

**S7 Tab. (Related to Fig 2c) Patients carrying damaging variants in DD/CHD genes.**

| Study ID | Gender | Case class | Gene           | Gene set                 | Variant class | Cardiovascular abnormality | Neuro-developmental disorders           | Other Abnormalities   |
|----------|--------|------------|----------------|--------------------------|---------------|----------------------------|---|---|
| 49477#   | M      | Complex    | <i>EPB41L1</i> | Possible DD<br>Confirmed | D-mis         |                            | Seizures                                | Microcephaly, abnormal ears, micropenis, facial dysmorphism, optic nerve hypoplasia |
|          |        |            | <i>POGZ</i>    | DD,CHD                   | LGD           |                            |   |   |
| 49480#   | F      | Isolated   | <i>NAA15</i>   | Probable DD,CHD          | LGD           |                            | NA                                      |   |
| 01-0147# | F      | Complex    | <i>STAG2</i>   | Putative CHD             | LGD           |                            | Moderate intellectual disability at 5yr | Low growth hormone and precocious puberty at 9yr                                    |
| 01-0450# | F      | Complex    | <i>SIN3A</i>   | Probable DD              | LGD           |                            | Schizoaffective disorder at 17yr        | Unilateral pelvic kidney, palate defect   |
| 01-0562# | M      | Complex    | <i>GATA6</i>   | Confirmed<br>CHD,DD      | D-mis         | ToF, 2VC                   | NA                                      | Intestinal malrotation requiring Ladd surgical correction.                          |
| 01-0568# | F      | Complex    | <i>CLCN4</i>   | Possible DD              | D-mis         |                            | Partial complex seizures at 6yr         | Bilateral hip dysplasia, umbilical hernia, failure to thrive                        |
| 01-0634# | M      | Complex    | <i>PRKACB</i>  | Putative CHD             | LGD           | VSD                        | Died                                    |   |
| 05-0039  | M      | Isolated   | <i>ATAD3A</i>  | Confirmed DD             | D-mis         |                            | Normal at 2yr                           |   |
| 04-0058  | F      | Isolated   | <i>KDM5B</i>   | Confirmed<br>DD,CHD      | D-mis         |                            | Lower than average at 2yr               |   |
| 01-0003  | M      | Isolated   | <i>MYT1L</i>   | Possible DD              | LGD           |                            | Developmental delay at 13yr             |   |
| 07-0009  | M      | Isolated   | <i>SRGAP3</i>  | Possible DD              | D-mis         |                            | NA                                      |   |
| 01-0768  | M      | Complex    | <i>RAF1</i>    | Confirmed<br>CHD,DD      | D-mis         |                            | Normal at 2yr                           | Left extralobar pulmonary sequestration   |

| Study ID | Gender | Case Class | Gene            | Gene Set         | Variant Class | Cardiovascular Abnormality                             | Neuro-developmental Abnormality   | Other Abnormalities  |
|----------|--------|------------|-----------------|------------------|---------------|--|-----------------------------------|--|
| 06-0018  | F      | Isolated   | <i>FOXP1</i>    | Confirmed DD     | LGD           |  | Moderate development delay at 2yr |  |
| 01-0644  | M      | Complex    | <i>ARID1B</i>   | Confirmed DD,CHD | LGD           | CoA  | Dandy-walker malformation; died   | Poorly developed scrotal sac with undescended testis, unable to palpate in the inguinal canal. |
| 01-0552  | M      | Complex    | <i>BRAF</i>     | Confirmed CHD,DD | D-mis         | 2VC  | NA                                |  |
| 07-0011  | F      | Isolated   | <i>ZFPM2</i>    | Possible DD      | LGD           |  | Died                              |  |
| 01-0596  | M      | Isolated   | <i>EMX2</i>     | Possible DD      | LGD           | RA/IVC thrombosis at birth, dilated aortic root at 5yr | Normal at 2yr                     |  |
| 01-0424  | F      | Isolated   | <i>WT1</i>      | Confirmed DD     | D-mis         |  | Normal at 2yr                     |  |
| 01-0098  | F      | Complex    | <i>WT1</i>      | Confirmed DD     | D-mis         |  | NA                                | Right hydronephrosis, hypotonia  |
| 02-0023  | M      | Complex    | <i>PTPN11</i>   | Confirmed CHD,DD | D-mis         | Univentricular defect                                  | Died                              |  |
| 04-0047  | F      | Isolated   | <i>CIC</i>      | Possible DD      | D-mis         |  | Normal at 2yr                     |  |
| 01-0342  | F      | Isolated   | <i>HSD17B10</i> | Confirmed DD     | D-mis         |  | NA                                |  |
| 01-0113  | M      | Complex    | <i>NACC1</i>    | Confirmed DD     | D-mis         |  | Died                              | Pyloric stenosis   |
| 03-0013  | F      | Isolated   | <i>MEIS2</i>    | Putative CHD     | D-mis         |  | NA                                |  |
| 04-0059  | F      | Isolated   | <i>LAMA5</i>    | Putative CHD     | LGD           |  | Normal at 2yr                     |  |

Cases with damaging variants in *MYRF* are shown in Table 3 of the main text. Abbreviations: contraction of aorta (CoA), two-vessel cord (2VC), Tetralogy of Fallot (ToF), right atrium and inferior vena cava (RA/IVC), not evaluated for neurodevelopment outcome (NA)  
#: Those cases have been reported in the previous studies(Yu, Bennett et al. 2014, Longoni, High et al. 2017).