|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PID** | **Reference** | **Reference (PMID)** | **PID in previous publication** | **Additional clinical data or updated information given** |
| 5 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 5 (FV) | ✓ |
| 7 | Staufner et al., 2020 | 31761904 | 7 | ✓ |
| 8 | Staufner et al., 2020 | 31761904 | 8 | ✓ |
| 9 | Staufner et al., 2020 | 31761904 | 9 | ✓ |
| 12 | Staufner et al., 2020 | 31761904 | 12 | ✓ |
| 15 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 6 (FVI) | 🗶 |
| 16 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 7 (FVII) | ✓ |
| 17 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 8 (FVII) | ✓ |
| 18 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 9 (FVIII) | ✓ |
| 20 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 11 (FX) | ✓ |
| 21 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 14 (FXIII) | 🗶 |
| 22 | Segarra et al., 2015 | 26286438 | Patient 1 (FXIV) | ✓ |
| 24 | Mégarbané et al., 2008; Capo-Chichi et al., 2015 | 19012336; 26578240 | Patient 1 | ✓ |
| 25 | Mégarbané et al., 2008; Capo-Chichi et al., 2015 | 19012336; 26578240 | Patient 2 | ✓ |
| 26 | Capo-Chichi et al., 2015 | 26578240 | Patient 3 | ✓ |
| 27 | Balasubramanian et al., 2017 | 27789416 | Patient 1 | 🗶 |
| 28 | Balasubramanian et al., 2017 | 27789416 | Patient 2 | 🗶 |
| 29 | Kortüm et al., 2017 | 28031453 |  | ✓ |
| 30 | Regateiro et al., 2017 | 28576691 | Patient 1 | ✓ |
| 31 | Regateiro et al., 2017 | 28576691 | Patient 2 | ✓ |
| 35 | Li et al., 2017 | 28629372 | Patient 1 | ✓ |
| 36 | Li et al., 2017 | 28629372 | Patient 2 | ✓ |
| 42 | Kim et al., 2017  | 28425089 | Patient 10A | 🗶 |
| 43 | Kim et al., 2017  | 28425089 | Patient 10B | 🗶 |
| 44  | Wang et al., 2018 | 32023706 |  | 🗶 |
| 45 | He et al., 2017 | 29262476 |  | 🗶 |
| 46 | Staufner et al., 2020 | 31761904 | 46 | ✓ |
| 47 | Palagano et al., 2018; Prontera et al., 2011 | 29929043; 22052670 | Patient 1 | ✓ |
| 48 | Palagano et al., 2018 | 29929043 | Patient 2 | ✓ |
| 55 | Staufner et al., 2020 | 31761904 | 55 | ✓ |
| 56 | Staufner et al., 2020 | 31761904 | 56 | ✓ |
| 58 | Staufner et al., 2020 | 31761904 | 58 | ✓ |
| 59 | Staufner et al., 2020 | 31761904 | 59 | ✓ |
| 60 | Staufner et al., 2020 | 31761904 | 60 | ✓ |
| 64 | Staufner et al., 2020 | 31761904 | 64 | ✓ |
| 65 | Fischer-Zirnsak et al., 2019 | 31015584 | Patient 1 | 🗶 |
| 67 | Fischer-Zirnsak et al., 2019 | 31015584 | Patient 3 | 🗶 |
| 69 | Staufner et al., 2020 | 31761904 | 69 | ✓ |
| 70 | Ono et al., 2019  | 30622725 |  | 🗶 |
| 71 | Ono et al., 2019  | 30622725 |  | 🗶 |
| 77 | Li et al., 2018 | 30592236 |  | 🗶 |
| 84 | Staufner et al., 2020 | 31761904 | 84 | ✓ |
| 85 | Thuriot et al., 2018/ Buote, 2015 | 29388948 |  | 🗶 |
| 88 | Lenz et al., 2021 | 34386911 | 88 | ✓ |
| 90 | Song et al., 2019 | - | Patient 1 | 🗶 |
| 96 | Suzuki et al., 2020 | 32805445 | Patient 1 | ✓ |
| 97 | Li et al., 2020 | 32812336 | 1 | ✓ |
| 99 | Li et al., 2020 | 32812336 | 3 | ✓ |
| 101 | Li et al., 2020 | 32812336 | 5 | ✓ |
| 102 | Li et al., 2020 | 32812336 | 6 | ✓ |
| 103 | Li et al., 2020 | 32812336 | 7 | ✓ |
| 108 | Li et al., 2020 | 32812336 | 12 | ✓ |
| 113 | Khoreva et al., 2020 | 33042920 | 1 | ✓ |
| 114 | Khoreva et al., 2020 | 33042920 | 2 | ✓ |
| 115 | Khoreva et al., 2020 | 33042920 | 3 | ✓ |
| 120 | - | - | - | ✓ |
| 121 | Jiang et al., 2022 | 33520894 |  | 🗶 |
| 123 | Lacassie et al., 2020 | 32297715 |  | ✓ |
| 133 | - | - | - | ✓ |
| 134 | - | - | - | ✓ |

**Supplementary table S1:** References including PMID and patient number in previous publication for all previously published individuals and information on whether additional clinical data or updated information is given. PID patient identification number.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PID** | **Sex assigned at birth** | **Age at last visit (years)** | **Alive**  | **Age at death (years)/ cause of death** | **Liver transplantation/ Age at transplantation (years)** |
| 5 | M | 16 | ✓ |  | 🗶 |
| 7 | F | 17.5 | ✓ |  | 🗶 |
| 8 | F | 4 | ✓ |  | 🗶 |
| 9 | F | 17 | ✓ |  | 🗶 |
| 12 | F | 3.4 | 🗶 | 3.4/ ALF | 🗶 |
| 15 | M | 7 | ✓ |  | 🗶 |
| 16 | F | 17 | ✓ |  | 🗶 |
| 17 | F | 19 | ✓ |  | 🗶 |
| 18 | M | 15 | ✓ |  | 🗶 |
| 20 | F | 23 | ✓ |  | 🗶 |
| 21 | F | 19 | ✓ |  | 🗶 |
| 22 | M | 18 | ✓ |  | 🗶 |
| 24 | M | 1.5 | 🗶 | 1.5/ ALF | 🗶 |
| 25 | F | 3.7 | 🗶 | 3.7/ ALF | 🗶 |
| 26 | M | 2 | 🗶 | 2/ ALF | 🗶 |
| 27 | M | 10 | ✓ |  | 🗶 |
| 28 | M | 6 | ✓ |  | 🗶 |
| 29 | F | 10.5 | ✓ |  | 🗶 |
| 30 | F | 3.9 | 🗶 | 3.9/pneumonia + ELT | 🗶 |
| 31 | F | 14 | ✓ |  | 🗶 |
| 35 | M | 6.9 | ✓ |  | 🗶 |
| 36 | M | 4.7 | ✓ |  | 🗶 |
| 42 | M | 11 | ✓ |  | 🗶 |
| 43 | M | 8 | ✓ |  | 🗶 |
| 44  | F | 4 | ✓ |  | 🗶 |
| 45 | F | 2.3 | ✓ |  | 🗶 |
| 46 | F | 2.6 | ✓ |  | 🗶 |
| 47 | F | 24 | ✓ |  | 🗶 |
| 48 | F | 22 | ✓ |  | 🗶 |
| 55 | F | 3.4 | ✓ |  | 🗶 |
| 56 | F | 8.9 | ✓ |  | 🗶 |
| 58 | F | 16 | ✓ |  | 🗶 |
| 59 | F | 2.3 | 🗶 | 2.3/ ALF | 🗶 |
| 60 | M | 4.3 | ✓ |  | 🗶 |
| 64 | F | 1.3 | 🗶 | 1.3/ ALF | 🗶 |
| 65 | M | 2.7 | 🗶 | 2.7/ ALF | 🗶 |
| 67 | M | 19 | ✓ |  | 🗶 |
| 69 | M | 4 | ✓ |  | ✓/ 2 |
| 70 | M | 7 | ✓ |  | 🗶 |
| 71 | M | 5 | ✓ |  | 🗶 |
| 77 | M | 10.4 | ✓ |  | 🗶 |
| 84 | F | 4.5 | ✓ |  | 🗶 |
| 85 | M | 3 | ✓ |  | 🗶 |
| 88 | M | 2.7 | ✓ |  | 🗶 |
| 90 | M | 5.4 | ✓ |  | 🗶 |
| 96 | M | 34.6 | 🗶 | 34.6/ debilitation during hospitalization for treatment of autoimmune haemolytic anaemia and hepatic hydrothorax | 🗶 |
| 97 | F | 4.4 | 🗶 | 4.5/ ALF | 🗶 |
| 99 | F | 6.8 | ✓ |  | 🗶 |
| 101 | F | 4.3 | ✓ |  | 🗶 |
| 102 | F | 1.3 | 🗶 | 1.3/ ALF | 🗶 |
| 103 | M | 6.7 | ✓ |  | 🗶 |
| 108 | M | 2.8 | ✓ |  | 🗶 |
| 113 | M | 13 | ✓ |  | 🗶 |
| 114 | F | 5 | ✓ |  | 🗶 |
| 115 | M | 9 | 🗶 | 9/ unknown, during Covid-19 infection | 🗶 |
| 120 | M | 22 | ✓ |  | 🗶 |
| 121 | F | 4 | ✓ |  | 🗶 |
| 123 | F | 30 | ✓ |  | 🗶 |
| 133 | F | 4 | ✓ |  | 🗶 |
| 134 | M | 2.7 | ✓ |  | 🗶 |

**Supplementary table S2: Cohort description including** sex assigned at birth, age at last visit, **s**tatus on survival and if not age at and cause of death as well as liver transplantation and age at transplantation.

PID patient identification number, F female, M male, ALF acute liver failure, ELT elevated liver transaminases

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Abnormality of the liver** | **Abnormality of growth** | **Abnormality of the skeletal system** | **Abnormality of the** **nervous system** | **Abnormality** **of the** **integument** | **Abnormality of the immune system** | **Abnormality** **of the** **musculature** | **Others** |
| **Genotype** | **PID** | **Age at last visit** | **ALF** | **cELT** | **SGA** | **Short stature** | **Abnormality of the vertebral column** | **Reduced bone mineral density** | **Delayed closure of fontanels** | **Neurodeve-lopment delay** | **Optic atrophy** | **Abnormality of the integument** | **Reduced NK-cell count** | **Decreased circulating IgG level** | **Pelger-Huët anomaly** | **Muscular hypotonia** | **Diabetes mellitus** | **Facial dysmor-phism** | **High pitched voice** |
|  |  |  | HP:0006554 | HP:0002910 | HP:0001518 | HP:0004322 | HP:0000925 | HP:0004349 | HP:0001476 | HP:0012758 | HP:0000648 | HP:0001574 | HP:0040218 | HP:004315 | HP:0011447 | HP:0001620 | HP:0000819 | HP:0001999 | HP:0001620 |
| **β-propeller** | 1 | 24 | 1.5 | Y | Y | N | N | N | Y | Y | Y | N | Y | n.a. | N | N | Y | N | Y | n.a. |
|  | 25 | 3.7 | Y | Y | N | n.a. | N | Y | Y | Y | N | Y | N | N | N | Y | N | Y | n.a. |
|  | 26 | 2 | Y  | N | n.a. | n.a. | N | Y | Y | Y | N | Y | n.a. | n.a. | N | Y | N | Y | n.a. |
| 2 | 30 | 3.9 | N | n.a. | Y | Y | n.a. | N | n.a. | N | n.a. | N | n.a. | N | n.a. | n.a. | n.a. | Y | n.a. |
|  | 31 | 14 | Y | N | Y | Y | N | Y | n.a. | N | N | N | N | N | n.a. | N | N | Y | n.a. |
| 3 | 16 | 17 | Y | N | N | N | N | N | N | N | N | N | n.a. | n.a. | N | N | n.a. | Y | N |
|  | 17 | 19 | Y | N | Y | Y | N | Y | N | N | N | N | n.a. | N | Y | N | n.a. | N | N |
| **β-propel-ler/sec39** | 4 | 70 | 7 | Y | N | Y | Y | n.a. | n.a. | n.a. | N | N | N | n.a. | n.a. | Y | N | N | N | n.a. |
|  | 71 | 5 | N | N | n.a. | N | n.a. | n.a. | n.a. | N | N | N | n.a. | n.a. | Y | N | N | N | n.a. |
| 5 | 12 | 3.4 | Y | N | N | N | N | N | N | N | N | N | n.a. | n.a. | N | N | N | N | N |
|  | 64 | 1.3 | Y | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| **Sec39** | 6 | 55 | 3.4 | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | N | N | N | N | N | N |
|  | 56 | 8.9 | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | N | N | N | N | N | N |
| 7 | 18 | 15 | Y | N | N | N | N | N | N | N | N | N | n.a. | n.a. | n.a. | N | N | N | N |
|  | 133 | 4 | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | n.a. | N | N | N | N | N |
|  | 134 | 2.7 | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | n.a. | n.a. | N | N | N | N |
| 8 | 58 | 16 | Y | N | N | N | n.a. | n.a. | n.a. | N | N | n.a. | n.a. | n.a. | n.a. | N | n.a. | N | n.a. |
|  | 59 | 2.3 | Y | N | N | N | n.a. | n.a. | n.a. | N | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | N | n.a. |
| 9 | 101 | 6.2 | Y | N | N | N | N | N | N | N | N | N | n.a. | N | n.a. | N | N | N | N |
|  | 102 | 1.3 | Y | N | n.a. | n.a. | N | N | N | N | N | N | n.a. | N | n.a. | N | N | N | N |
| 10 | 60 | 4.3 | Y | Y | n.a. | N | N | n.a. | N | N | N | N | Y | Y | N | N | N | N | N |
|  | 88 | 2.7 | Y | Y | N | N | N | N | N | N | N | N | N | N | n.a. | N | N | N | N |
| **c-terminal** | 11 | 42 | 11 | N | N | Y | Y | N | n.a. | n.a. | Y | Y | Y | n.a. | Y | Y | N | n.a. | Y | n.a. |
|  | 43 | 8 | N | N | Y | Y | Y | n.a. | n.a. | N | Y | Y | n.a. | Y | Y | N | n.a. | Y | n.a. |
| 12 | 47 | 24 | N | N | Y | Y | Y | Y | Y | Y | Y | Y | n.a. | n.a. | n.a. | Y | N | Y | n.a. |
|  | 48 | 22 | N | N | Y | Y | N | n.a. | Y | Y | Y | Y | n.a. | N | n.a. | Y | n.a. | Y | Y |
| 13 | 113 | 15 | N | N | Y | Y | N | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
|  | 114 | 9 | N | Y | Y | Y | N | Y | n.a. | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 14 | 85 | 3 | N | Y | Y | Y | n..a | n.a. | Y | Y | Y | Y | n.a. | n.a. | Y | Y | N | Y | n.a. |
|  | 120 | 23 | N | N | n.a. | Y | n.a. | Y | n.a. | n.a. | Y | N | Y | Y | n.a. | Y | Y | Y | Y |

**Supplementary Table S3: Clinical characteristics of all individuals sharing the same genotype.** If the clinical characteristic applies it is marked “yes”, if not “no” and missing data is marked “not available”. Concordance for the characteristic is shown in green, discordance in red. If there was only data for one of each genotype’s patient it is shown in yellow, if there was no data for any of the genotype’s patients the field is coloured white.

PID patient identification number, YS age in years, ALF Acute liver failure, cELT continuously elevated liver transaminases, SGA small for gestational age, NK-cell natural killer cell, IgG Immunoglobulin G, N no, Y yes, n.a. not available.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Abnormality of the liver** | **Abnormality of growth** | **Abnormality of the skeletal system** | **Abnormality of the nervous system** | **Abnormality of the integument** | **Abnormality of the immune system** | **Abnormality of the musculature** | **Others** |
|  | **genotype** | **PID** | **Age at last visit** | **ALF** | **cELT** | **SGA** | **Short stature** | **Abnormality of the vertebral column** | **Reduced bone mineral density** | **Delayed closure of fontanels** | **Neurodevelopment delay** | **Optic atrophy** | **Abnormality of the integument** | **Reduced NK-cell count** | **Decreased circulating IgG level** | **Pelger-Huët anomaly** | **Muscular hypotonia** | **Diabetes mellitus** | **Facial dysmor-phism** | **High pitched voice** |
|  |  |  | HP:0006554 | HP:0002910 | HP:0001518 | HP:0004322 | HP:0000925 | HP:0004349 | HP:0001476 | HP:0012758 | HP:0000648 | HP:0001574 | HP:0040218 | HP:004315 | HP:0011447 | HP:0001620 | HP:0000819 | HP:0001999 | HP:0001620 |
| **β-propeller** | M-1 | 22 | **18** | Y | N | Y | Y | Y | Y | n.a. | N | Y | Y | Y | Y | Y | N | N | Y | Y |
| 46 | **2.6** | Y | Y | Y | Y | Y | Y | n.a. | Y | N | N | N | Y | n.a. | N | n.a. | Y | Y |
| M-2 | 7 | **17.5** | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 8 | **7.2** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | N | Y | Y |
| **Sec39** | M-3 | **9** | **17** | Y | N | Y | Y | N | N | n.a. | N | n.a. | N | n.a. | N | Y | N | N | Y | Y |
| 15 | **7** | Y | N | n.a. | Y | n.a. | N | n.a. | Y | N | N | n.a. | n.a. | n.a. | N | n.a. | N | n.a. |
| M-4 | 5 | **16** | Y | N | N | N | N | N | N | N | N | N | n.a. | n.a. | N | N | N | Y | N |
| 20 | **23** | Y | N | N | N | N | N | n.a. | N | N | N | N | n.a. | N | N | N | Y | N |
| 69 | **4** | Y | N | N | N | N | n.a. | N | N | N | N | n.a. | Y | n.a. | N | N | N | N |
| M-5 | 21 | **19** | Y | N | N | N | N | N | N | N | N | N | n.a. | N | n.a. | N | n.a. | N | n.a. |
| 84 | **4.5** | Y | N | Y | Y | n.a. | N | n.a. | N | N | N | N | N | n.a. | N | N | Y | Y |
| M-6 | 35 | **6.7** | Y | N | N | N | N | N | N | N | N | N | n.a. | N | n.a. | N | N | N | N |
| 36 | **4.7** | Y | N | N | N | N | N | N | N | N | N | n.a. | N | n.a. | N | N. | N | N |
| 44 | **4** | Y | N | n.a. | N | n.a. | n.a. | N | N | n.a. | N | n.a. | n.a. | n.a. | N | n.a. | N | N |
| 90 | **5.4** | Y | N | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | Y | N | Y | n.a. | n.a. | n.a. | n.a. |
| 97 | **4.4** | Y | N | N | N | N | N | N | N | N | N | n.a. | N | n.a. | N | N | N | N |
| 99 | **6.8** | Y | N | N | N | N | N | N | N | N | N | n.a. | Y | N | N | N | N | N |
| 101\* | **4.3** | Y | N | N | N | N | N | N | N | N | N | n.a. | N | n.a. | N | N | N | N |
| 102\* | **1.3** | Y | N | n.a. | n.a. | N | N | N | N | N | N | n.a. | N | n.a. | N | N | N | N |
| 103 | **6.7** | Y | N | N | N | N | N | N | N | N | N | n.a. | N | N | N | N | N | N |
| 121 | **4** | Y | N | N | N | N | N | N | N | N | N | n.a. | n.a. | n.a. | N | n.a. | N | N |
| **c-terminal** | M-7 | 27 | **10** | N | N | Y | Y | Y | Y | Y | n.a. | Y | Y | n.a. | Y | Y | n.a. | n.a. | Y | Y |
| 28 | **6** | N | N | Y | Y | N | Y | Y | n.a. | Y | Y | N | Y | Y | N | n.a. | Y | Y |
| 29 | **10.5** | N | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 42\* | **11** | N | N | Y | Y | N | n.a. | n.a. | Y | Y | Y | n.a. | Y | Y | N | n.a. | Y | n.a. |
| 43\* | **8** | N | N | Y | Y | Y | n.a. | n.a. | N | Y | Y | n.a. | Y | Y | N | n.a. | Y | n.a. |
| 45 | **2.3** | N | Y | Y | Y | n.a. | Y | Y | Y | Y | Y | n.a. | Y | n.a. | n.a. | n.a. | Y | n.a. |
| 65 | **2.7** | Y | Y | Y | Y | n.a. | n.a. | Y | Y | n.a. | Y | n.a. | n.a. | Y | n.a. | n.a. | Y | n.a. |
| 67 | **19** | N | Y | Y | Y | Y | n.a. | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | n.a. |
| 85\* | **3** | N | Y | Y | Y | n..a | n.a. | Y | Y | Y | Y | n.a. | n.a. | Y | Y | N | Y | n.a. |
| 96 | **34.5** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 113\* | **13** | N | N | Y | Y | N | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 114\* | **5** | N | Y | Y | Y | N | Y | n.a. | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 115 | **9** | Y | Y | Y | Y | N | Y | n.a. | Y | Y | Y | Y | Y | Y | Y | N | Y | n.a. |
| 120\* | **22** | N | N | n.a. | Y | n.a. | Y | n.a. | n.a. | Y | N | Y | Y | n.a. | Y | Y | Y | Y |
| 123 | **30** | N | N | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y |
| M-8 | 77 | **11** | N | N | N | Y | n.a. | n.a. | n.a. | N | Y | N | Y | Y | Y | N | N | Y | n.a. |
| 108 | **2.8** | N | Y | Y | Y | N | N | N | Y | N | N | n.a. | N | N | N | N | N | N |

**Supplementary Table S4: Clinical characteristics of all individuals sharing one missense variant and having a loss-of-function variant in trans.** If the clinical characteristic applies it is marked “yes”, if not “no” and missing data is marked “not available”. Concordance for the characteristic is shown in green, discordance in red. If there was only data for one of each missense variant’s patient it is shown in yellow, if there was no data available the field is coloured white.

PID patient identification number, YS age in years, ALF Acute liver failure, cELT continuously elevated liver transaminases, SGA small for gestational age, NK-cell natural killer cell, IgG Immunoglobulin G, N no, Y yes, n.a. not available.

\* Also included in supplementary table S3, share their genotype with another individual.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PID** | **Reference** | **Reference (PMID)** | **PID in previous publication** | **Additional clinical data or updated information given** |
| 2 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 2 (FII) | ✓ |
| 4 | Haack et al., 2015; Staufner et al., 2016 | 26073778; 26541327 | Patient 4 (FIV) | ✓ |
| 68 | Staufner et al., 2020 | 31761904 | 68 | ✓ |
| 94 | Chavany et al., 2020 | 32146038 | Patient 2 | 🗶 |
| 105 | Li et al., 2020 | 32812336 | 9 | ✓ |
| 129 | Lipinski et al., 2021 | 34427841 |  | ✓ |

**Supplementary table S5:** References including PMID and patient number in previous publication for all individuals having a homozygous missense variant and all individuals sharing the missense variant and having a loss-of-function variant in trans with information on whether additional clinical data or updated information is given. PID patient identification number.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PID** | **Sex assigned at birth** | **Age at last visit (years)** | **Alive**  | **Age at death (years)/ cause of death** | **Liver transplantation/ Age at transplantation (years)** |
| 2 | F | 30 | ✓ |  | 🗶 |
| 4 | F | 45 | ✓ |  | 🗶 |
| 68 | F | 6.8 | ✓ |  | 🗶 |
| 94 | M | 3 | ✓ |  | ✓/ 1,9 |
| 105 | F | 3.5 | 🗶 | 3.5/ ALF | 🗶 |
| 129 | F | 5 | ✓ |  | 🗶 |

**Supplementary table S6:** Cohort description of all individuals having a homozygous missense variant and all individuals sharing the missense variant and having a loss-of-function variant in trans including sex assigned at birth, age at last visit, **s**tatus on survival and if not age at and cause of death as well as liver transplantation and age at transplantation. PID patient identification number, F female, M male, ALF acute liver failure, ELT elevated liver transaminases.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **PID** | **Region/ domain of NBAS affected** | **Allele 1 nucleotide change** | **Allele 1 protein change** | **Allele 2 nucleotide change** | **Allele 2 protein change** |
| 2 | sec39 | c.[2708T>G] | p.[Leu903Arg] | c.[2708T>G] | p.[Leu903Arg] |
| 4 | sec39 | c.[2708T>G] | p.[Leu903Arg] | c.[2827G>T] | p.[Glu943\*] |
| 68 | sec39 | c.[2822G>A] | p.[Arg941His] | c.[2822G>A] | p.[Arg941His] |
| 94 | sec39 | c.[2822G>A] | p.[Arg941His] | c.[2423+404G>A] | p.[Arg809Phefs\*10] |
| 105 | sec39 | c.[2809C>G] | p.[Pro937Ala] | c.[2809C>G] | p.[Pro937Ala] |
| 129 | sec39 | c.[2809C>G] | p.[Pro937Ala] | c.[del exon 43-52] | p.[?] |

**Supplementary table S7:** *NBAS* variants (NM\_015909.3; NP\_056993.2) of all individuals included in this study having a homozygous missense variant and all individuals sharing the missense variant and having a loss-of-function variant in trans.

PID Patient identification number.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Abnormality of the liver** | **Abnormality of growth** | **Abnormality of the skeletal system** | **Abnormality of the nervous system** | **Abnormality of the integument** | **Abnormality of the immune system** | **Abnormality of the musculature** | **Others** |
| **genotype** | **PID** | **Age at last visit** | **ALF** | **cELT** | **SGA** | **Short stature** | **Abnormality of the vertebral column** | **Reduced bone mineral density** | **Delayed closure of fontanels** | **Neurodevelopment delay** | **Optic atrophy** | **Abnormality of the integument** | **Reduced NK-cell count** | **Decreased circulating IgG level** | **Pelger-Huët anomaly** | **Muscular hypotonia** | **Diabetes mellitus** | **Facial dysmor-phism** | **High pitched voice** |
| HP:0006554 | HP:0002910 | HP:0001518 | HP:0004322 | HP:0000925 | HP:0004349 | HP:0001476 | HP:0012758 | HP:0000648 | HP:0001574 | HP:0040218 | HP:004315 | HP:0011447 | HP:0001620 | HP:0000819 | HP:0001999 | HP:0001620 |
| H-1 | 55\* | **3.4** | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | N | N | N | N | N | N |
| 56\* | **8.9** | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | N | N | N | N | N | N |
| 18\* | **15** | Y | N | N | N | N | N | N | N | N | N | n.a. | n.a. | n.a. | N | N | N | N |
| 133\* | **4** | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | n.a. | N | N | N | N | N |
| 134\* | **2.7** | Y | N | n.a. | N | N | N | N | N | N | N | n.a. | n.a. | n.a. | N | N | N | N |
| H-2 | 2 | **30** | Y | N | Y | N | N | N | N | N | N | N | Y | N | N | N | N | Y | N |
| 4 | **45** | Y | N | n.a. | Y | N | N | N | Y | N | N | Y | N | N | N | N | Y | N |
| H-3 | 129 | **5** | Y | N | N | N | N | N | N | Y | N | N | N | N | N | Y | N | Y | N |
| 68 | **6.8** | Y | N | N | N | N | N | n.a. | N | N | N | n.a. | n.a. | n.a. | N | N | N | N |
| H-4 | 94 | **3** | Y | N | n.a. | n.a. | n.a. | n.a. | n.a. | N | N | n.a. | Y | n.a. | n.a. | N | N | N | n.a. |
| 105 | **3.5** | Y | N | Y | Y | N | N | N | N | N | N | n.a. | N | n.a. | N | N | Y | N |

**Supplementary Table S8: Clinical characteristics of all individuals having a homozygous missense variant and all individuals sharing the missense variant and having a loss-of-function variant in trans.** If the clinical characteristic applies it is marked “yes”, if not “no” and missing data is marked “not available”. Concordance for the characteristic is shown in green, discordance in red. If there was only data for one of each missense variant’s patient it is shown in yellow, if there was no data available the field is coloured white.

PID patient identification number, YS age in years, ALF Acute liver failure, cELT continuously elevated liver transaminases, SGA small for gestational age, NK-cell natural killer cell, IgG Immunoglobulin G, N no, Y yes, n.a. not available.

\* Also included in supplementary table S3, share their genotype with another individual.

**Supplementary Figure S1: Comparison of ASAT, ALAT and INR during each individual’s most severe episode of acute liver failure (ALF) in relation to number in sibling sequence.** Laboratory result for each first sibling are shown in blue, for the second sibling in red and for the third sibling in green. Data not included if not available in at least two individuals per genotype the. Laboratory results during ALF episodes after implementation of an emergency protocol are marked with a star ( ).

 β -propeller β -propeller/ Sec 39

 Sec 39

ASAT aspartate aminotransferase, ALAT alanine aminotransferase, INR international normalized ratio.