, while underexpression due to deletion or hypermethilation would be predicted to exert protective effects against NAFLD. An association between *PARVB* polymorphisms and development/progression of NAFLD has been documented in some studies (Kitamoto et al., 2015; Larrieta-Carrasco et al., 2018). Interstitial deletions of chr. 22q13 encompassing *PARVB* yield macrosomy and macrocephaly, possibly through the overactivation of the AKT-PTEN pathway (Disciglio et al., 2014).
9. *SAMM50* encodes for a mitochondrial outer membrane protein promoting the formation of mitochondrial intermembrane space bridging complexes. Long-term reductions in Samm50 result in the complete loss of mitochondrial cristae, depletion of respiratory complexes, decreased ATP production, increased ROS levels, fragmented mitochondria and increased autophagy flux,

consequently promoting PINK1-Parkin1-mediated mitophagy (Jian et al., 2018). Several studies have found a positive association between NAFLD and polymorphisms located in *SAMM50*, which may facilitate hepatic fibrosis by hampering mitochondrial function (Larrieta-Carrasco et al., 2018; The eMERGE Network, 2019).

10. *PNPLA3* encodes for an enzyme with triacylglycerol lipase and acylglycerol transacylase activities. *PNPLA3* transcription rates are inversely correlated with the severity of liver fibrosis (Sandhu et al., 2019). The M allele at SNP rs738409 (p.I148M) significantly reduces *PNPLA3* enzymatic activity toward glycerolipids and is strongly associated with NAFLD, alcoholic liver disease, and with cirrhosis and hepatocellular carcinoma in patients with NAFLD (The eMERGE Network, 2019). The MM genotype at rs738409 has been found associated with BPD (Kenneson & Funderburk, 2017). Finally, *PNPLA3* is highly expressed in podocytes and the MM genotype conveys enhanced risk of chronic renal disease (Mantovani et al., 2020).
11. *SULT4A1* is expressed only in neurons, throughout fetal life and infancy. It encodes an enzyme that sulfonates a variety of substrates and plays a pivotal role in modulating catecholamine, steroid and thyroid hormone levels. *SULT4A1*$^{-/-}$ mice manifest tremors, ataxic gait, and early death (Garcia et al., 2018). *SULT4A1* has been identified as a candidate gene for SCZ (Meltzer et al., 2008). Genome-wide expression analysis unveiled its profound downregulation in intracranial ependymomas (Modena et al., 2006).
12. *MPPED1* is highly expressed in the cortical plate of the embryonic mouse dorsal telencephalon, and to a lesser extent in the cerebral cortex postnatally. Its expression is sustained throughout life in hippocampal CA1 neurons (Chen et al., 2010). Mpped1 in vivo may modulate neuronal function through its metallophosphodiesterase activity and potential roles in SCZ and BPD have been hypothesized (Chen et al., 2010), but no direct evidence has been produced to date.
13. *SCUBE1* is primarily expressed in endothelial cells and platelets, but also in liver, kidney and the developing CNS. It promotes arterial thrombosis via its adhesive EGF-like repeats. In mice, *SCUBE1* is involved in early craniofacial development (Xavier et al., 2009), whereas in human kidney injury it favors renal tubular cell proliferation and re-epithelialization (Zhuang et al., 2010). Rare de novo disruptive *SCUBE1* missense variants have been detected in patients with obsessive–compulsive disorder (Cappi et al., 2020).
14. *BIK* encodes for a component of the Bcl-2 homology domain 3 (BH3)-only protein family involved in apoptosis. In particular, it is a pro-apoptotic tumor suppressor gene, critical to apoptosis selection in mature human B lymphocytes. In renal cell carcinoma, its expression is blunted either by loss of heterozygosity, or by DNA methylation. *BIK* deletions and mutations have been detected in human gliomas, colorectal cancers, head cancers, and in peripheral B-cell lymphomas (Chinnadurai et al., 2008).
15. *SREBF2*, also known as *SREBP2*, encodes for the sterol regulatory element (SRE)-binding transcription factors-2 involved in lipid homeostasis, fostering embryonic survival and limb patterning through the sonic-hedgehog pathway (Vergnes et al., 2016). It is significantly associated with SCZ (Stokowy et al., 2018). Reduced expression of *SREBF2* from the hypomorphic allele in *SREBF2*$^{-/hyp}$ mice (i.e., expressing 80%–90% lower levels of *SREBF2* through a Cre recombinase design) allows embryonic survival but is associated with reduced body weight and early death in females, whereas males survive but display lower cholesterol content in the liver and reduced expression of SREBP target genes (Vergnes et al., 2016).

### 3.4 | Category 4: Other genes

This group includes 178 genes listed in Table S4. These genes currently lack evidence of pathogenicity in humans and/or animal models, when haploinsufficient. This list encompasses 65 protein coding genes; 61 long noncoding RNA genes (lncRNA); 29 pseudogenes; 10 micro-RNA genes (miRNA); 8 uncategorized genes; 2 Piwi-interacting RNA genes (piRNA); 2 long intergenic noncoding RNAs (lncRNA) and 1 Clone/mRNA (Figure S1 and Table S4). *ATX10* is also included in this list, because its pathogenicity in spinocerebellar ataxia 10 is due to repeat expansion and gain-of-function toxic effects, not to haploinsufficiency.

## 4 | DISCUSSION

Patients with PMS show great interindividual variability in developmental trajectories, language skills, behavior, neurological signs, and in several comorbidities (Table 1). The haploinsufficiency of *SHANK3* can by itself determine PMS and this gene is considered the major player in causing the neurodevelopmental and behavioral features of this syndrome. However, patients with chr. 22 interstitial deletions not involving *SHANK3* at times present a clinical phenotype similar to the PMS phenotype caused by terminal 22q13 deletions (Simenson et al., 2014; Sarasua 2014a; Disciglio et al., 2014), suggesting that haploinsufficiency of 22q13 genes other than *SHANK3* plays an important role in shaping the PMS phenotype in each single patients. Based on the evidence summarized so far, we shall now provide an overview of how different dominant, recessive and morphogenetic genes, in addition to *SHANK3*, can contribute to each of the main neurological and systemic features defining the PMS phenotype. An overview of genotype–phenotype correlations ordered by locus, chromosomal position (telomeric to centromeric) and affected system/organ is provided with Table 5.

### 4.1 | Neurodevelopmental and neurological disorders

ASD represents the most recurrent behavioral comorbidity in PMS patients. Its incidence is highly variable, ranging from 26% to 84% depending on how patients are evaluated and diagnosed (Sarasua

**TABLE 5** Genotype–phenotype correlations of genes spanning the 22q13 deleted segment, ordered from telomeric to centromeric by Mb and highlighted in dark gray if autosomal dominant, mid-gray if autosomal recessive, light gray if morphogenetic and/or polygenic. See notes below, for gene not highlighted

| Mb | GENES | CNS | PNS | MYO | NDD, ID | ASD | PSYCH | REGR | EPI | MRI | MACR | MICR | STR | EYE | EAR | GI | HEPA | RENAL | HEART | IMM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 51 | *RABL2B* | | | | | | | | | | | | | x | | | x | x | | |
| | *SHANK3* | x | x | x | x | x | x | x | x | x | | | | | | x | | x | x | |
| | *ARSA* | x | x | | | | x | x | | x | | | | x | | x | | | | |
| | *MAPK8IP2* | x | | | | x | | | | | | | | | | | | | | |
| | *CHKB* | | | x | x | | | | | | | x | | | | | | | x | |
| 50 | *TYMP* | x | x | x | x | | x | x | x | x | | | x | x | | x | | | x | x |
| | *SCO2* | x | | x | x | x | | x | x | | | | x | x | | | | | x | |
| | *SBF1* | x | x | | x | | | | | x | | x | x | | x | | | | | |
| | *PLXNB2* | x | | | | | | | | x | | | | | | | | x | | |
| | *TUBGCP6* | x | | | x | | | | x | x | | x | | x | | | | | | |
| | *MLC1* | x | | | x | | x | x | x | x | x | | | | | | | | | |
| | *ALG12* | x | | | x | | | | | x | | x | x | x | x | x | | | x | x |
| | *BRD1* | x | | | | | x | | | | | | | x | | | | | | |
| 49 | | | | | | | | | | | | | | | | | | | | |
| 48 | | | | | | | | | | | | | | | | | | | | |
| 47 | | | | | | | | | | | | | | | | | | | | |
| 46 | *CELSR1* | x | | | x | x | x | | | x | | x | | | | | | x | x | |
| | *TRMU* | x | | x | | | | x | | | | x | | | x | x | x | | | |
| | *ATXN10*[a] | x | x | | x | | x | x | x | x | | | x | | | | | | | |
| 45 | *FBLN1* | x | | | x | | | | | x | | | | | | | | x | x | |
| | *UPK3A* | | | | | | | | | | | | | | | | | x | | |
| | *PRR5* | x | | | | | x | | | | | | | | | | x | | | |
| 44 | *PARVB* | | | x | x | | | | | | x | | | | | | x | | | |
| | *SAMM50* | | | | | | | | | | | | | | | | x | | | |
| | *PNPLA3* | | | | | | x | | | | | | | | | | x | x | | |
| | *SULT4A1* | x | | | | | x | x | | | | | | | | | | | | |
| 43 | *MPPED1* | | | | x | | | | | | | | | x | | | | x | | |
| | *SCUBE1* | | | | | | x | | | | | | | | | | | x | | |
| | *BIK*[b] | | | | | | | | | | | | | | | | | | | |
| | *CYB5R3* | x | | | x | | | | | x | | x | x | | | | | | | |
| | *RNU12* | x | | | | | | | | | | | | | | | | | | |

(Continues)

**TABLE 5** (Continued)

| Mb | GENES | CNS | PNS | MYO | NDD, ID | ASD | PSYCH | REGR | EPI | MRI | MACR | MICR | STR | EYE | EAR | GI | HEPA | RENAL | HEART | IMM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 42 | *TCF20* | x | | | x | x | x | | x | | x | | x | x | | x | | | | |
| | *NDUFA6* | x | | x | x | | x | x | x | x | | | | x | | x | | | x | |
| | *NAGA* | x | x | | x | x | | | x | x | | | | x | x | | | | x | |
| | *TNFRSF13C* | | | | | | | | | | | | | | | x | | | | x |
| | *SREBF2* | | | | | | x | | | | | | | | | | x | | | |

Abbreviations: ASD, autism spectrum disorder; CNS, central neurological signs: pyramidal extrapyramidal cerebellar signs and cranial nerve defects; EPI, epilepsy; EYE, retinopathy, blindness, myopia and/or keratokonus; EAR, deafness; GI, gastrointestinal symptoms; HEART, cardiac malformations or abnormalities; HEPA, liver failure, metabolic disorder, and/or obesity; IMM, immunodeficiency, recurrent infections; MYO, myopathy; MRI, Brain MRI abnormalities; MACR, macrocephaly and overgrowth; MICR, microcephaly; NDD, ID, neurodevelopmental delay, intellectual disability; PNS, peripheral neurological signs: peripheral neuropathy; PSYCH, bipolar disorder, schizophrenia, catatonia; REGR, motor and cognitive regression; RENAL, malformations of the kidney and/or of the urinary tract; STR, strabismus and/or ptosis.

[a]*ATXN10*—AD but not highlighted, because its pathogenic mechanism is due to neurotoxic gain-of function for repeat expansion.

[b]*BIK*—involved in multiple types of cancer.

et al., 2011; Soorya et al., 2013). Some authors have found a significantly smaller mean deletion size in PMS patients with ASD, compared to the average size of PMS patients without ASD (3.39 vs. 6.03 Mb, respectively) (Sarasua et al., 2011). These results would point toward larger deletions producing more severe cognitive and behavioral deficits able to obscure autistic traits. Others have described a positive correlation between dysmorphic features, number of medical comorbidities, sociocommunication deficits measured using the ADI and a larger deletion size (Soorya et al., 2013). *SHANK3* deletions or mutations represent a monogenic cause of ASD. Increased excitatory activity in striatal neurons during early development has been described in *SHANK3* KO mice, paired with a preferential impairment of the indirect striatal pathway, resulting in repetitive grooming behavior (Wang et al., 2017). Furthermore, these mice exhibit a reduction in mGLUR-mediated long-term depression, which may also be implicated in ASD (Wang et al., 2017).

In addition to syndromic autism, PMS can also encompass several neurodevelopmental and neurological features (Table 1), which may be explained also by haploinsufficiency in other genes (Tables 2–4). Among autosomal dominant genes, *TCF20* in the strongest candidate to produce neurodevelopmental derangement and severe neurological signs (Torti et al., 2019; The DDD Study, 2019), while evidence of dominant roles for *SCO2* appear less convincing (Pronicka et al., 2013; Frye et al., 2016). Another autosomal dominant disease due to the 22q13 gene *ATXN10*, *spinocerebellar ataxia type 10* (*SCA10*), is not being considered in the present analysis, because it is not due to haploinsufficiency or loss-of-function, but rather to an heterozygous *ATTCT* repeat expansion yielding gain-of-function neuronal toxicity (Figure S1 and Table S4). It is defined by sluggishly progressive cerebellar ataxia, dysarthria, dysphagia, ID, seizures, mild pyramidal signs, parkinsonism, peripheral neuropathy, and at times psychotic symptoms (Matsuura & Ashizawa, 2002). An involvement of *ATXN10* and/or *CELSR1* has been proposed in the onset of neurodevelopmental phenotypes present in carriers of interstitial deletions sparing *SHANK3* (Palumbo et al., 2018).

An atypical developmental trajectory or particularly severe neurodevelopmental and/or neurological symptoms in a child already diagnosed with PMS should raise concern over autosomal recessive *MLC* (Hamilton et al., 2018), *ALG12-CDG* (Tahata et al., 2019), *MC1DN33* (Alston et al., 2018) or *RCM* type II (Percy & Lappin 2008), possibly due to compound heterozygous mutation + deletion. In addition, homozygous *TUBGCP6* mutations can cause "microcephaly-Seckel syndrome spectrum" with severe ID and neurological deficits (Martin et al., 2014), while *PARVB* is correlated with X-linked ID, *MM* and *LGMD2B* diseases (Disciglio et al., 2014). Homozygous *CHKB* mutations cause muscular dystrophy (Mitsuhashi et al., 2011), while *TRMU* variants produce hypotonia and infantile myopathy (Gaignard et al., 2013). Peripheral neuropathy, ID, pyramidal, extrapyramidal or cerebellar signs may characterize the *CMT4B3* (Flusser et al., 2018), *Schindler* (Ferreira & Gahl, 2017), *MLD* (Beerepoot et al., 2019) and *MNGIE-MTDPS1* (Pacitti et al., 2018) diseases; in the same way, *RNU12* is associated with cerebellar signs (Elsaid et al., 2017).

Animal models suggest a role for several other 22q13 genes in *CNS* development and maturation, for which no counterpart in human pathology has yet been described. *RABL2B* knockout mice display a phenotype typical of ciliopathies, similar to Bardet-Biedl Syndrome; however, to this date, human ciliopathies have not unveiled mutations in this gene (Kanie et al., 2017). *MAPK8IP2* is involved in early neurodevelopment (Roessler et al., 2018) and *MAPK8IP2*$^{-/-}$ mice show autistic-like behaviors (Giza et al., 2010). Altered social behavior and neurocognitive deficits relevant to schizophrenia, accompanied by loss of striatal parvalbumin-containing interneurons, have also been recorded in BRD1$^{+/-}$ mice (Qvist et al., 2017; 2018). *CELSR1* mutant mice exhibit a reduced number of cortical neurons and behavioral impairment. In fact, *CELSR1*$^{Emx1cKO}$ mice are hyperactive, show abnormal exploratory behavior and social withdrawal (Boucherie et al., 2018). The relationship between *CELSR1* and the onset of neurodevelopmental phenotypes in PMS patients has been suggested (Palumbo et al., 2018). *SULT4A1* knockout mice display early severe neurological symptoms, decreased weight gain and death at P21-P25 (Garcia et al., 2018). Mice lacking *PLXNB2* exhibit defects in neural tube closure (McDermott et al., 2018). Importantly, the Domino tool available on VarSome platform (Quinodoz et al., 2017; Kopanos et al., 2018) estimates as "very likely dominant" five morphogenetic genes listed above (*MAPK8IP2*, *BRD1*, *CELSR1*, *FBLN1*, *SREBF2*) and "either dominant or recessive" three additional genes (*RABL2B*, *PLXNB2*, *SULT4A1*), pointing toward probable functional influences exerted by haploinsufficiency for at least some of these loci.

## 4.2 | Psychiatric disorders

Additional psychiatric disorders in PMS patients include BPD, psychotic symptoms in the context of mood episodes, and SCZ spectrum disorder. Regression of previously acquired motor, cognitive, and communication skills, usually beginning in adolescence or early adulthood, is another puzzling phenomenon which occurs in 28%–43% of PMS patients (Reierson et al., 2017). Another severe co-morbidity observed in as many as 53% of PMS patients is represented by catatonia, characterized by motor and autonomic dysregulation (Kohlenberg et al., 2020). The onset of these clinical conditions is often triggered by infections, hormonal changes or stressful life events (Kohlenberg et al., 2020). All psychiatric comorbidities, as well as behavioral regression, have been observed also in patients with only *SHANK3* haploinsufficiency, but other genes may contribute. Rare mutations or common variants at *MLC1* (Selch et al. 2007), *PRR5-ARHGAP8* (McElroy et al., 2018), *BRD1* (Nyegaard et al., 2010), *SULT4A1* (Meltzer et al., 2008), *SREBF2* (Stokowy et al., 2018), and *PNPLA3* (Kenneson & Funderburk, 2017) have been associated with SCZ spectrum disorders, and/or BPD. *CYP2D6* is involved in the metabolism of several endogenous neuroactive substrates, such as endocannabinoids and neuroactive steroids, and may be associated with differences in human behavior, cognition, personality and psychopathology (Peñas-Lledó & Llerena, 2014). In general, greater risk of comorbid BPD, ASD, hyperactivity and self-injurious behavior is present among patients with ring(22) as compared to patients with terminal deletions. Conceivably, the abnormal neural networking produced by 22q13 haploinsufficiency involving *SHANK3* and other genes could predispose to the development of affective and psychotic disorders through several mechanisms: (a) less efficient top-down control exerted by the neocortex on limbic circuitry, (b) less resilient recovery processes, and (c) greater vulnerability to long-term neurodegeneration.

Cognitive and motor regression can often follow the onset of acute psychiatric disorders (Kohlenberg et al., 2020). No association between regression and deletion size has been reported (Reierson et al., 2017). However, genes encoding proteins involved in mitochondrial functions, especially the electron transport chain, could be involved in the onset of regression and in early neurological deterioration (Frye et al., 2016). In particular, *TRMU*, *NDUFA6*, and *SCO2* influence the activities of mitochondrial complexes I and IV. Meanwhile, genotype–phenotype correlations based on deletion size do not support the role of several other 22q13 genes involved in mitochondrial function, including *ACO2*, *CPT1B*, *GRAMD4*, and *RABL2B* (Frye et al., 2016; Mitz et al., 2018). Second, the haploinsufficiency of some autosomal recessive genes could conceivably enhance vulnerability to mitochondrial dysfunction and promote behavioral regression, when in the context of an existing 22q13 deletion, through epistatic interactions with other deleted genes and/or epigenetic influences. Of note, neurological deterioration and cognitive/behavioral regression are hallmarks of autosomal recessive *MLD* (Beerepoot et al., 2019), *MLC* (Hamilton et al., 2018) and *MNGIE-MTDPS1* (Pacitti et al., 2018). A similar predisposing role toward regression could also be attributed to *SULT4A1*, which has been previously found associated with mitochondrial function and oxidative stress (Hossain et al., 2019), as well as with pathomorphic effects in schizophrenia (Meltzer et al., 2008).

## 4.3 | Epilepsy

Prevalence estimates for comorbidity rates of epilepsy with PMS vary greatly from 17% to 70%, depending on sampling and on whether febrile seizures are counted as "epilepsy" or not (Holder & Quach, 2016). Excluding febrile seizures, this comorbidity is present in approximately 20%–25% of PMS patients (Dhar et al., 2010; Kolevzon et al., 2014). *SHANK3* loss of function probably enhances vulnerability to epilepsy, but the mechanism is still unclear. To date, no significant difference in deletion size has been found in PMS patients with and without epilepsy (Sarasua et al., 2014a; Reierson et al., 2017). Nonetheless, several genes in the 22q13 region, if mutated or deleted, can cause disorders often involving also epilepsy: these include *TCF20*, *SCO2*, *ARSA*, *TYMP*, *TUBGCP6*, *MLC1*, *NDUFA6*, *NAGA* and *ATXN10* (Table 5).

## 4.4 | Neuroimaging

Structural brain MRI abnormalities have been described in a highly variable subgroup of PMS patients, ranging from 44% to 100%

(Soorya et al., 2013; Kolevzon et al., 2014) (Table 1). In addition, patients with r(22) display *NF2* features, such as intracranial meningiomas or vestibular schwannomas (Zirn et al., 2012; Kolevzon et al., 2014). Some anomalies can be reliably ascribed to *SHANK3*, as they were identified in patients carrying intragenic deletions or point mutations (Soorya et al., 2013). Importantly, the presence of major brain MRI abnormalities in patients carrying larger deletions may be due to one of the autosomal recessive syndromes described above, which should be duly sought (see Conclusions). In fact, *MLD* (Beerepoot et al., 2019) and *MNGIE-MTDPS1* diseases (Pacitti et al., 2018) are characterized by peculiar white matter lesions; also *MLC1* usually causes white matter abnormalities and subcortical cysts (Hamilton et al., 2018). Cerebellar white matter atrophy accompanied by gray matter degeneration in several brain regions have been described in *SCA10* (Matsuura & Ashizawa, 2002). Cerebellar hypoplasia, progressive white matter lesions and cortical atrophy have been associated with *MC1DN33* disease (Alston et al., 2018), whereas white matter abnormalities and atrophy of many brain structures are present in *Schindler disease* (Ferreira & Gahl, 2017). *ALG12-CDG* is marked by pachygyria, hypoplastic cerebellar vermis, cisterna magna enlargement and hypoplasia of the corpus callosum (Tahata et al., 2019); similarly, *CMT4B3* disease produces cerebellar atrophy (Flusser et al., 2018).

Lastly, also some morphogenetic genes can contribute to cerebral malformations. Cortical atrophy, white matter lesions and syringomyelia have been described in three consanguineous patients carrying a missense mutation in *FBLN1* (Bohlega et al., 2014). A reduction in cortical and gyral size has been associated with human *TUBGCP6* loss-of-function mutations (Martin et al., 2014). Moreover, animal models suggest a role of *CELSR1* in yielding reduced numbers of cortical neurons and abnormal brain architecture (Boucherie et al., 2018). *PLXNB2* knockout mice show aberrant granule cell proliferation and differentiation, leading to reduced cerebellar fissure formation and fusion of cerebellar folia (Friedel et al., 2007). *MAPK8IP2* null mice display reduced Purkinje cell dendritic arborizations (Giza et al., 2010). Therefore, although human cases have not been reported, *CELSR1*, *PLXNB2* and *MAPK8IP2* may represent plausible candidates for cerebral and cerebellar structural phenotypes, respectively (Aldinger et al., 2013).

### 4.5 | Craniofacial dysmorphisms

Minor aspecific dysmorphic features are well delineated in PMS patients (Soorya et al., 2013; Sarasua et al., 2014a,b and 2014b; Kolevzon et al., 2014) (Table 1). Some features such as dolichocephaly, large fleshy hands, dysplastic toenails, full brow, tall stature, as well as macrocephaly, facial asymmetry, and 2/3 toe syndactyly were found to be associated with larger deletion size (Sarasua et al., 2011; Sarasua et al., 2014a). Overall, a correlation between the number of dysmorphic features and deletion size has been reported (Soorya et al., 2013; Sarasua et al., 2014a). Indeed, craniofacial dysmorphisms were reported in patients carrying mutations in *TCF20*, *ALG12*, *NAGA*, *CELSR1* and *SCUBE1*, genes involved in early craniofacial development also in rodents (Xavier et al., 2009).

### 4.6 | Macrocephaly, microcephaly, and growth

Most patients with PMS show normal body growth and head circumference (Soorya et al., 2013). However, a consistent minority display macrocephaly, microcephaly and/or abnormal growth rates and final stature (Table 1). A correlation between macrocephaly and deletion size (>5 Mb) has been postulated (Sarasua et al., 2014a), and several genes in the distant 22q13 deleted segment may contribute. The study of interstitial deletions yielding a PMS-like phenotype points toward *PARVB* haploinsufficiency as one of the main contributors to macrocephaly and overgrowth, possibly through an excessive activation of PI3K-AKT signaling (Disciglio et al., 2014). A small minority of patients carrying dominant pathogenic mutations in the *TCF20* locus also display macrocephaly and/or overgrowth (Torti et al., 2019). Homozygous *MLC1* mutations determine macrocephaly since the first year of life (Hamilton et al., 2018). On the contrary, microcephaly has been described in autosomal recessive diseases involving *SBF1*, *CHKB*, *TUBGCP6*, *ALG12*, *TRMU*, and *CYB5R3*, while *CELSR1* has been implicated only in animal models.

### 4.7 | Sensory organs

The visual system can be affected by different 22q13 genes in separate eye compartments, distinguishing anterior chamber, retina and extrinsic muscles. Refractive defects involving lens, cornea and/or anteroposterior eye diameters, usually in the form of severe myopia or keratoconus, are produced by dominant mutations/deletions in *TCF20* (Torti et al., 2019) and *SCO2* (Tran-Viet et al., 2013), are associated with several autosomal recessive conditions due to homozygous mutations in *TYMP*, while lens abnormalities are also present in *BRD1*$^{-/-}$ mice. Retinal degeneration, either affecting rods and cones, ganglionar cells and/or the pigmented epithelium, have been associated with dominant *SCO2* mutations, autosomal recessive mutations in *TYMP*, *TUBGCP6*, and *ALG12*, or documented in *RABL2B*$^{-/-}$ mice. Ophthalmoplegia and/or strabismus are present in dominant *TCF20* mutations, as well as homozygous *TYMP*, *SBF1*, and *ALG12* mutations. Importantly, dominant effects of *SCO2* on the visual system are somewhat controversial: incomplete penetrance or clinical pictures requiring homozygous gene inactivation are likely.

Deafness is a rare instance, which has been described only in autosomal recessive conditions produced by biallelic inactivation of *SBF1*, *TRMU*, and *NAGA*.

### 4.8 | Gastrointestinal and hepatic symptoms

Gastrointestinal (GI) symptoms are frequent comorbidities in PMS patients (Table 1). *SHANK3* is expressed in myenteric neurons and

*Shank3αβKO* mice exhibit abnormal GI morphology, possibly increase intestinal permeability and microbiota dysregulation (Sauer et al., 2019). Some GI symptoms may thus be justified by *SHANK3* haploinsufficiency, although other 22q13 genes are possibly involved (Table 5). Dominant disorders caused by *TCF20* variants are commonly associated with constipation (Torti et al., 2019). Several autosomal recessive disorders are associated with GI symptoms (Table 3). The major clinical features of *MNGIE-MTDPS1* include severe gastrointestinal dysmotility associated with gut microbiome dysbiosis (Pacitti et al., 2018). In *MC1DN33* disease, dysphagia and feeding difficulties are often described (Alston et al., 2018); in *CVID* the main clinical features are autoimmune inflammatory colitis and liver dysfunction (Pescador Ruschel & Vaqar, 2020).

Hepatic disorders are sometime reported in PMS patients. The c.444C > G variant (p.I148M) located in the *PNPLA3* gene has been associated with decreased enzymatic activity, leading to macrovesicular liver steatosis and predisposition to develop steatohepatitis and fibrosis (Boccuto et al., 2018). Several studies have found a positive association between elevated transaminase serum levels or NAFLD and polymorphisms located in the *PNPLA3*, *SAMM50* and *PARVB* gene cluster (The eMERGE Network, 2019). *PNPLA3* appears to provide the most consistent contributions (Kitamoto et al., 2014; The eMERGE Network, 2019). *SAMM50* may facilitate hepatic fibrosis by hampering mitochondrial function (Larrieta-Carrasco et al., 2018; The eMERGE Network, 2019), but the other two flanking loci, *PARVB* and especially *PNPLA3*, may provide greater genetic and/or epigenetic contributions (Kitamoto et al., 2014,2015), although interethnic differences may also apply. *TRMU* is involved in autosomal recessive acute reversible infantile-onset liver failure (Gaignard et al., 2013). *RABL2B*$^{-/-}$ mice develop hepatic steatosis with decreased liver fatty acid oxidation (Kanie et al., 2017), but evidence in humans is lacking.

### 4.9 | Kidney and urinary tract malformations

Kidney malformations are moderately frequent, ranging from 17% to 38% of PMS patients (Kolevzon et al., 2014) (Table 1). These are mostly observed in carriers of larger deletions, suggesting a key role for genes other than *SHANK3* (Soorya et al., 2013). In particular, two genes, *CELSR1* and *UPK3A*, are strong candidates for urogenital anomalies (Palumbo et al., 2018). *CELSR1* can prevent the excessive growth of the murine kidney tubules, while loss-of-function mutations can lead to renal malformations in humans (Brzóska et al., 2016). *UPK3A* mutations may represent a rare monogenic cause or provide additive contributions to the risk of developing complex polygenic kidney diseases (Jiang et al., 2004; Jenkins et al., 2005; Schönfelder et al., 2006; Hwang et al., 2014). Recently, the *PNPLA3* polymorphism rs738409 (I148M) was correlated also with chronic kidney disease (Mantovani et al., 2020). Additional genes proposed to possibly play a role in renal malformations based on animal models, include *SCUBE1*, involved in renal tubular cell proliferation (Zhuang et al., 2010); *PLXNB2*, with *KO* mice exhibiting smaller kidneys and fewer branches of the ureteric epithelium (Perälä et al., 2011); *FBLN1*, relevant to the development of renal glomeruli (Kostka et al., 2001); and *RABL2B*, whose null mice display a phenotype similar to Bardet-Biedl syndrome, including major renal malformations (Kanie et al., 2017).

### 4.10 | Heart defects

Cardiac anomalies are variably present in up to 25% of PMS patients (Table 1). Their presence, assessed only through retrospective chart reviews and parent questionnaires (Kolevzon et al., 2014), was mainly observed in carriers of larger 22q13 deletions (Soorya et al., 2013). Among genes causing autosomal recessive diseases, several can produce cardiac malformations: *SCO2*, *TYMP* (Pacitti et al., 2018), *NAGA* (Ferreira & Gahl, 2017), *NDUFA6* (Alston et al., 2018), *CHKB* (Mitsuhashi et al., 2011), and *ALG12* (Tahata et al., 2019). Among morphogenetic genes, cardiac malformations have been described in humans carrying gain-of-function mutations in *CELSR1* (Qiao et al., 2016), and in *FBLN1*$^{-/-}$ mice (Cooley et al., 2008).

### 4.11 | Immune dysfunction and allergies

*SHANK3* is expressed in T-cells, where it acts as a scaffolding protein (Redecker et al., 2006), but evidence of its involvement in immune function is still scanty. Among autosomal recessive genes, *TNFRSF13C* mutations responsible for *CVID* are distinguished by low immunoglobulin levels, recurrent infections, autoimmune disorders, atopic dermatitis and vasculitis (Simenson et al., 2014; Pescador Ruschel & Vaqar, 2020). *TYMP* mutations yielding *MNGIE-MTDPS1* are frequently associated with recurrent infections and with gut flora alterations, which may also impact on adaptive immune responses (Pacitti et al., 2018). Finally, *ALG12-CDG* is characterized by hypogammaglobulinemia and B cell dysfunction, yielding severe infections (Tahata et al., 2019). Another gene, *NFAM1*, controls B-lymphocyte proliferation and has been purported to promote atopic dermatitis and IgE levels (Simenson et al., 2014), but evidence of direct pathogenetic roles in humans is lacking (Table S4).

## 5 | CONCLUSIONS

PMS is characterized by large interindividual differences at the clinical level, and by the lack of recurrent breakpoints yielding a gradient of highly different deletion sizes. Although *SHANK3* is regarded as the critical gene for core PMS symptoms, this article describes the potential contributions to clinical PMS manifestations by additional genes located in the largest 22q13 deleted region present in our sample. To this aim, genes have been classified based on their genetic mechanism of human disease generation, because this classification is aimed at subsequently verifying which genes actually do contribute to specific features of PMS in a sizable number of patients. Only the direct effects of 22q13 genes have been considered in our work, because

indirect effects mediated by the broader interactome, while scientifically interesting, could loosen the clinical connection between genotype and phenotype, reducing specificity, reliability, and predictive power in clinical settings. Particularly important in the context of PMS are autosomal dominant genes, namely *SCO2*, *UPK3A* and *TCF20*, in addition to *SHANK3*, because their clinical disease correlates would be predicted to affect all deletion carriers (Table 2). The literature currently supports full penetrance for *SHANK3* and *TCF20*, while *SCO2* and *UPK3A* have produced conflicting results and/or evidence of incomplete penetrance. However, disease penetrance will need to be verified specifically in PMS patients, especially for *SCO2* and *UPK3A* in the ocular and renal systems, respectively. In fact, penetrance could be differentially modulated by the presence of a 22q13 deletion, as compared to allele-inactivating mutations present on a wild-type genetic background. Secondly, the clinical pictures produced by genes involved in autosomal recessive disorders are especially relevant to clinicians, in order to identify compound heterozygous inactivation of both alleles. In the presence of more severe and/or peculiar clinical presentations (Table 3 and Table S2), it is critical to search for the presence of a mutation in the nondeleted allele, able to produce compound heterozygous biallelic inactivation. This search may be performed with targeted gene sequencing, if the clinical phenotype points toward a strong candidate gene, but clinical centers of excellence caring for many PMS patients may opt for the design of a dedicated next-generation sequencing (NGS) panel encompassing all functionally relevant 22q13 genes (Tables 2–4). Lastly, morphogenetic genes may confer additive co-dominant contributions, which can be initially explored assessing the association between deletion size and malformations for each system, organ and apparatus (Antonio M. Persico, Arianna Ricciardello and Coll., manuscript in preparation). Also the consequences of gene × gene and gene × environment interactions may be synergistically favored by haploinsufficiency at two or more 22q13 loci relevant to the development of the same system or apparatus.

In summary, deeper knowledge of genotype–phenotype correlations is indispensable to better understand the complexity and variability of PMS, promoting: a) clinically helpful predictions through a structured and genetically personalized medical work-up; b) targeted sequencing of specific genes based on phenotype or, alternatively, use of an unbiased NGS approach to explore all functional 22q13 genes (Tables 2–4); c) the identification of biological markers of developmental trajectory in children and disease progression in adolescents and adults; and d) the selection of possible targets for novel drug treatments.

The conceptual framework proposed in the present study, aimed at investigating genotype–phenotype correlations in PMS based on deletion size, is indeed worthwhile but displays some limitations, which must be duly acknowledged. The large clinical differences sometimes observed between PMS patients carrying identical deletions, and the surprising degree of severity displayed by some patients carrying very small deletions, both clearly point toward the critical role played by factors other than deletion size in shaping PMS at the clinical level. These factors may include: a) additional mutations, CNVs, small indels or epigenetic silencing in genes located in the nondeleted 22q13 allele; b) mutations or CNVs involving genes located outside the 22q13 deleted region or on other chromosomes; c) mutations or allelic variation in still unidentified genes that function as epistatic modifiers of *SHANK3* or, more broadly, in genes belonging to the interactome of 22q13 deleted genes; d) epigenetic factors, modulating gene expression especially from the nondeleted allele; e) constitutional mosaicism or dynamic mosaicism due to ring(22) instability; f) abnormal expression of non-coding RNAs that play an active role in transcriptional regulation during neurodevelopment; g) greater penetrance of familial genetic loading for other psychiatric disorders, like BPD, in the presence of 22q13 deletions or *SHANK3* mutations; h) somatic mutations producing abnormal neural networks or microscopic neuroanatomic malformations small enough not to be detected by usual neuroimaging methods; and i) environmental factors, such as ischemic hypoxic encephalopathy following perinatal asphyxia at birth. Evidently, the haploinsufficiency of different sets of genes located in the 22q13 region, depending on deletion size, can only partly explain phenotypic variability in PMS. However, reaching a conclusive definition of deletion size contributions to phenotypic variability in PMS will be instrumental to then move ahead to determine the role of additional genetic and epigenetic factors, either located in the 22q13 region or elsewhere in the genome.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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