**SUPPLEMENTAL FIGURES AND TABLES**

**FIGURE LEGENDS**

**Figure S1. Schematic illustration of the predicted genetic outcomes of different variant types in *ABL1*.**

Splice variants typically lead to premature termination codons (PTCs) more than 50–55 base pairs (bp) upstream of the most 3’ exon–exon junction, causing nonsense-mediated decay (NMD) and resulting in no protein (left panel). Congenital heart defects and skeletal malformations (CHDSKM) syndrome missense variants result in full-length proteins with potentially altered function (middle panel). In contrast, truncating variants in the last exon downstream of the last exon-exon junction in human ABL1 deficiency syndrome (HADS) possibly escape NMD, producing truncated proteins (right panel). Adapted from Maquat et al.(1). Created in BioRender. Saida, K. (2025) https://BioRender.com/dqs39rh.

**Figure S2. Identified splice variant leads to a reduction of *ABL1* mRNA expression in affected proband.**

**A-B)** Quantification of the *ABL1* mRNA abundance via qRT-PCR showed a significant (**A;** *ABL1*-201, ENST00000318560.6) or partial (**B;** *ABL1*-202, ENST00000372348.9) reduction of *ABL1* mRNA in III-401 (red)compared to a healthy control (green, CTRL). These data indicate the degradation of the aberrantly spliced transcript by NMD. AU: arbitrary units; \*, p<0.05 student’s t-test

**Figure S3. mRNA expression of *ABL1* in human newborn umbilical cord tissue.**

Using RT-PCR, the expression of both *ABL1* mRNA transcripts (*ABL1-201*, ENST00000318560.6 and *ABL1-202*, ENST00000372348.9) could be confirmed in the umbilical cord of a healthy human newborn.

|  |  |
| --- | --- |
| **Primer ID** | **Sequence** |
| ABL1\_201\_e1e2\_F | TGGAAGAAGCCCTTCAGC |
| ABL1\_e3\_R1 | TTGGTTTGGGCTTCACACC |
| ABL1\_202\_e1e2\_F | GAACATGAAGCCCTTCAGC |
| EEF1A\_1F | GGCATCGACAAAAGAACCAT |
| EEF1A1\_1R | CCCAGGCATACTTGAAGGAG |
| EEF1A1\_2F | GCTGCTGAGATGGGAAAGG |
| EEF1A1\_2R | ACAGTCAGCCTGAGATGTCC |
| ABL1\_202\_e1\_F | CTGACTTGTGGAGATGCAGC |
| ABL1\_201\_e1\_F | TGGGCTGCAAATCCAAGAAG |
| ABL1\_e3\_R2 | AGGTTTTCCTTGGAGTTCC |
| ABL1\_e7\_F | TGAGCAGGTTGATGACAGG |
| ABL1\_e8\_R | CTCATACACCTGGGACAG |

**Table S1. Primers and respective sequences used for RT- and RT-qPCR.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Reference** | **Trimester exposure** | **Tyrosine kinase Inhibitor** | **Fetal anomaly** | **No. omphalocele / total number of exposed embryos/fetuses** |
| **Case series** | | | | |
| **Pye et al.**(2) | first | Imatinib | Scoliosis, **small exomphalos** | **3 / 125** |
| unkown | Imatinib | **Exomphalos**, right renal agenesis and hemivertebrae |
| first | Imatinib | Hypoplastic lungs, **exomphalos**, left duplex kidney, right absent kidney, hemivertebrae, and right shoulder anomaly |
| **Madabhavi et al.**(3) | unknown | Imatinib | **Omphalocele** | **1 / 10** |
| **Chelysheva et al.**(4) | unknown | Nilotinib | **Omphalocele** | **1 / 60** |
| **Abruezze et al.**(5) | unknown | Dasatinib | **Omphalocele** | **1 / 80** |
|  |  |  |  | **Total 6 / 275 (~ 1 / 46)** |
| **Case report** | | | | |
| **Étienne et al**.(6) | first | Nilotinib | **Large omphalocele** | **1** **/ 2** |

**Table S2. Reported pregnancies with tyrosine kinase inhibitors (TKIs) exposure to the embryo/fetus and omphalocele as pregnancy outcome** (from ancient Greek umbilicus, and hernia; also spelled omphalocele; synonym: exomphalos)