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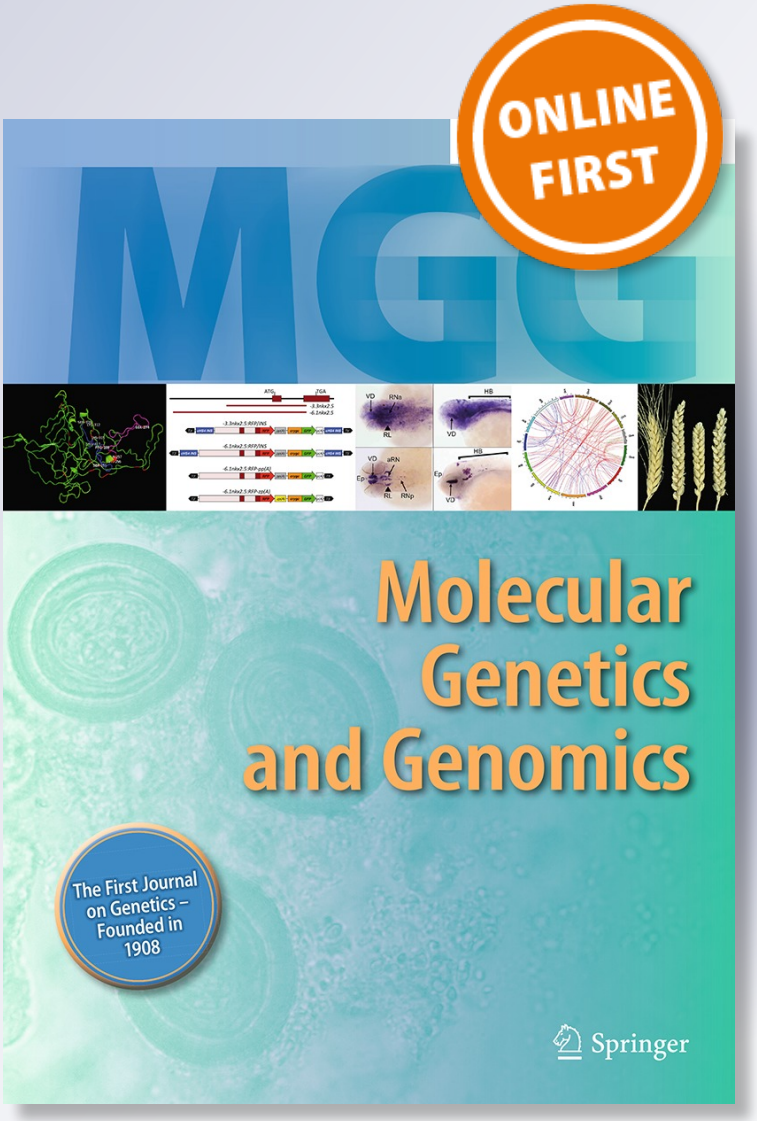

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REVIEW

Primordial dwarfism: overview of clinical and genetic aspects

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Abstract Primordial dwarfism is a group of genetic disorders which include Seckel Syndrome, Silver–Russell Syndrome, Microcephalic Osteodysplastic Primordial Dwarfism types I/III, II and Meier–Gorlin Syndrome. This genetic disorder group is characterized by intra-uterine growth retardation and post-natal growth abnormalities which occur as a result of disorganized molecular and genomic changes in embryonic stage and, thus, it represents a unique area to study growth and developmental abnormalities. Lot of research has been carried out on different aspects; however, a consolidated review that discusses an overall spectrum of this disorder is not accessible. Recent research in this area points toward important molecular and cellular mechanisms in human body that regulate the complexity of growth process. Studies have emerged that have clearly associated with a number of abnormal chromosomal, genetic and epigenetic alterations that can predispose an embryo to develop PD-associated developmental defects. Finding and associating such fundamental changes to its subtypes will help in re-examination of alleged functions at both cellular and developmental levels and thus reveal the intrinsic mechanism that leads to a balanced growth. Although such findings have unraveled a subtle understanding of growth process, we further require active research in terms of identification of reliable biomarkers for different subtypes as an immediate requirement for clinical utilization. It is hoped that further study will advance the understanding of basic mechanisms regulating growth relevant to human health. Therefore, this review has been written with an aim to present an overview of chromosomal, molecular and epigenetic modifications reported to be associated with different subtypes of this heterogenous disorder. Further, latest findings with respect to clinical and molecular genetics research have been summarized to aid the medical fraternity in their clinical utility, for diagnosing disorders where there are overlapping physical attributes and simultaneously inform about the latest developments in PD biology.

Keywords Primordial dwarfism · Subtypes · Clinical · Genetics

Introduction

Growth is a complex process and a fundamental attribute of all living organisms which is achieved primarily by a positive balance between cellular proliferation and apoptosis (Daniel et al. 2008). It is a highly regulated and continuous phenomenon controlled by genetic, metabolic and environmental factors. Failure of regulation of growth pathway leads to growth disorders with two extreme outcomes—undergrowth and overgrowth but the complex molecular level mechanisms involved in the regulation of prenatal and postnatal growth yet remain to be fully understood. In the present review, we shall discuss a form of severe growth retardation called Primordial Dwarfism (PD) which is majorly a genetic disorder. This disorder is controlled by a

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strong genetic component that regulates a complex network of endocrine factors integrating them with cellular proliferation, differentiation and apoptotic processes in target tissues, particularly so at the growth centres of the long bones (Müller et al. 2012).

PD is a rare group of disorders characterized by both prenatal and postnatal growth retardation where the individuals are extremely small for their age even as a fetus. Its prevalence report estimates 4 million babies to die in the first 4 weeks of life (the neonatal period) with almost 99 % of neonatal deaths (Lawn et al. 2011; Cousens et al. 1995). Such individuals in the fetal stage are often diagnosed to have Intrauterine Growth Retardation (IUGR) and the average birth weight for affected individuals is very low, with overall proportion of the body being smaller for gestational age (SGA) and both the sexes getting equally affected (Codd et al. 2009). Further, IUGR is known to confer perinatal morbidity and mortality and affects 10 % of all pregnancies (Unterscheider et al. 2013). Recent molecular level studies found the signaling pathways like insulin growth factor signaling, hippo signaling cascade, the mitogen-activated protein kinase (MAPK) pathway and potent morphogen regulators like TGF-β, Notch and Wnt to play a key role in molding organisms size.

Thus, PD represents an interesting group of genetic disorders where the results of cellular growth by different pathways, its disruption and altered growth can be well studied. Owing to the immense diversity within these individuals and its overlapping features with other genetic diseases, we have summarized its subtypes, clinical features, chromosomal changes and susceptible genes that have been reported to be linked with development of the five PD subtypes in this review.

Subtypes of primordial dwarfism

Clinically, PD is a highly heterogeneous condition and can be grouped into five major subtypes. Most individuals with PD have a reduction in head size in proportion to or smaller than their body size. This is the most characteristic feature of PD which distinguishes it from other forms of dwarfism and is classified as 'microcephalic primordial dwarfism' and it includes Seckel syndrome (SS), Majewski/Microcephalic osteodysplastic primordial dwarfism (MOPD) Types I/III, Type II, and Meier–Gorlin syndrome (MGORS). However, there is a separate group of patients found with normal head size called as Silver–Russell syndrome (SRS) (Klingseisen and Jackson 2011). The 5 subtypes have distinguishing clinical features and inheritance patterns which have been summarized in Table 1. Further, a flow chart on possible diagnostic evaluation of suspected PD patients has been represented in Fig. 1 and the different factors that contribute to early developmental defects have been represented in Fig. 2. The associated chromosomal abnormalities and mutated genes that alter the particular gene functions in PD subtypes have been given in Table 2.

Clinical features of primordial dwarfism

Extreme clinical heterogeneity in PD and its subtypes can be attributed to a number of altered physical features. Patients with SS have been reported to have characteristic facial appearance, with beaked nose, microcephaly, scoliosis, hip dislocation, delayed bone age, radial head dislocation, and seizures (Sugio et al. 1993). Other anomalies such as zygomatic and mandibular hypoplasia, sternal abnormalities, clinodactyly, low-set ears with hypoplastic

Table 1 Subtypes existing in primordial dwarfism, their distinguishing clinical features and inheritance pattern

Primordial dwarfism subtypes	Category (with respect to head size)	Distinguishing clinical features	Inheritance pattern
Seckel syndrome	Microcephalic primordial dwarfism (brain size reduced to a third of normal volume)	Extremely small head with narrow face, dental alterations, beak-like protrusion of nose, receding mandible	Autosomal recessive
Majewski/Microcephalic osteodysplastic primordial dwarfism (MOPD) types I/III		Dry skin, sparsity of hairs and eyebrows	Autosomal recessive
MOPD type II		Prominent nose and eyes, abnormally small or missing teeth, and a high squeaky voice	Autosomal recessive
Meier–Gorlin syndrome		Underdeveloped ears, absent/hypoplastic patellae	Autosomal recessive
Silver–Russell syndrome	Normal head size	Small triangular face, micrognathia, dental anomalies	Autosomal dominant or autosomal recessive and genomic imprinting

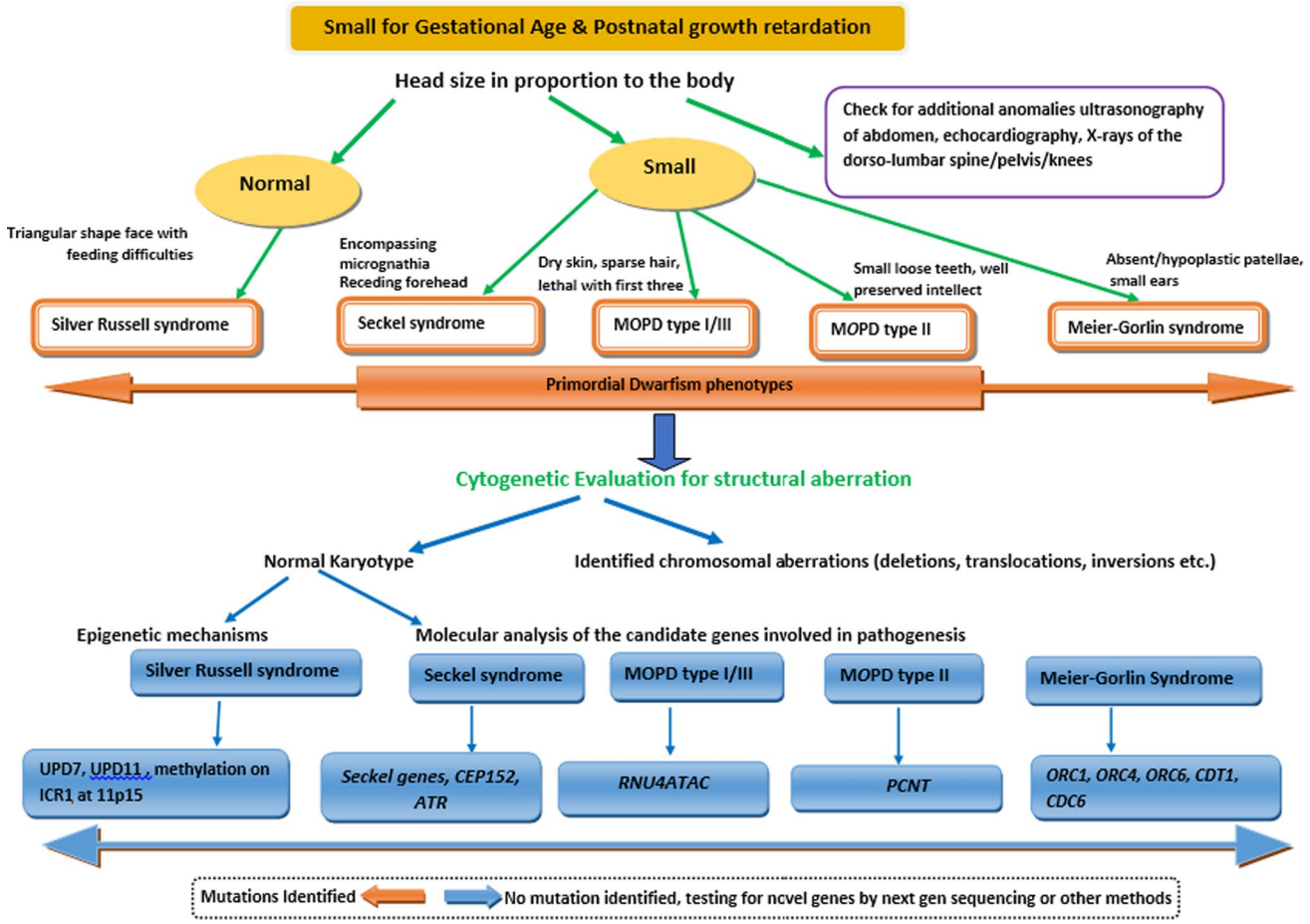

Fig. 1 Diagnosis of primordial dwarfism at various levels: clinical, cytogenetic and molecular level detection approaches

lobules and large eyes with downslanting palpebral fissures, beaked-like protrusion of nose, narrow face and receding lower jaw have also been reported (Sisodia et al. 2014; Harshavardhan et al. 2007). Some rare conditions like polyarteritis nodosa, (Kutlu et al. 2004) osteosarcoma, (Faivre et al. 2002) dental anomalies, (Kjaer et al. 2001; De Coster et al. 2006; Regen et al. 2010) moyamoya syndrome, (Codd et al. 2009), dermatologic involvement with atopic dermatitis, diffuse hypopigmented macules and papules, (Brackeen et al. 2007), dislocation of eye lens (Seider et al. 2002; Reddy and Starr 2007) and morgagni hernia (Onder et al. 2007) have also been reported.

In 1982, Majewski et al. reviewed the literature and distinguished three types of 'osteodysplastic primordial dwarfism' with generalized bony anomalies ('osteodyplastic') from non-osteodysplastic 'Seckel syndrome' characterized by less severe growth retardation, more severe microcephaly and mental retardation where the growth is severely stunted that the patients reach the average height of newborn by the age of 3 or 5 (Majewski and Goecke 1982; Majewski et al. 1982a, b; Bober et al. 2010). Therefore, owing to such differences, the subtypes have been classified into 3 categories, i.e., MOPD I, MOPD II and MOPD III. MOPD I affected patients have been reported to have corpus callosum agenesis, seizures, attacks of apnea, hair thinness including scalp hair, eye lashes and eyebrows. They also have short vertebrae, elongated clavicles, bent femurs, hip displacement, and microcephaly. On the other hand, MOPD II patients are characterized by squeaky voice, microdontia, widely spaced primary teeth, poor sleep patterns, delayed mental development, frequent sickness, breathing problems, eating problems, hyperactivity, farsightedness, brain aneurysms and delayed bone age in addition to microcephaly (Hall et al. 2004; Bober et al. 2010; Majewski et al. 1982b). Other marked features include intrauterine and postnatal growth failure, mental and statomotor retardation and disproportionate short stature due to short limbs. Characteristic skeletal abnormalities comprise small iliac wings with flat acetabular angles, coxa vara, V-shaped distal femoral metaphyses, triangular distal femoral epiphyses as well as pseudoepiphyses of metacarpals, short first metacarpals and brachymesophalangy

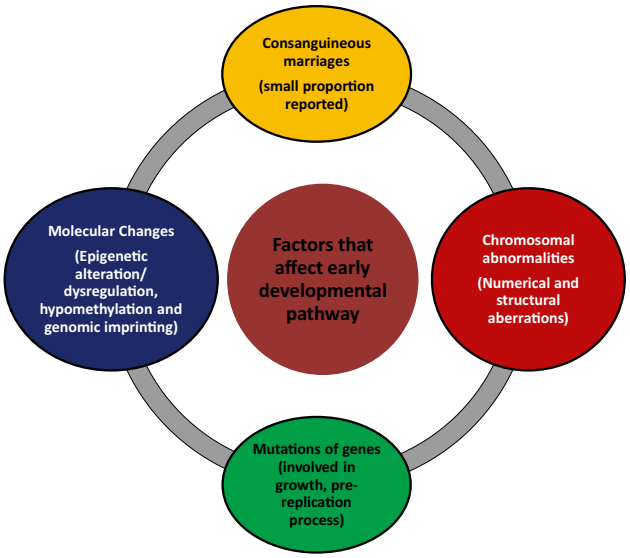

Fig. 2 Factors that contribute to early developmental defects include consanguineous marriages although a small proportion of studies report this, chromosomal aberrations that include numerical and structural alterations, mutations of various genes involved in growth process pathways and pre-replication process and molecular level alterations that include epigenetic changes

(Majewski and Goecke 1998). In addition to all these features, common hematologic abnormalities such as leukocytosis and thrombocytosis have also been observed in these patients (Unal et al. 2014). The other subtype MOPD III is characterized by intrauterine dwarfism with platyspondyly and anomalies of pelvis and clavicles (Majewski et al. 1982b). Interstingly, MOPD I and III exhibit some common manifestations such as dry skin, sparseness of hair, eyebrows and severe malformations in cerebral cortex but both the conditions have a poor prognosis and distinction between Type I and III is based on radiological criteria. Short and bowed humeri, femora and dislocation of hips are considered typical of type I whereas type II is characterized by elongated clavicles, cleft vertebral arches, lumbar platyspondyly, abnormal pelvis and enlarged metaphyses (Sigaudy et al. 1998). However, despite such characteristic physical differences, many researchers are now of the view that MOPD subtype I and MOPD subtype III are phenotypic variations of the same entity and hence should be grouped together (Meinecke and Passarge 1991; Pierce and Morse 2012).

In the fourth subtype SRS, patients are characterized by low birth weight, short stature, minor features such as macrocephaly, clinodactyly, body asymmetry, craniofacial dysmorphism, distinctive triangular face, prominent forehead resulting in a pseudohydrocephalic appearance and poor post-natal growth (Rao et al. 2003; Hajdas-Kudela et al. 1997; Price et al. 1999). It has been observed that final height in SRS patients is higher as compared to other PD subtypes and

Table 2 The chromosomal abnormalities, mutated genes and the faulty functions affecting the specific primordial dwarfism subtypes

Primordial dwarfism subtypes	Reported chromosomal abnormalities	Genes reported to be mutated	Relevant faulty gene functions
Seckel syndrome	Increased chromosomal instability at fragile sites after replicative stress and specific cases of	ATR, ATRIP, CENPJ, CEP152, RBBP8	Involved in signaling of DNA damage response, Centriole biogenesis, genome stability and regulation of cell proliferation
Majewski/microcephalic osteodysplastic primordial dwarfism (MOPD) types I/III	–	U4atac	Component of minor spliceosome complex
MOPD type II	–	PCNT, IGF1R	Essential for centrosome structure, function, regulation of cell cycle and signaling of cell growth and survival control
Meier–Gorlin syndrome	–	ORC1,ORC4, ORC6, CDT1,CDC6	Encodes components of the prereplication process and functional role during replication
Silver–Russell syndrome	mUPD, mosaic trisomy, duplications, deletions, microdeletions translocations hypomethylation, DNA methylation changes, genomic imprinting, epigenetic alterations and unambiguous copy number changes	CUL7, OBSL1, SGCE, ZFP57, NF1, CSH1	Disrupts the ability and interferes in process of ubiquitination, regulates microtubules dynamics, imprinting disorder, gene silencing, prevents cell overgrowth and regulation of growth control

that they have webbed toes, non-descended testicles, hypospadias, weak muscle tone, delayed bone age, thin upper lip, high pitched voice, small chin, delayed closure of the fontanel, hypoglycemia, and a broad forehead which may appear to be triangular in shape and large for their small body size with few patients exhibiting hemi-hypertrophy signs as well (Bongers et al. 2001; Russell 1954).

The other type, i.e., MGORS is characterized by microtia, mid-face hypoplasia, micrognathia, lower limb arthrogryposis and cryptorchidism (Meier et al. 1959; Gorlin et al. 1975). Additionally, other findings report short stature, slender body build, craniofacial anomalies, delayed skeletal development, hypogonadism, absent/hypoplastic patellae, markedly small ears, bilateral microtia, triad of pre- and postnatal growth retardation, variable degree of deafness, curved clavicles, deformed ribs, elbow dislocation, evident pre- and post-natal growth impairment and microcephaly (Boles et al. 1994; Bicknell et al. 2011b).

Reported chromosomal changes in primordial dwarfism and its subtypes

Chromosomal studies in SS have reported locus SCKL1, SCKL2 and SCKL3 to be mapped to chromosomes 3q22.1–q24, 18p11.31–q11.2 and 14q23, respectively (Goodship et al. 2000; Borglum et al. 2001 and Kilinç et al. 2003). Aberrations in chromosomes and chromosomal instability have been reported in few cases (Butler et al. 1987) and increased chromosomal instability has been reported at common fragile sites following replicative stress (Bobabilla-Morales et al. 2003; Casper et al. 2004). Deletion in short arm of chromosome 18 has been reported by Panigrahi et al. (2009) and a normal karyotype with increase in length of the satellite on the p arm of chromosome 15 was reported by Ramalingam et al. (2012).

In SRS, a plethora of chromosomal changes specific to case reports have been described. Eggermann et al. (2010) reported duplication of chromosome 11p15 and an unbalanced translocation t(11;15)(p15.5:p12). Similarly, Coutton et al. (2012) found duplication of 17p13.1 which is a known region that harbors putative candidate genes responsible for SRS. On the other hand, Lin et al. (2010) through whole genome array analysis in 5 patients and Spengler et al. (2010) in 1 patient reported microdeletions on chromosomes, i.e., 1q23q24.3, 7p15.3, 13q31.3, 14q32.31, 15q26.2 and 12q14, respectively. Further, these patients have also been reported to carry chromosomal translocations, i.e., t(17;20)(q25;ql3) (Ramirez-Duenas et al. 1992) and t(11;16)(p13;q24.3) (Rao et al. 2003). Other chromosomal abnormalities include mosaic trisomy 7 (Abdelhedi et al. 2014) and a deletion in chromosome 17 (17q22–q24) (Eggermann et al. 1998).

However, in addition to these chromosomal aberrations, 50 % of SRS cases have maternal uniparental disomy (UPD) of chromosome 7 and hypomethylation of H19 gene but 50 % of SRS patients still remain without known genetic/epigenetic alterations. Genomic imprinting which is a way of epigenetic regulation and dysregulation of 11p15 has been reported in a number of SRS cases and, further, recent investigations also show UPD outside the chromosome 7, DNA methylation changes in imprinted gene loci outside 11p15.5 and abnormalities in DNA methylation in multiple loci (Dias et al. 2012). Additionally, new cis-acting and trans-acting factors that regulate 11p15 imprinting and hypomethylation of ICR1 (telomeric imprinting centre) domain and small copy number variations have also been reported (Demars and Gicquel 2012). Large number of unambiguous CNCs (copy number changes) and a heterozygous deletion of chromosome 15q26.3 including the IGF1R gene (2.6 Mb), an atypical distal 22q11.2 deletion (1.1 Mb), and a pseudo-autosomal region duplication (2.7 Mb) in a male patient with no UPD of chromosome 7 or 11 was reported by Bruce et al. (2010) in their study involving 22 SRS patients. Further, Bonaldi et al. (2011) document the involvement of microduplication restricted to ICR2 domain when maternally transmitted while epigenetic alterations on chromosome 11p15, H19 promoter, distal region of ICR1 and hypomethylation of the DMR (differentially methylated region) of the H19 gene were reported by Horike et al. (2009) and Lin et al. (2010), respectively. Fascinatingly, recent advancements in molecular biology have provided evidence for Methylation-Specific (MS) pyrosequencing in enhancing the detection of molecular defects in SRS which highlights the importance of methylation status of 11p15.5 in playing an important role in fetal growth (Lee et al. 2013).

On the other hand, such chromosomal changes in other subtypes of PD, i.e., MOPD Types I/III, Type II and MGORS have not been reported yet.

Reported genes likely to be involved in primordial dwarfism and its subtypes

Growth deficiency can be attributed to genes that play a decisive role in growth control and its related pathways since disease severity and susceptibility are affected by normal genetic variations with different splicing efficiency (Wang and Cooper 2007). Moreover, recent studies have suggested that the phenotypic variability shown by PD patients could be due to exonic mutations of various functional genes relevant to corresponding phenotypes (Klingseisen and Jackson 2011).

Studies on SS reportedly identified hypomorphic splicing mutation and compound heterozygous mutation

in 'ataxia telangiectasia' and rad3-related (*ATR*) gene (O'Driscoll et al. 2003; Mokrani-Benhelli et al. 2013) as a causal genetic defect. However, a few years later Ogi et al. (2012) identified mutations in *ATRIP* gene that encodes for an interacting partner of *ATR* among SS patients. This finding reported a novel pathway in PD and showed that defective ATR–ATRIP complex leads to impaired DNA damage response mechanisms and difficulties during replication from which cells cannot recover. Further, experiments by Alderton et al. (2004) in seckel cell lines found that defects in ATR-signaling pathway result in failed checkpoint arrests. It has also been suggested that *ATR* gene deficiency causes genomic instability due to defective ATR-dependent DNA damage signaling and thus leads to SS (Mokrani-Benhelli et al. 2013). *ATR* gene has also been reported to play an important role in telomere maintenance during and/or after telomere replication and thus it can play a vital role in contributing to genomic instability (Pennarun et al. 2010). Similarly, mutations in gene *CENPJ* and *CEP152* can cause SS by affecting the cellular responses to DNA damage and early growth (Al-Dosari et al. 2010). *CENPJ* gene mutation affects another pathway of early development that leads to increased cell death due to mitotic failure during embryonic development and results in proportionate dwarfism that is associated with CENPJ-Seckel syndrome (Al-Dosari et al. 2010; McIntyre et al. 2012). Similarly, identification of *CEP152* mutations in SS has shown that its impaired function leads to the accumulation of genomic defects through enhanced activation of ATM signaling and increased H2AX phosphorylation which is a measure of accumulated replicative stress. Thus, this centrosomal protein which helps in maintaining the genomic integrity and the ability to respond to DNA damage can cause defects in cells growth process (Kalay et al. 2011). Additionally, this gene has also been reported to hold answer for human microcephaly development because of its vital role in disproportionate increase in total brain size and its knockdown leading to centriolar or ciliary defects. Although the exact function remains yet to be decipherd this study still points to the involvement of this gene in microcephaly development which is a key feature of SS (Guernsey et al. 2010). Moreover, investigations by Rauch et al. (2008) and Kalay et al. (2011) clearly show that *CEP152* mutations lead to impaired mitotic spindle formation and delay in mitotic progression that disturbs the stem cells. Consequently, impaired centrosome function can affect stem cells asymmetric cell division and perturb the 'stem cell identity' process disturbing the early neurogenesis course again suggesting its critical role in microcephaly development. Further, a previous study by Borglum et al. (2001) had identified the locus SCKL2 to chromosome 18p11.31–q11.2 in a particular family and a decade later Qvist et al. (2011) reported two mutations within *CTIP* (*RBBP8*) gene in the same family that led to an expression of C-terminally truncated form of CtIP. The study by the latter group suggested that the mutation within the *CTIP* gene is the molecular cause for the disease in the SCKL2 described family. Additionally, another interesting study has also reported a homozygous missense mutation in *RBBP8* gene combined with a heterozygous exonic deletion of *NRXN1* for Seckel/Jawad syndrome-like phenotype (Agha et al. 2014).

In MOPD I subtype, Abdel-Salam et al. (2011)and Nagy et al. (2012) documented a homozygous mutation in *RNU4ATAC* gene (g.55G > A) that codes for U4atac snRNA and a bialleleic mutation in the same gene, respectively. The former study was also the first one to report on vasculopathy and pigmentary disorders in MOPD I that were not reported in previous MOPD I patients. Simultaneously, He et al. (2011) showed that the introduction of wild-type U4atac snRNA into MOPD I cells enhanced U12-dependent splicing that is found to be defective in such patients and highlighted the essential role of minor spliceosome components in human development. A similar conclusion on the role of spliceosome machinery U4atac snRNA in early human development and postnatal survival was also reported by Edery et al. (2011). Further, Jafarifar et al. (2014) recently studied the molecular basis of mutations in *RNU4ATAC* employing a variety of in vitro and in vivo assays. There results found only one mutation (124G>A) from a total of nine mutations to significantly reduce the expression of U4atac snRNA and four mutations (30G>A, 50G>A, 50G>C and 51G>A) to show impaired binding of essential protein components of the U4atac/U6atac di-snRNP in vitro and in vivo. Thus, this study reports that MOPD I-associated *RNU4ATAC* mutations can affect multiple facets of minor snRNA function.

Research on MOPD II using genetic linkage analysis found mutations that cause biallelic loss-of-function in centrosomal pericentrin (*PCNT*) gene (Rauch et al. 2008; Unal et al. 2014). The absence of *PCNT* gene results in disorganized mitotic spindles and misaggregation of chromosomes and simultaneously mutations in other related genes, i.e., *MCPH1, CDK5RAP2, ASPM, CENPJ,* and *CEP152* can contribute to primary microcephaly in these patients. Further, Müller et al. (2012) using genetic assessment found a novel heterozygous mutation (p.Leu1361Arg) affecting a highly conserved residue of *IGF1R* in a female patient, which suggested a disturbance within the somatotropic axis. Additionally, they also found two compound heterozygous mutation (p.[Arg585X];[Glu1774X]) in *PCNT* gene and specified the diagnosis to be MOPD II. Concomitantly, with the use of new sophisticated technology, a novel subtype of MOPD has also been reported by employing whole exome sequencing on two affected sisters. This study reports two very rare missense variants in *NIN* gene, which encodes for a centrosomal protein ninein involved in

asymmetric cell division. Further, knockdown experiments of this gene led to findings of specific and novel defects which revealed the intricate role of this gene in morphogenesis process (Dauber et al. 2012).

In the other subtype of PD, i.e., SRS, Stark et al. (2010) reported a patient exhibiting atypical Silver–Russell phenotype with myoclonus-dystonia syndrome and suggested the hypothesis of *SGCE* gene to be involved in abnormal imprinting. Another study by Spengler et al. (2009) tried to determine the role of *ZFP57* mutation influence on *H19/IGF2* DMR in 30 SRS patients and their results showed homozygosity for a novel variant in exon 6 of *ZFP57* in one patient with the parents of the patient found to be heterozygote for the mutation. However, the study could not provide any evidence for the *ZFP57* mutation as a cause for 11p15-hypomethylation. Further, Eggermann et al. (1998) in a case report suggested a heterozygous deletion in growth hormone gene (*CSH1*) cluster to be involved in etiology of SRS. The *CSH1* gene deletion was found to be inherited from the father and since CSH concentrations decrease in pregnancies with intrauterine growth retardation, its deletion was hypothetically thought to be involved in SRS but its alleged role in IUGR still remains to be unclear.

In MGORS, mutations in pre-replication complex encoding genes like *ORC1, ORC4, ORC6, CDT1* and *CDC6* have been reported to be implicated in its development (Bicknell et al. 2011a, b; Guernsey et al. 2011; de Munnik et al. 2012; Kuo et al. 2012). Studies by the above groups have also reported that site-specific missense mutations that result in amino acid residue substitutions are more dominant in MGORS, which includes E127G and R105Q in Orc1, Y174C in Orc4, Y232S in Orc6, T323R in Cdc6 and R462Q in Cdt1. Moreover, Hossain and Stillman (2012) in their findings suggest mutation in *ORC1* to contribute to pronounced microcephaly and dwarfism in MGORS. They report that Orc1 inhibition of Cyclin E–CDK2 kinase activity occurs by a different mechanism in MGORS patients that is affected by *ORC1* mutations. The mutation Orc1 R105Q alters the Cyclin E–CDK2 kinase inhibitory activity and causes reduplication of both centrioles and centrosomes in human cells which contributes to severe form of microcephaly and dwarfism. Such mutant cells increase the nuclear volume and slow down the process of proliferation of cells and lead to defects in regulation of centriole and centrosome copy numbers. Further, it has been suggested that this mutation causes defect in binding of Orc1 to methylated histones that affects DNA replication which is severe than mutations found in other pre-RC proteins, i.e., (Orc4, Orc6 and Cdt1) with the exact mechanism yet to be figured. Other studies like a parallel cohort study of 45 patients by de Munnik et al. (2012) report that growth is reflected by both height and head circumference influenced by molecular causes like *ORC1* mutations that lead to severe growth retardation followed by *ORC4* mutations. Study by Stiff et al. (2013) reports that ORC1-deficient cells exhibit striking defects in primary cilia formation. This study reports the possibility that reduced efficiency in primary cilia could contribute to the clinical features shown by these patients. Additionally, two recent studies have also suggested the role of minichromosome maintenance 2–7 complexes (MCM2-7) (McIntosh and Blow 2012; Riera et al. 2013) in chronic activation of licensing check points that can lead to shortcomings in cell proliferation and in DNA replication and thus these specific areas can harbor the answers for MGORS development too.

Apart from studies involving the specific subtypes of PD, recent research by Shaheen et al. (2012, 2014a, b) has added a number of novel genes to be linked with PD in general. In their findings, they report the first evidence for a biallelic truncating *BRCA2* mutation, *XRCC4* mutation, a homozygous truncating mutation in *CRIPT* and a novel mutation in *IGF1* gene among PD patients. Additionally, they also report a novel locus for Seckel syndrome in a consanguineous multiplex family and a homozygous truncating mutation in *DNA2* as its likely cause. They also report a novel locus on 4q25-q28.2 with a five base-pair deletion in *PLK4* gene that encodes for a master regulator of centriole duplication and deficiency in *POC1A* gene that codes for a centriolar protein that impairs the basic centriolar function. Further, a recent study by Mirzaa et al. (2014) found the first evidence for a kinetochore-based mechanism to be involved in PD; their findings also described novel compound heterozygous variants in *CENPE* in two siblings. *CENPE* encodes for a core kinetochore component which functions to mediate chromosome congression of misaligned chromosomes and also in spindle microtubule capture during mitosis. Similarly, Payne et al. (2014) in their study report compound heterozygous frameshift mutations in *NSMCE2* gene (also called as *MMS21*) in 2 PD patients that exhibited extreme insulin resistance and gonodal failure. *NSMCE2* gene is a part of structural maintenance of chromosome (SMC) that helps maintain the chromatin structure and regulates gene expression. There are 3 known SMC complexes of which cohesion and condensin are important for sister chromatid cohesion and condensation while the third complex SMC5-6 which includes the E3 SUMO-ligase NSMCE2 is less known about. It was found that these mutations reduced the NSMCE2 expression in patient cells and experiments using fibroblast cells from the patients and its subsequent expression restored the abnormalities observed (i.e., micronucleus and nucleoplasmic bridge formation, delayed recovery of DNA synthesis). Thus, this report pointed that *NSMCE2* gene plays a role in recovery from DNA damage and mutations in it could lead to dwarfism.

Diagnosis, management and support to the patients affected with primordial dwarfism

Clinical evaluation, imaging and other relevant genetic and cytogenetic investigations can help delineate the overlapping features of similar genetic disorders. There are a number of other conditions overlapping with PD phenotype that should be considered during differential diagnosis. These have been summarized in Table 3. With regard to diagnostic development, recent studies suggest 2- and 3-dimensional sonography (Napolitano et al. 2009) and magnetic resonance imaging (MRI) of the affected fetal brain to be helpful in the prenatal diagnosis of SS (Takikawa et al. 2008). Clinical changes like hematological alterations associated with SS can be well managed by bone marrow transplantation (Rayburg et al. 2008; Darrigo et al. 2014) and current studies have suggested p38 as a novel target for pharmacological intervention too (Tivey et al. 2013). Although the use of growth hormone as a treatment option by Stanhope et al. (1991) was investigated in IUGR with no positive growth response, recent studies have encouraged its trial and its use has been found to be effective in very few IUGR studies. Investigations by Birkebaek et al. 2011 in SS patient reports increase in final stature but its possible significance in hormonal change and subsequent growth still remains unclear.

Similarly, investigations in MOPD II by Bober et al. (2012) and Faienza et al. (2013) using treatment with human growth hormone and recombinant insulin-like growth factor-1 (rhIGF-1) report no substantial conclusive result in improvement of final stature. The use of rhIGF-1 did not restore the typical physiological action of IGF-1. However, no such experiments have been carried out in MOPDI/III patients. Further, Kiliç et al. (2012) in a specific case study report a MOPD II patient to develop moyamoya disease complicated by recurrent stroke attacks emphasizing the possible neurological complications in such patients. Therefore, management of MOPD II patients worsens when risk factors include neurologic symptoms like motor/speech problems, headache, seizures, cognitive difficulties which is indicative of an evolving neurovascular process and, therefore, care should be taken to avoid any possible cerebrovascular risk factors that may deteriorate the condition further and make the management tough (Perry et al. 2013).

In contrast to the above studies, recombinant growth hormone therapy in an SRS patient by Mascarenhas and Ayyar (2012) reports significant improvement in height and suggests its use in the affected children. Another study involving a patient with multiple pituitary deficiencies showed a satisfactory improvement in height but the positive outcome was suggested to be a result of normomethylation and hypopituitarism status that could have helped in increase of final growth (Gucev et al. 2009). Further, considering the varied level of changes reported in this subtype, Eggermann et al. (2012) suggest the role of epigenetic testing to be as useful as genetic testing and the development of one technique that can detect both. It has been suggested that targeted or whole epigenome array and next-generation sequencing (NGS) can help circumvent current problems arising by analysis of single/selected imprinted loci and mosaic cases, thus allowing genome and epigenome-wide detection in both qualitative and quantitative way. As a result, detections involving genome-wide identification of point mutations leading to aberrant methylations or imprinting disorder phenotypes by one technique can influence routine diagnostics in a constructive way.

Concomitantly, growth studies in MGORS patients by de Munnik et al. (2012) also report increase in growth velocity and, to the best of our knowledge, are probably the only experiment conducted in MGORS patients till date. Consequently, although the use of growth hormone therapy in SGA cases with dysmorphism is not quite promising and is still debatable, it, however, opens up a new possible area of understanding growth hormone defects and its use as a therapeutic option in SGA syndromes.

Additionally, supportive therapy that includes special education, speech and language therapy, behavioral therapy, occupational therapy, community services for families and suggested that medications should be provided. There should also be neurologic follow-up from birth to adulthood to detect behavioral difficulties, hyperactivity, attention disorder, and motor problems (spasticity), and to monitor for evidence of seizures, which can be late onset. Further, periodic neuropsychological evaluation and schooling to the individual's abilities can substantially contribute to supporting them.

Conclusion

PD is an extremely heterogeneous group (genetically and clinically) of disorders presenting with IUGR and sophisticated tools/criteria can often assist in simplifying the otherwise tough diagnosis. It is a group of human single-gene disorders where growth, development and related mechanisms are irrevocably affected. As such, mammalian body growth is rapid during early life and slows down with age; this growth deceleration occurs in multiple tissues and is guided by local mechanisms specific for the tissues. Different organs use different types of information to regulate adult organ size and this appears to be coordinated temporally, conditionally and evolutionarily and, therefore, it can be said that determination of body size/proper growth of a fetus is a result of complex integration of several factors (Widdowson 1970). Genetic studies involving mice and

Table 3 Genetic disorders having overlapping features with primordial dwarfism

Genetic disorder	Overlapping features	Differentiating features	Subtype found to be overlapped with
3 M syndrome (Yakut short stature syndrome)	Autosomal recessive, prenatal and postnatal growth failure, unusual facial features (triangle-shaped face) and skeletal abnormalities-slender tubular bones, joint laxity, clinodactyly	Limb length asymmetry (body asymmetry), other characteristic radiologic findings and much shorter than SRS Foreshortened vertebral bodies are characteristic	Silver–Russell syndrome
Fanconi anemia	Growth retardation, thumb abnormality, hyperpigmentation, early onset bone marrow failure, chromosomal breakages, predisposition to leukemia/cancers	Hematologic manifestations are predominant Different complementation groups, and FANCD genes	Seckel syndrome
Severe insulin resistance (Donohue syndrome)	Prenatal and postnatal growth retardation, emaciation, absence of subcutaneous fat, decreased muscle mass, hirsutism, and low-set, poorly developed ears, hypertrichosis, hypoglycemia, acanthosis nigricans	Insulin receptor defect	Silver–Russell syndrome
Nijmegen breakage syndrome (NBS)	Growth retardation and pre or postnatal onset of microcephaly, receding forehead with characteristic facial, prominent mid-face with long nose, large ears, recurrent infections, chromosomal breakage	Defective p95-a member of the MRE11/RAD50 double-strand break-repair complex and cytogenetic abnormalities	Seckel syndrome
Cornelia de Lange syndrome (CDLS)	Facial dysmorphism, including coarse facies, arched eyebrows, synophrys, anteverted nares, long philtrum, thin lips, and 'carp' mouth, prenatal and postnatal growth retardation, and mental retardation	50–60 % of the cases of CDLS are due to mutation in the NIPBL gene. NIPBL forms a dimer with MAU2 that is essential for loading the cohesin complex onto sister chromatids	Seckel syndrome
Bloom syndrome	Autosomal recessive, pre and postnatal growth retardation, pigmentation abnormalities, mild microcephaly, chromosomal breakages	Malar hypoplasia, erythema of face, pigment abnormalities, photosensitivity, increased risk of tumors	Microcephalic osteodysplastic primordial dwarfism

rats have uncovered common genetic program that slows down growth in organs like kidney, lung and heart in both these model organisms. The common program involves down-regulation of many genes and it has been seen that knockdown of these genes in vitro inhibits cell proliferation and its knockout in vivo inhibits growth. These down-regulated, growth-promoting genes include growth factors such as *Igf2, Mdk* and *Ptn* and transcription factors such as *Ezh2, Mycn, Peg3* and *Plagl1*. Thus, it can be said that downregulation of a large set of growth-promoting genes can be seen as a potential reason for growth deceleration (Lui et al. 2010). Similarly, in humans the growth process seems to be even more complex since there are different kinds of tissues and organs with complex and essential regulation systems set by nature which include organ checkpoints (Lui and Baron 2011; Leevers and McNeill 2005), control of whole organism by GH/IGF-1 (Netchine et al. 2011), signaling pathways that stimulate growth, those that restrict cell size and number (Lui and Baron 2011) and also regulation of tissue morphogenesis by morphogens (Leevers and McNeill 2005; Crickmore and Mann 2008). Thus, it can be said that proper development of any organism requires a high-fidelity regulatory network that should control and coordinate the patterning of growth process.

Extensive studies in growth process has been carried out by developmental geneticists that have shown seven signaling pathways (Notch, Wnt, TGF-β, Hedgehog, receptor tyrosine kinase, nuclear receptor, and Jak/STAT) that mediate majority of cell fate decisions (Barolo and Posakony 2002). However, in recent times, Hippo pathway (Hpo) that controls organ size by coordination of cell growth, proliferation and apoptosis has emerged as a potential signaling cascade that controls size. Hpo signaling pathway has been comprehensively studied in *Drosophila* and less is known about it in other species. The biochemical and genetic interactions notable in *Drosophila* may or may not be recapitulated in mammals and thus studies are needed that can extend the understanding of this pathway and provide strengthening results in organ size control in mammals. Most of the genetic testing is being done by use of knockout mice but the characteristic mutants observed in *Drosophila* lack so in mice, thus transgenic models that can effectively manipulate Hpo pathway components spatially and temporally need to be developed (Pan 2007). Studies in humans by Lango et al. (2010) involving epidemiological parameters and analysis of a number of growth related genes report that height is a highly heritable trait and that most of the genes fall into pathways of Hedgehog, TGF-beta and growth hormones with a number of genes revealing statistically strong association with skeletal growth defects. Further, this genome-wide association study (GWAS) though reports several candidate genes to be playing a role in human growth, some genes have been reported that show no connections to growth biology and interestingly one of the genes, IGF1R, reported to be mutated in MOPDII patient has been found to be one of the genes associated with the 180 height associated loci reported in the study. This observation leads us to think about the alleged role of other documented genes in PD subtypes and their association with growth biology as most of them do not represent in the GWAS study. Nevertheless, the effects of quantitative trait loci and mechanisms/pathways that can influence the involvement of these genes in growth defects, though remains obscure, cannot be ignored. Thus, studies that provide input on the role of molecular level changes such as mutations in genes and chromosomal changes that adversely affect body size and concurrent phenotypic features of individuals are important independent contributions to the field. The consequences of these molecular changes often manifest as unusual features in affected lives and these changes often lead to varying phenotypes. Further, the different subtypes in PD have their own molecular signature defects among patients and at times with additional unique changes not reported in earlier cases.

Thus, identification of molecular, genetic and chromosomal level changes has been beneficial in providing useful insights into the PD subtypes. Various factors that can contribute to PD can be grouped into chromosomal abnormalities, mutations in growth related genes and pre-replication genes, epigenetic changes and consanguineous marriages (Fig. 2). Among all these factors, only a few proportion of studies suggest consanguineous marriages with specific modes of inheritance while most of them can be said to be sporadic in nature. Latest studies have also deciphered a number of defects in cellular processes like centrioles and centrosome functions, cell cycle and DNA damage checkpoints and mitosis to be involved in aberrant functions. A complex interplay between cell proliferation and cell death, symmetric and asymmetric division, normal and aberrant differentiations seems to contribute in PD development. Nevertheless, the specific roles and interactions between these cellular activities are still an unsolved area with respect to its role in growth development. Exciting discoveries are being made in this area of IUGR where several molecular mechanisms have been linked with peculiar defects in growth. Thus, this area presents an interesting arena to study cellular growth-related abnormalities and how its disruption affects several growth parameters and subsequent manifestations of unusual clinical features. Therefore, in the present article, we have summed up the different subtypes under PD, their clinical features, overlapping and distinguishing features from other growth-related disorders, chromosomal abnormalities, mutated genes and treatment options available for management.

Thus, in conclusion we suggest that this review will help in providing the recent perceptive on the advancements

in growth biology and developmental defects, be helpful in clinical utility and aid in better and reliable diagnosis, especially where there is overlapping of physical features. Further, it can be said that the use of other sophisticated techniques like family based genome/exome sequencing, deep NGS, proteomics and use of transgenic model systems can contribute to the identification of numerous SNPs, chromosomal aberrations, mutations, biomarkers and signaling pathways a highly effective approach (Veltman and Brunner 2012) for easier identification and also to provide the implication of such genetic changes on future generations. Although studies are at an earlier stage, developmental and cellular studies on cell lines of these patients will also provide unknown and interesting research output in the arena of human developmental biology. Simultaneously, identification of genes responsible, chromosomal changes observed specific to the subtypes and identification of biomolecular markers can throw new light in evaluating and screening of young PD subjects in a faster and reliable manner, thus facilitating appropriate genetic counseling and prenatal diagnosis in affected families.

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Compliance with ethical standards

Conflict of interest The authors declare that no conflict of interest exists.

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