

**Table S1. Key clinical manifestations and genetic findings in patients with confirmed genetic etiology of DD/ID**

| Case | Sex | Phenotype                            | Gene           | Variant                                 | Inheritance | Variant type/ACMG classification | OMIM   |
|------|-----|--------------------------------------|----------------|---|-------------|----------------------------------|--|
| 1.   | M   | DD, SD, cataract, strabismus, myopia | <i>LONP1</i>   | NM_004793.4<br>c.2014C>T<br>p.Arg672Cys | AR          | Missense/pathogenic variant      | CODAS syndrome<br>OMIM:600373  |
| 2.   | M   | DD, LA, encephalopathic crises       | <i>PDHA1</i>   | NM_001173456<br>c.C522G<br>p.F174L      | X           | Missense/pathogenic variant      | Pyruvate dehydrogenase E1-alpha deficiency<br>OMIM:312170                          |
| 3.   | F   | DD, encephalopathic crises           | <i>PCCA</i>    | NM_001127692<br>c.839dupT<br>p.I280fs   | AR          | Insertion/likely pathogenic      | Propionic acidemia<br>OMIM: 606054   |
|      |     |                                      |                | NM_000282.4<br>c.T1964G<br>p.V655G      |             | Missense/ unknown significance   |  |
| 4.   | F   | ID, epilepsy                         | <i>CACNA1D</i> | NM_001128840.3<br>c.C2621A<br>p.P874Q   | AD          | Missense/unknown significance    | Primary aldosteronism, seizures, and neurologic abnormalities<br>OMIM: 615474      |
| 5.   | F   | ID, Epilepsy, SM                     | <i>PIK3R2</i>  | NM_005027<br>c.2183G>A<br>p.Arg728His   | AD          | Missense/pathogenic              | Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 1<br>OMIM: 603387 |

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| 6.  | M | DD, sensorineural hearing loss | <i>GJB2</i>    | NM_004004<br>c.71G>A<br>p.W24X            | AR | Nonsense/pathogenic            | Deafness, autosomal recessive 1A OMIM: 220290                               |
|     |   |                                | <i>KAT6A</i>   | NM_006766<br>c.2904G>C<br>p.R968S         | AD | Missense/ unknown significance | Arboleda-Tham syndrome OMIM:616268  |
| 7.  | M | Noonan syndrome susp.          | <i>PTPN11</i>  | NM_002834<br>c.417G>C<br>p.Glu139Asp      | AD | Missense/pathogenic            | Leopard syndrome OMIM:151100  |
| 8.  | M | DD, hypotonia, FD              | <i>ARID1B</i>  | NM_001244813<br>c.4774G>T<br>p.Gln84Ter   | AD | Missense/likely pathogenic     | Coffin-Siris syndrome 1 OMIM: 135900  |
| 9.  | M | DD, SD                         | <i>MYH3</i>    | NM_002470<br>c.533+1G>A                   | AD | Splicing/likely pathogenic     | Arthrogryposis, distal, type 2A (Freeman-Sheldon) OMIM:193700               |
|     |   |                                | <i>SYNGAP1</i> | NM_006772<br>c.C892T<br>p.P298S           |    | Missense/ unknown significance | Intellectual developmental disorder, autosomal dominant 5 OMIM:612621       |
| 10. | F | DD, LA, epilepsy, FTT          | <i>SCN2A</i>   | NM_001040143<br>c.2567G>A<br>p.Arg856Gln  | AD | Missense/ unknown significance | Developmental and epileptic encephalopathy 11 OMIM:613721                   |
| 11. | F | ID, FD, hyperactivity, SM      | <i>TCF4</i>    | NM_001083962.2<br>c.771C>G<br>p.Asp257Glu | AD | Missense/ unknown significance | Pitt-Hopkins syndrome OMIM: 610954  |
| 12. | F | ID, FD                         | <i>DDX3X</i>   | NM_001193417<br>c.1641insT                | X  | frameshift/ pathogenic         | Intellectual developmental disorder, X-linked syndromic, Snijders Blok type |

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|     |   |  |                |  |    |                                | OMIM: 300958   |
| 13. | F | ID, SM   | <i>NALCN</i>   | NM_052867<br>c.2003_2006del                    | AD | Frameshift/ pathogenic         | Hypotonia, infantile, with psychomotor retardation and characteristic facies 1<br>OMIM: 615419     |
| 14. | M | DD, myoclonic epilepsy, unilateral renal agenesis, FD        | <i>GATA3</i>   | NM_001002295<br>c.G827a<br>p.R276q             | AD | Missense/pathogenic            | Hypoparathyroidism, sensorineural deafness, and renal dysplasia – Barakat syndrome<br>OMIM: 146255 |
|     |   |  | <i>NSD1</i>    | NM_022455<br>c.A3570t<br>p.L1190f              |    | Missense/ unknown significance | Sotos/Beckwith_Wiedemann syndrome<br>OMIM :130650  |
| 15. | F | ID, SD   | <i>RPS6KA3</i> | NM_004586.3<br>c.1603-1G>A                     | X  | Missense/ unknown significance | Coffin-Lowry syndrome<br>OMIM: 303600  |
| 16. | M | DD   | <i>TCF4</i>    | NM_001243226.2<br>c.826C>T<br>p.Arg276Ter      | AD | Insertion/pathogenic           | Pitt-Hopkins syndrome<br>OMIM: 610954  |
| 17. | F | DD, FD, muscular hypertonia, FTT                             | <i>CREBBP</i>  | NM_004380.2<br>c.5641_5642delAG<br>p.Ser1881fs | AD | Frameshift/pathogenic          | Rubinstein-Taybi syndrome 1<br>OMIM: 180849  |
| 18. | M | DD, hypotonia, involuntary movements, sensorineural deafness | <i>ALDH5A1</i> | NM_170740.1<br>c.1265G>A<br>p.Gly422Asp        | AR | Missense/pathogenic            | Succinic semialdehyde dehydrogenase deficiency<br>OMIM: 271980                                     |
| 19. | M | DD, FD, valvular pulmonary stenosis                          | <i>SOS1</i>    | NM_005633.3<br>c.1367T>A<br>p.Phe623Ile        | AD | Missense/likely pathogenic     | Fibromatosis, gingival<br>OMIM: 135300   |
| 20. | F | DD, FD   | <i>KMT2A</i>   | NM_001197104.1<br>c.7789C>T<br>p.Gln2597X      | AD | Insertion/likely pathogenic    | Wiedemann-Steiner syndrome<br>OMIM: 605130   |

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| 21. | F | DD, LA  | <i>TMEM70</i>  | NM_017866.6<br>c.317-2A>G                 | AD | Splicing/pathogenic               | Mitochondrial complex V<br>(ATP synthase) deficiency, nuclear type 2<br>OMIM: 614052 |
| 22. | F | ID, FD, hypotonia                                 | <i>CAMK2A</i>  | NM_001363989.1<br>C413C>T<br>p.Pro138Leu  | AD | Missense/ unknown<br>significance | Intellectual<br>developmental disorder,<br>autosomal dominant 53<br>OMIM: 617798     |
| 23. | F | ID  | <i>MECP2</i>   | NM_004992.3<br>c.916C>G<br>p.Arg306Cys    | AD | Missense/pathogenic               | PPM-X syndrome<br>OMIM: 300055   |
| 24. | M | DD, short stature, FD, congenital<br>heart defect | <i>LZTR1</i>   | NM_006767.4<br>c.850C>T<br>p.Arg284Cys    | AD | Missense/pathogenic               | Noonan syndrome 10<br>OMIM: 616564   |
| 25. | F | ID, FD, chronic renal insufficiency               | <i>IFT140</i>  | NM_014714.4<br>c.1565G>A<br>p.Gly522Glu   | AD | Missense/likely<br>pathogenic     | Short-rib thoracic<br>dysplasia 9 with or<br>without polydactyly<br>OMIM: 266920     |
|     |   |   |                | NM_014714.4<br>c.874G>A<br>p.Val292Met    |    | Missense/likely<br>pathogenic     |  |
| 26. | F | DD, short stature, FD                             | <i>RAF1</i>    | NM_001354689.3<br>c.781C>T<br>p.Pro261Ser | AD | Missense/pathogenic               | Noonan syndrome 5<br>OMIM: 611553  |
| 27. | M | DD, epilepsy                                      | <i>SCL16A2</i> | NM_006517.5<br>c.45G>A<br>p.Trp15x        | X  | Insertion/likely<br>pathogenic    | Allan-Herndon-<br>Dudley syndrome<br>OMIM: 300523                                    |

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| 28. | F | DD, FD, microcephaly                    | <i>CHD3</i>                                 | NM_001005271.3<br>c.5728C>G<br>p.Leu1910Val                            | AD | Missense/ unknown<br>significance | Snijders Blok-<br>Campeau syndrome<br>OMIM: 618205                                  |
|     |   |   | <i>TUBB2B</i>                               | NM_178012.5<br>c.1188C>G<br>p.His396Gln                                |    | Missense/ unknown<br>significance | Cortical dysplasia,<br>complex, with other<br>brain malformations 7<br>OMIM: 610031 |
| 29. | F | DD, FD                                  | <i>CHD3</i>                                 | NM_001005271.3<br>c.2917C>T<br>p.Pro973Ser                             | AD | Missense/ unknown<br>significance | Snijders Blok-<br>Campeau syndrome<br>OMIM: 618205                                  |
| 30. | M | ID, epilepsy, psychomotor<br>regression | <i>NPC1</i>                                 | NM_000271.5<br>c.3182T>C<br>p.Ile1061Thr                               | AR | Missense/pathogenic               | Niemann-Pick disease<br>OMIM: 257220  |
|     |   |   |   | NM_000271.5<br>c.2196dupT<br>p.Pro733fs                                |    | Frameshift/pathogenic             |   |
| 31. | M | DD, microcephaly, seizures              | <i>SPTAN1</i>                               | NM_001130438.2<br>c.6923_6928dupGC<br>ATGC<br>p.Arg2308_Met2309<br>dup | AD | Insertion/likely<br>pathogenic    | Developmental and<br>epileptic<br>encephalopathy 5<br>OMIM: 613477                  |
| 32. | F | ID, SM                                  | <i>UBE3A</i><br><i>EX9-10</i><br><i>DEL</i> | 15q11.2<br>microdetetion<br>EX9-10 DEL                                 | AD | Microdeletion/pathoge<br>nic      | Angelman syndrome<br>OMIM: 105830   |
| 33. | F | DD, blindness                           | <i>PEX6</i>                                 | NM_000287.4<br>c.1314_1321del<br>p.Leu438fs                            | AR | Frameshift/pathogenic             | Peroxisome biogenesis<br>disorder 4A (Zellweger)<br>OMIM: 614862                    |

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|     |   |   |                    | NM_000287.4<br>c.160_243del<br>p.Val54_Leu81del |    | Deletion/pathogenic            |   |
| 34. | M | DD, LA  | <i>MT-ATP8</i>     | NC_012920.1(ATP3_v001)<br>c.46A>C<br>p.Met16Leu | AR | Missense/ unknown significance | Mitochondrial complex V (ATP synthase) deficiency<br>OMIM: 516070 |
| 35. | M | DD  | <i>STAG2, XIAP</i> | Xq25(122927376_123283576) x2                    | X  | Microduplication/ pathogenic   | Xq25 duplication syndrome OMIM: 300979                            |
| 36. | F | DD  | <i>ARHGEF9</i>     | NM_001353923.1<br>c.601-2A>G                    | X  | Splicing/likely pathogenic     | Developmental and epileptic encephalopathy 8<br>OMIM:300607       |
| 37. | F | DD, epilepsy, microcephaly  | <i>PCDH19</i>      | NM_001105243<br>c.1081A>G<br>p.Ser361Gly        | X  | Nonsense/ likely pathogenic    | Developmental and epileptic encephalopathy 9<br>OMIM:300088       |
| 38. | F | DD, renal dysplasia, coarctation of aorta, FD                         | <i>KMT2D</i>       | NM_003482.3<br>c.10653_10654insT<br>p.Ala3552fs | AD | Frameshift/ likely pathogenic  | Kabuki syndrome 1<br>OMIM:147920                                  |
| 39. | M | ID, macrocephaly, recurrent otitis media                              | <i>AGO2</i>        | NM_012154.5<br>c.277G>A<br>p.Val93Met           | AD | Missense/unknown significance  | Lessel-Kreienkamp syndrome<br>OMIM:606229                         |
| 40. | F | DD, movement disorder, recurrent otitis media, skin hypopigmentations | <i>ARID2</i>       | NM_001347839<br>c.4181A>S<br>p.Glu1394Ala       | AD | Missense/ unknown significance | Coffin-Siris syndrome 6<br>OMIM: 617808                           |

|     |   |   |                                   |   |    |                             |  |
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| 41. | F | ID, short stature, FD   | <i>GNAS</i>                       | NM_000516.4<br>c.296delT<br>p.Leu99ArgfsTer12 | AD | Frameshift/pathogenic       | Pseudohypoparathyroidism Ia<br>OMIM: 103580  |
| 42. | M | DD, epilepsy, LA  | <i>PDHA1</i>                      | NM_000284.4<br>c.615C>G<br>p.Phe205Leu        | X  | Missense/likely pathogenic  | Pyruvate dehydrogenase E1-alpha deficiency<br>OMIM:312170  |
| 43. | F | DD, hypotonia, FTT, LA  | <i>PDHA1</i>                      | NM_001173454.1<br>c.597C>T<br>p.(Tyr199=)     | X  | Missense/pathogenic         | Pyruvate dehydrogenase E1-alpha deficiency<br>OMIM:312170  |
| 44. | M | DD, hypotonia   | <i>MED13L</i>                     | NM_015335.4<br>c.745A>T<br>p.Lys249X          | AD | Insertion/likely pathogenic | Impaired intellectual development and distinctive facial features with or without cardiac defects<br>OMIM:616789 |
| 45. | F | DD, microcephaly, seizures  | 2q37 deletion sy (multiple genes) | arr(GRCh37)2q37.2q37.3                        | AD | Microdeletion/pathogenic    | Chromosome 2q37 deletion syndrome<br>OMIM:600430   |
| 46. | F | ID, hypotonia, hyperactivity, ophthalmologic abnormalities, FD, hirsutism, cryptorchidism | <i>SMARCC2</i>                    | NM_001330288.2<br>c.1833+1G>A                 | AD | Splicing/pathogenic         | Coffin-Siris syndrome 8<br>OMIM:618362   |
| 47. | F | ID, hypotonia, movement disorder, sensorineural hearing impairment, bilateral ptosis, FD  | <i>ATP8A2</i>                     | NM_016529.6<br>c.1058-2A>G                    | AR | Splicing/likely pathogenic  | Cerebellar ataxia, impaired intellectual development, and dysequilibrium syndrome 4<br>OMIM:615268               |
| 48. | F | ID, developmental regression, hypotonia, optic nerve atrophy                              | <i>AIFM1</i>                      | NM_004208.4<br>c.1646C>T<br>p.Ala549Val       | X  | Missense/ likely pathogenic | Spondyloepimetaphyseal dysplasia, X-linked,  |

|     |   |  |                |  |    |                               |   |
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|     |   |  |                |  |    |                               | with hypomyelinating leukodystrophy<br>OMIM:300232                        |
| 49. | M | ID, hypotonia, cleft palate, club foot, feeding difficulties, growth delay, microcephaly, hearing impairment, crowded teeth, FD              | <i>SATB2</i>   | NM_001172509.2<br>c.847C>T<br>p.Arg283Ter                        | AD | Nonsense/pathogenic           | Glass syndrome<br>OMIM:612313   |
| 50. | M | ID, attention deficit hyperactivity disorder, FD   | <i>SETBP1</i>  | NM_015559.3<br>c.1873C>T<br>p.Arg625Ter                          | AD | Nonsense/pathogenic           | Intellectual developmental disorder, autosomal dominant 29<br>OMIM:616078 |
| 51. | M | DD, truncal hypotonia, joint contractures, FTT, cryptorchidism   | <i>SLC16A2</i> | NM_006517.5<br>c.611T>C  | X  | Missense/ likely pathogenic   | Allan-Herndon-Dudley syndrome<br>OMIM:300523                              |
| 52. | F | DD, growth delay, microphthalmia, iris and choroidea colobomas, optic nerve atrophy, preauricular tags, hypospadias, mild perinatal asphyxia | <i>PUF60</i>   | NM_078480.3<br>c.244-245del                                      | AD | Frameshift/pathogenic         | Verheij syndrome<br>OMIM:615583   |
| 53. | M | DD, aplastic anemia, macrocephaly, FD, VSD, renal anomalies  | <i>RPL5</i>    | NM_000969.5<br>c.175_176delGA                                    | AD | Frameshift/pathogenic         | Diamond-Blackfan anemia 6<br>OMIM: 612561                                 |
| 54. | M | DD, VSD, WPW syndrome, FTT, myopia, strabismus, hyperactivity, FD  | <i>ANKRD11</i> | NM_013275.6<br>c.3055A>G   | AD | Missense/unknown significance | KBG syndrome<br>OMIM: 148050  |
| 55. | F | DD, nystagmus, esotropia, hypotonia  | <i>PLP1</i>    | NM_000533.5<br>arr[GRCh37]<br>Xq22.1q22.2(102240878_103104983)x2 | X  | Duplication/pathogenic        | Pelizaeus-Merzbacher disease<br>OMIM: 312080                              |



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|-----|---|---|----------------|---|----|-------------------------------|--|
| 56. | F | DD, hypotonia, cleft lip and palate, deafness, kyphoscoliosis, FD   | <i>ACTG1</i>   | NM_001614.5<br>c.359C>T<br>p.Thr120Ile                  | AD | Missense/pathogenic           | Baraitser-Winter syndrome 2<br>OMIM: 614583                  |
| 57. | F | DD, autism, FD  | <i>SHANK3</i>  | NM_001372044.2<br>c.4365_4368del<br>p.Asp1456ProfsTer33 | AD | Frameshift/pathogenic         | Phelan-McDermid syndrome<br>OMIM: 606232                     |
| 58. | M | DD, hypotonia, involuntary movements, FD  | <i>MECP2</i>   | NM_001110792.2<br>c.509C>T<br>p.Thr170Met               | AD | Missense/pathogenic           | Rett syndrome<br>OMIM: 312750                                |
| 59. | M | DD, hypotonia, convergent strabismus, difficulty swallowing   | <i>CACNA1A</i> | NM_001127222.2<br>c.692T>G<br>p.Leu231Arg               | AD | Missense/ likely pathogenic   | Developmental and epileptic encephalopathy 42<br>OMIM:617106 |
| 60. | F | DD, FTT, bilateral calcaneovalgus, FD, macrocephaly   | <i>GCDH</i>    | NM_000159.4<br>c.1063C>T<br>p.Arg355Cys                 | AR | Missense/ likely pathogenic   | Glutarica ciduria, type I<br>OMIM: 231670                    |
|     |   |   |                | NM_000159.4<br>c.1169G>C<br>p.Gly390Ala                 |    | Missense/pathogenic           |  |
| 61. | F | DD, severe hypotonia, FD, agenesis of the corpus callosum, trigonocephaly, tracheoesophageal fistula, coarctation of the aorta, persistent ductus arteriosus, VSD, micropenis, cryptorchidism, umbilical hernia, hydronephrosis, talipes equinovarus, camptodactyly, long thumbs, pale skin and hypothyreosis | <i>KAT6B</i>   | NM_012330.4<br>c.3670dupA<br>p.Met1224AsnfsTer3         | AD | Frameshift/pathogenic         | SBBYSS syndrome<br>OMIM:603736                               |
| 62. | M | DD, epilepsy, tremor,behavior problems, ischemic brain lesions  | <i>CNOT3</i>   | NM_003482.4<br>c.926A>C                                 | AD | Missense/unknown significance | Intellectual developmental disorder                          |

|     |   |   |              |   |    |                               |  |
|-----|---|---|--------------|---|----|-------------------------------|--|
|     |   |   |              | p.His309Pro                                       |    |                               | with speech delay, autism, and dysmorphic facies<br>OMIM: 618672                             |
| 63. | F | Microphthalmia, chorioretinal coloboma, anal atresia, cleft palate, gastroesophageal reflux, FTT, FD, hypotonia, DD | <i>KMT2D</i> | NM_003482.4<br>c.13575dupA<br>p.Lys4527GlufsTer48 | AD | Frameshift/pathogenic         | Kabuki syndrome 1<br>OMIM: 147920  |
| 64. | M | DD, epilepsy  | <i>KCNQ2</i> | NM_172107.4<br>c.901G>A<br>p.Gly301Ser            | AD | Missense/pathogenic           | Developmental and epileptic encephalopathy 7<br>OMIM: 613720                                 |
| 65. | F | DD, hypotonia, hearing loss, FD, microcephaly, ASD, FTT   | <i>AFF4</i>  | NM_014423.4<br>c.772C>T<br>p.Arg258Trp            | AD | Missense/ likely pathogenic   | CHOPS syndrome<br>OMIM: 616368   |
| 66. | M | DD, congenital brain anomalies, microcephaly, epilepsy, growth retardation, feeding problems, FD                    | <i>BPTF</i>  | NM_182641.4<br>c.4416G>A<br>p.Met1472Ile          | AD | Missense/unknown significance | Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies<br>OMIM: 617755 |

**Legend:** DD – developmental delay, ID – intellectual disability, FD – facial dysmorphism, SD – skeletal dysplasia, LA– lactic acidosis, SM – stereotypic movements, FTT – failure to thrive, VSD – ventricular septal defect