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1 **TITLE:**

2 *LARP7* Variants and Further Delineation of the Alazami Syndrome Phenotypic Spectrum
3 among Primordial Dwarfisms: 2 Sisters

4

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34

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44 **ABSTRACT**

45 Alazami syndrome (AS) (MIM# 615071) is an autosomal recessive microcephalic primordial
46 dwarfism (PD) with recognizable facial features and severe intellectual disability due to
47 depletion or loss of function variants in *LARP7*. To date, 15 patients with AS have been
48 reported. Here we describe two consanguineous Algerian sisters with Alazami PD due to
49 *LARP7* homozygous pathogenic variants detected by whole exome sequencing. By comparing
50 these two additional cases with those previously reported, we strengthen the key features of
51 AS: severe growth restriction, severe intellectual disability and some distinguishing facial
52 features such as broad nose, malar hypoplasia, wide mouth, full lips and abnormally set teeth.
53 We also report significant new findings enabling further delineation of this syndrome:
54 disproportionately mild microcephaly, stereotypic hand wringing and severe anxiety,
55 thickened skin over the hands and feet, and skeletal, eye and heart malformations. From
56 previous reviews, we summarize the main etiologies of PD according to the involved
57 mechanisms and cellular pathways, highlighting their clinical core features.

58

59 **Keywords:** Alazami syndrome; primordial dwarfism; *LARP7*; intellectual disability.

60

61 INTRODUCTION

62 Primordial dwarfism (PD) encompasses a highly clinically and genetically heterogeneous
63 group of disorders mainly characterized by severe pre- and post-natal growth retardation.

64 More specifically, PD is defined by both height and weight being several standards of
65 deviation (SD) below the age-adjusted mean and without major skeletal dysplasia(1).

66 Various molecular mechanisms underlie this group of disorders(2,3), including impaired
67 mitotic mechanics(4–6), abnormal insulin-like growth factor 1 (IGF1) or 2 expression(7),
68 abnormal response to DNA damage(8,9), defective spliceosomal machinery(10), abnormal
69 replication licensing(11,12), and transcriptional regulation abnormalities(13). The latter
70 mechanism is involved with depletion or loss of function mutations of La RibonucleoProtein
71 domain family 7 (*LARP7*, MIM# 612026)(14). The *LARP7* is a chaperone protein required
72 for both stability and function of the RNA(15).

73 Pathogenic variants in *LARP7* are responsible for Alazami syndrome (AS) (MIM#
74 615071)(16), a recently described autosomal recessive PD associated with recognizable facial
75 features and severe intellectual disability (ID). To date, 15 patients have been reported
76 (13,17–19).

77 Here, we describe two additional consanguineous Algerian sisters with Alazami PD due to
78 *LARP7* pathogenic variants. We strengthen some key features of AS and report significant
79 new findings in comparison with previously reported cases to further delineate this syndrome.

80 We focus on differences between AS and other PD disorders and suggest a simple diagram to
81 map six main PD disorders, including AS, sorted by two core clinical features.

82

83 MATERIAL AND METHODS

84 The patients were referred for clinical suspicion of Rett syndrome without *MeCP2* variant to
85 the reference center for developmental anomalies at the University Hospital of Montpellier,
86 France.

87 Written informed consent was obtained from the parents of both sisters for Whole Exome
88 Sequencing (WES), as was consent for publication of this case report and photographs.

89 Genomic DNA was extracted from whole blood of the two affected children and their
90 unaffected parents. Samples from one affected child (patient 1) and her mother underwent
91 WES performed by the Centre National de Génotypage, Institut de Génomique, Commissariat
92 à l’Energie Atomique. After complete DNA quality control (quantification in duplicate, DNA
93 integrity evaluation, absence of PCR inhibitors verification), genomic DNA (3 µg) was
94 captured by an in-solution enrichment method (Human All Exon v5 – 50 Mb, Agilent
95 Technologies, Santa Clara, CA, USA). Library preparation and exome enrichment (~20.000
96 targeted genes) was performed automatically by using NGSx (Perkin Elmer, MA, USA) and
97 Bravo (Agilent Technologies, CA, USA), respectively, according to the manufacturer’s
98 instructions (SureSelect, Agilent Technologies CA, USA). After normalisation and quality
99 control, exome-enriched libraries were sequenced by using the Illumina HiSeq2000 system
100 (Illumina, CA, USA) as paired-end 100-bp reads. Samples were sequenced as pools of 4
101 samples per lane, to obtain an average coverage of 70 to 80 X, with at least 80% of the target
102 nucleotides covered at 30 X. Image analysis and base-calling involved use of the Illumina
103 Real Time Analysis (RTA) Pipeline. Sequence-quality parameters were assessed daily during
104 the 12 days of sequencing. Standard bioinformatics analysis of sequencing data was based on
105 the Illumina pipeline (CASAVA1.8.2) to generate a FASTQ file for each sample. Reads were
106 mapped against the genomic sequences (human genome version hg19) of the targeted genes
107 with the alignment algorithm ELANDv2 (multiseed and gapped alignments). Genetic
108 variation annotation and filtration involved use of the Dijon in-house pipeline, as recently

109 described in Nambot et *al.*(20) To further filter out the variants, we applied one set of criteria:
110 “gene known to be related to a human disease in OMIM database (table S1: column I)” and
111 “allele frequency < 0.01 in all public databases ESP, ExAC, GnomAD" (table S1: columns O
112 to R)”. We analyzed each survived variant after filtration through its biological consistency
113 and phenotypic relevance. Candidate variant and familial segregation were confirmed by
114 Sanger sequencing for both affected sisters (patients 1 and 2) and each parent.

115 PATIENT REPORTS

116 *Patients 1 and 2*

117 The sisters were the only children of consanguineous Algerian parents. The family history
118 was negative. Both pregnancies were uneventful but without medical follow-up. Both sisters
119 were born at term, at home. Birth measurements were not reported. The sisters did not present
120 feeding difficulties in infancy. Clinical examination was performed when the sisters were age
121 26 and 22. Clinical features are summarized and compared with previously reported patient
122 features in Table 1.

123 Both sisters presented severe growth retardation and disproportionate mild microcephaly:
124 occipitofrontal circumference (OFC) decrease was less severe than height decrease (at least 2
125 SD discrepancy between OFC and height) (Table 1). Both presented severe ID, including
126 absence of speech. They did not recognize known people from unknown people. They both
127 presented a severe anxiety. They had autistic behaviors such as stereotypic hand wringing, but
128 gripping and handling were possible (Figure 1a). Both had lower-limb spasticity and
129 increased tendon reflexes. Upper-limb joint mobility (wrist and elbow) was abnormally
130 decreased.

131 The sisters had poor appetite, very selective eating behavior (almost exclusively dairy
132 products) and chronic constipation. Physical examination revealed facial features in both
133 (Figure 1b). They featured proximally placed fourth toes and thumbs (Figure 2a), thickened

134 skin over the hands (Figure 1c) and feet and cutis marmorata (Figure 1d). Pubertal
135 development milestones were normal for both sisters (first periods at age 12).

136 *Patient 1*

137 In addition to the facial features shared with her sister, patient 1 presented sparse eyebrows,
138 narrow and short palpebral fissures with deep-set eyes, a bifid tip on the nose and a short
139 philtrum. She had neurosensorial disability, with low vision on left side and a keratoconus on
140 the right eye, which caused blindness on this side. She needed a Botox injection to treat the
141 spasticity. She had experienced tonicoclonic seizures at age 6 and received valproate for 1
142 year. She could smile. Daytime toilet training was achieved at age 4.

143 *Patient 2*

144 Patient 2 began to walk at age 3 and a half. Toilet training was never achieved. She could not
145 smile.

146 *Paraclinical investigations*

147 Skeletal X-rays showed slender bones with increased cortical thickness (Figure 2b), a thin
148 calvarium with low-density skullcap, fingerprint marks (Figure 2c) and high vertebrae with
149 small intervertebral disks.

150 Metabolic screening and micro-array comparative genomic hybridization findings were
151 unremarkable. Molecular genetic study was negative for genes involved in Rett Syndrome
152 (MIM#312750)(21), congenital variant of Rett Syndrome (MIM#613454)(22) and Early
153 Infantile Epileptic Encephalopathy type 2 (MIM#300672)(23)(*MeCP2*, *FOXG1* and *CDKL5*,
154 respectively) as was chromosome breakage study. Brain MRI was normal but CT-scan
155 revealed small brains without calcification. Abdominal and renal ultrasonography findings
156 were normal. Otoacoustic emissions were normal.

157 RESULTS

158 On WES, patient 1 showed a homozygous frameshift variant in exon 7 of *LARP7*:
159 c.524_525insTT (p.(Ala176Leufs*37)) (NM_001267039.1 ; SCV000743091). This
160 homozygous variant was confirmed in both sisters. Each parent was heterozygous for this
161 *LARP7* variant.

162 Because the *LARP7* variant is a frameshift variant in a gene whose loss of function is a known
163 mechanism of disease, totally absent from controls in population databases (Exome
164 Sequencing Project, 1000 Genomes Project and Genome Aggregation Database), detected as
165 homozygous for this recessive disorder, we classified this variant as pathogenic with a strong
166 level of evidence.(24)

167 After filtration strategy, 124 variants were left (listed in table S1), including 50 variants in
168 genes known to be related to an autosomal dominant disease and 74 variants in genes known
169 to be related to an autosomal recessive disease.

170 DISCUSSION

171 AS was defined by Alazami *et al.* in 2012(13) as a novel autosomal-recessive PD syndrome
172 characterized by severe growth restriction with onset at birth and severe ID, related to
173 pathogenic variants in *LARP7*. The original phenotypic spectrum has been expanded and
174 includes recognizable facial features, such as triangular face, prominent forehead, deep-set
175 eyes, sparse eyebrows, broad nose, widely spaced teeth and wide mouth(19) and behavioral
176 concerns such as anxiety and hypersensitivity to hearing stimuli(18).

177 We report two new patients with AS. They strengthen previous descriptions because our
178 patients share several key features with those in the literature: severe growth restriction and
179 some distinguishing facial features. They highlight the facial pattern (including broad nose,
180 malar hypoplasia, wide mouth and abnormally set teeth) as a core feature of AS. However, we
181 highlight some additional features that are summarized in Table 1.

182 The discrepancy between height and OFC decrease severity is noteworthy and observed in all
183 patients previously reported. This suggests that mild, even absent, microcephaly may fully
184 match AS. This feature clearly differentiates AS from other microcephalic PDs such as Seckel
185 syndrome and Microcephalic Osteodysplastic Primordial Dwarfisms (MOPDs)(5,28).

186 Our patients present potentially misleading behavioral diagnostic features: Rett-like
187 stereotypical hand wringing and severe anxiety. In addition to other behavioral concerns
188 previously described, these features seem to be entirely part of the phenotypic spectrum of
189 AS. Interestingly for the categorization among other PD, these behavioral features clearly
190 differentiated from Meier-Gorlin and Silver-Russel syndromes(11,29,30).

191 Cutis marmorata, seen in other PDs such as MOPD type 2, has never been reported and seems
192 rare in AS, whereas thickened skin over the hands and feet appears more frequent and could
193 be a recognizable physical sign (Figure 1c).

194 The skeletal (slender bones with increased cortical thickness and abnormally set toes and
195 fingers), eye (keratoconus) and heart (atrial septal defect) malformations are remarkable and
196 could be searched in other AS patients.

197 We suggest that these additional clinical findings belong to the AS phenotypic spectrum
198 considering that they are in the overlapping part of the two sisters phenotypes. It could be
199 interesting to further investigate all previously reported patients with AS in order to confirm
200 the presence or absence of these apparently novel findings.

201 Nevertheless, multiple diagnosis is reported in about 1.4% to 7.2% of patients with complex
202 phenotypes who undergo WES(31). Furthermore, prospective annual reanalysis of WES has
203 been showed to improve diagnostic yield, highlighting that truly pathogenic variants can be
204 missed by WES(20). Thus, we could not completely exclude the possibility of a multiple
205 molecular diagnosis in these siblings that would have not been identified by WES at time of
206 analyzing. It could also be argued that one or several other potentially modifier variants

207 detected in the WES might contribute to these additional finding. In this regard, we carefully
208 analyzed all survived variants and attempted to identify those which could be relevant
209 candidate as potentially modifying the causing variant. Among all 124 variants listed in table
210 S1, none had both sufficient biological consistency and phenotypic relevance to be pointed
211 out.

212 Figure 3, based on previous reviews(1,2,32) summarizes the main etiologies of PD: Seckel
213 syndrome, MOPDs, Meier-Gorlin syndrome, IGF1 and IGF1-receptor deficiency syndromes,
214 Silver-Russel syndrome and AS. In an attempt to map AS and these different syndromes in a
215 practical simple manner, we present a streamlined diagram sorted by two core features: ID
216 and microcephaly severity. We mentioned as well the involved mechanisms and cellular
217 pathways. In this regard, AS is a PD with severe ID and mild microcephaly or normal OFC
218 and an LARP7-related syndrome involving transcriptional regulation abnormalities. MOPD
219 and Seckel syndrome both are PDs with severe ID and severe microcephaly. Both MOPD and
220 Seckel syndrome may be linked to an abnormal mitosis and are part of the Centromeric
221 Protein J- and Pericentrin-related syndromes. MOPD may also be linked to a defective
222 spliceosomal machinery and is an RNU4ATAC-related syndrome. Seckel syndrome may also
223 be linked to a perturbed DNA damage response and is part of the ATR-, ATRIP- and RBBP8-
224 related Seckel syndromes. Meier-Gorlin syndrome and IGF1 and IGF1-receptor deficiency
225 syndromes are both PDs with severe microcephaly and normal cognitive development (CD)
226 or mild ID, related to abnormal replication licensing and abnormal GH-IGF1 signaling,
227 respectively. Silver-Russel syndrome is a PD with normal or subnormal CD and normal OFC
228 due to abnormal IGF2 expression.

229 In conclusion, we suggest further delineation of the AS phenotypic spectrum, which includes
230 PD with possibly disproportionate mild even absent microcephaly, commonly severe ID,
231 some recognizable facial and skeletal features and frequent behavioral autistic or Rett-like

232 features. This delineation might be helpful for the clinical diagnosis process, including for
233 “WES as a first-line test and back to phenotype” approach.

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237 **FIGURE LEGENDS**

238 **Figure 1: Patients 1 and 2: clinical features.**

239 **a.** Behavioral pictures at age 26 and 22, respectively (upper left picture), and age 24 (upper
240 right picture). Both presented autistic behaviors such as stereotypic hand wringing.

241 **b.** Front, lateral and global views at age 21 (patient 1) and 17 years (patient 2). Both presented
242 facial features: broad nose, malar hypoplasia, wide mouth, full lips and abnormally set teeth.
243 This pattern of facial features is shared with most patients with Alazami syndrome previously
244 reported. It highlights this facial pattern as a core feature of Alazami syndrome. In addition,
245 patient 1 presented sparse eyebrows, narrow and short palpebral fissures with deep-set eyes, a
246 bifid tip of nose and a short philtrum. Note disproportionate mild microcephaly compared
247 with severe short stature.

248 **c.** Palmar side of hands: both sisters presented thickened skin over the hands (and feet, not
249 shown).

250 **d.** Skin pictures: both sisters presented extended cutis marmorata.

251 **Figure 2: Skeletal features and X-rays views.**

252 **a.** Both sisters presented abnormally set fourth toes and proximally set thumbs (left upper
253 pictures).

254 **b.** Skeletal X-rays showing slender bones (black arrows) with increased cortical thickness
255 (pairs of white arrows). Only patient 2 X-rays are shown (lower pictures), from left to right:
256 front views of the hips, left knee, left forearm and right arm.

257 **c.** Head X-rays showing a thin calvarium with low-density skullcap and fingerprint marks
258 (white arrows). Only patient 2 X-rays are shown.

259 **Figure 3: Main etiologies of primordial dwarfism (PDs) according to two core features
260 and linked to the involved mechanisms and cellular pathways.**

261 As an example, Microcephalic Osteodysplastic Primordial Dwarfisms (MOPDs) and Seckel
262 syndrome both are PDs with severe intellectual disability and severe MC. Both MOPDs and
263 Seckel syndrome may be linked to abnormal mitosis and are part of the Centromeric Protein J-
264 and Pericentrin-related syndromes. MOPD may also be linked to a defective spliceosomal
265 machinery and is an RNU4ATAC-related syndrome. Seckel syndrome may also be linked to a
266 perturbed DNA damage response and is part of the ATR-, ATRIP- and RBBP8-related Seckel
267 syndromes. For further description of this figure, see the Discussion.

268 *PD: primordial dwarfism, ID: intellectual disability, CD: cognitive development, MC:*
269 *microcephaly, OFC: occipito-frontal circumference, MOPD: Microcephalic Osteodyplastic*
270 *Primordial Dwarfism.*

271 **Table 1.** Comparison of clinical features of presented patients and previously reported
 272 patients with Alazami syndrome.

| | <i>Alazami et al.</i> (13) | <i>Najmabadi et al.</i> (17) | <i>Ling et al.</i> (18) | <i>Hollink et al.</i> (19) | Patient 1 | Patient 2 | Total |
|---|----------------------------|------------------------------|-------------------------|----------------------------|--------------------|--------------------|--------------|
| ID (severe) | 10/10 | 2/2 | 1/1 | 2/2 | Yes (No speech) | Yes (No speech) | 17/17 |
| Biometry | | | | | | | |
| Weight (SD) | -2 to -4.5 | NR | -5,5 | -1 to -3 | -2.8 | -3.5 | NC |
| Height (SD) | -4 to -10.5 | NR | -4 | -2.5 to -3 | -6.5 | -6.8 | NC |
| OFC (SD) | -1.5 to -7 | <-2 | -1 | -2 to -4 | -3.5 | -3.5 | NC |
| DMM | 8/9 | NR | 1/1 | 0/2 | + | + | 11/14 |
| Facial features | | | | | | | |
| Triangular face | 9/9 | NR | 1/1 | 1/2 | - | - | 11/14 |
| Prominent forehead | + (NC) | NR | 1/1 | 2/2 | - | - | NC |
| Narrow and short palpebral fissures | 7/9 | NR | 0/1 | 1/2 | + | - | 8/14 |
| Deep-set eyes | 9/9 | NR | 1/1 | 2/2 | + | - | 12/14 |
| Sparse eyebrows | 9/9 | NR | 0/1 | 1/2 | + | - | 11/14 |
| Low set ears | 6/9 | NR | 1/1 | 0/2 | - | - | 7/14 |
| Malar hypoplasia | 8/9 | NR | 1/1 | 1/2 | - | + | 10/14 |
| Broad nose | 9/9 | NR | 0/1 | 2/2 | + | + | 12/14 |
| Short philtrum | 9/9 | NR | 0/1 | 1/2 | + | - | 11/14 |
| Wide mouth | 9/9 | NR | 1/1 | 1/2 | + | + | 13/14 |
| Full lips | 5/9 | NR | 1/1 | 2/2 | + | + | 10/14 |
| Widely spaced teeth/tooth misalignment | 8/9 | NR | 1/1 | 2/2 | + | + | 13/14 |
| Skeletal, muscle and skin features | | | | | | | |
| Scoliosis | 2/9 | NR | NR | 1/2 | + | - | 4/13 |
| Hypermobility of distal tips | NR | NR | 0/1 | 1/2 | + | - | 2/5 |
| Abnormally set toe(s)/fingers | NR | NR | 0/1 | 1/2 | + | + | 3/5 |
| Skeletal anomalies | NR | NR | 0/1 | 1/2 | + | + | 3/5 |
| Thickened skin over the hands and feet | 5/9 | NR | 0/1 | 1/2 | + | + | 8/14 |
| Cutis marmorata | NR | NR | 0/1 | 0/2 | + | + | 2/5 |
| Behavioral features | | | | | | | |
| Anxiety | NR | NR | 1/1 | 1/2 | - | - | 2/5 |
| Self-mutilation of hands | 2/9 | NR | 1/1 | | - | - | 3/12 |
| Stereotypic | NR | NR | 0/1 | 0/2 | + | + | 2/5 |

| | | | | | | | |
|--------------------------------------|-----|----|-----|-----|---|----|------|
| behavior including hand wringing | | | | | | | |
| Selective eating behavior | NR | NR | 0/1 | 0/2 | + | + | 2/5 |
| Other features | | | | | | | |
| Seizures | NR | NR | 0/1 | 0/2 | + | - | 1/5 |
| Ocular anomalies | NR | NR | 0/1 | 0/2 | - | +* | 1/5 |
| Strabismus | 4/9 | NR | 0/1 | 0/2 | - | - | 4/14 |
| Atrial septal defect | NR | NR | 0/1 | 0/2 | - | + | 1/5 |
| Disturbed sleep/sleep apnea episodes | NR | NR | 0/1 | 0/2 | + | + | 2/5 |

273 *NR: not reported, NC: non-countable, DMM: disproportionate mild microcephaly,*

274 **Keratoconus*

275

276

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376

377 **Supplemental data:**

378 **Table S1: List of all survived variants after filtration strategy (lines 3 to 52: variants in**
379 **genes related to an autosomal dominant disease; lines 53 to 126: variants in genes**
380 **related to an autosomal recessive disease).**

381 *See Excel table S1 attached*

382



Figure 1: Patients 1 and 2: clinical features.

a. Behavioral pictures at age 26 and 22, respectively (upper left picture), and age 24 (upper right picture). Both presented autistic behaviors such as stereotypic hand wringing.

b. Front, lateral and global views at age 21 (patient 1) and 17 years (patient 2). Both presented facial features: broad nose, malar hypoplasia, wide mouth, full lips and abnormally set teeth. This pattern of facial features is shared with most patients with Alazami syndrome previously reported. It highlights this facial pattern as a core feature of Alazami syndrome. In addition, patient 1 presented sparse eyebrows, narrow and short palpebral fissures with deep-set eyes, a bifid tip of nose and a short philtrum. Note disproportionate mild microcephaly compared with severe short stature.

c. Palmar side of hands: both sisters presented thickened skin over the hands (and feet, not shown).

d. Skin pictures: both sisters presented extended cutis marmorata.

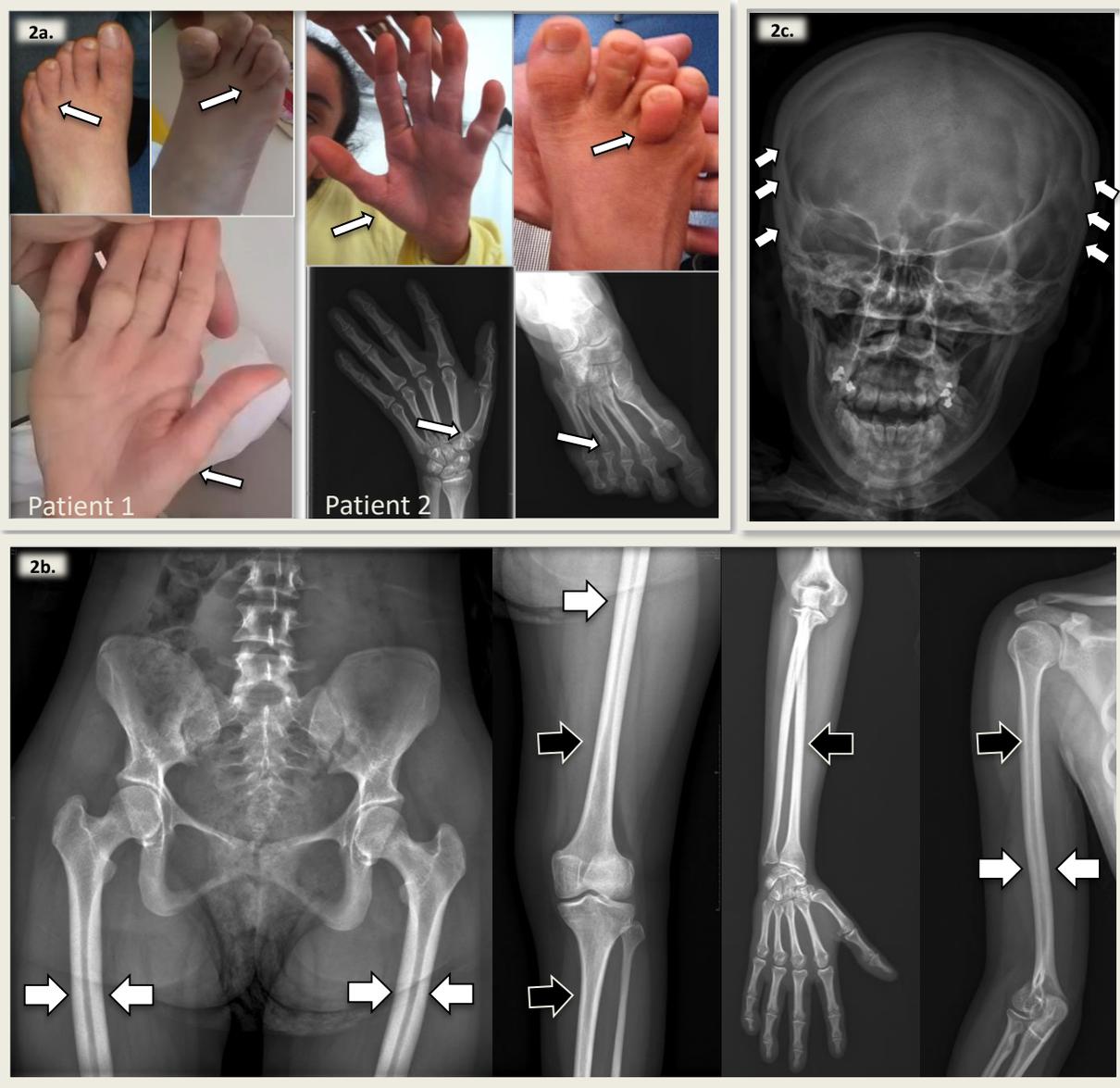


Figure 2: Skeletal features and X-rays views.

a. Both sisters presented abnormally set fourth toes and proximally set thumbs (left upper pictures).

b. Skeletal X-rays showing slender bones (black arrows) with increased cortical thickness (pairs of white arrows). Only patient 2 X-rays are shown (lower pictures), from left to right: front views of the hips, left knee, left forearm and right arm.

c. Head X-rays showing a thin calvarium with low-density skullcap and fingerprint marks (white arrows). Only patient 2 X-rays are shown.

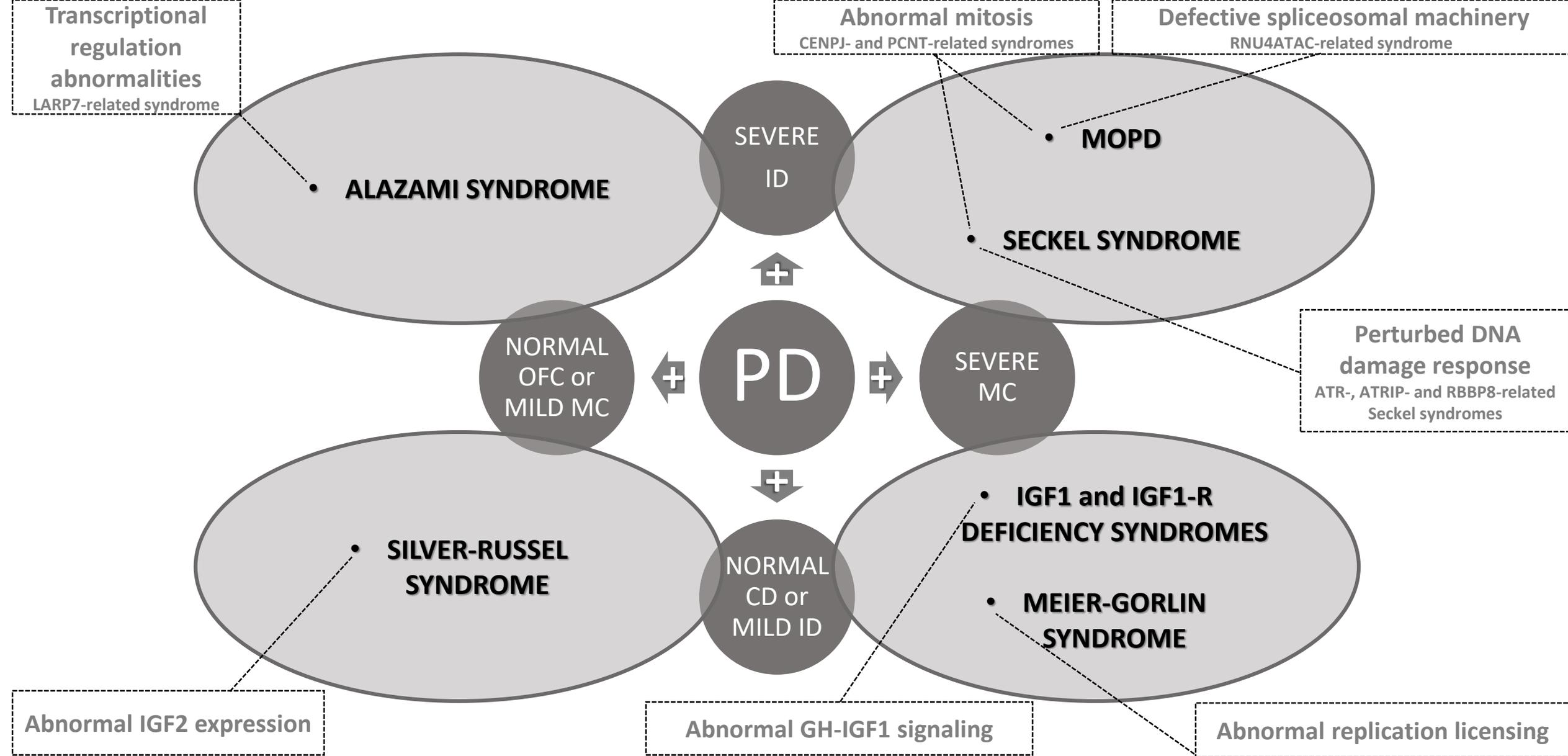


Figure 3: Main etiologies of primordial dwarfism sorted with two core-features and linked to the involved mechanisms and cellular pathways. For instance, MOPD and Seckel syndrome both are PD with severe ID and severe MC. Both MOPD and Seckel syndrome may be linked to a abnormal mitosis and are part of the CENPJ- and PCNT-related syndromes. MOPD may also be linked to a defective spliceosomal machinery and is a RNU4ATAC-related syndrome. Seckel syndrome may also be linked to a perturbed DNA damage response and is part of the ATR-, ATRIP- and RBBP8-related Seckel syndromes. For further description of this figure, see in discussion.
 PD: primordial dwarfism, ID: intellectual disability, CD: cognitive development, MC: microcephaly, OFC: occipito-frontal circumference, MOPD: Microcephalic Osteodyplastic Primordial Dwarfism.