NEW CASE OF CDC42 DEFICIENCY WITH ADDITIONAL PATHOGENIC VARIANTS IN UNC13D AND DNAH8 GENES

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Background and aims

CDC42-deficiency (or Takenouchi-Kosaki syndrome) is autosomal-dominant disorder associated with congenital malformations, bone marrow failure (BMF), HLH and autoinflammation.

We reported a case of 12-y.o girl with cytopenia since birth, congenital malformations and B-cell immunodeficiency.

Clinical case

Patient manifested with thrombocytopenia firstly diagnosed in 3m. Congenital malformations includes perineal anus ectopia, sensorineural deafness and facial dysmorphism. Hepatosplenomegaly (+1.5-+6.5sm) was firstly noted at 8m and is preserved until now. Leucopenia (1-3.5×109/L) and thrombocytopenia (7-140×109/L) have been observed throughout patient's life. Infectious episodes have occurred infrequently: pneumonia at 3 and 10yrs, second episode was complicated with bronchiolitis, hydrothorax, hydropericardium. Chromosomal aberrations and instability were not revealed.

Table 1. Results of panel sequencing (Invitae immunodeficiency panel, 452 genes)

Gene	Variant	Zygosity
CDC42	c.203G>A (p.Arg68Gln)	het
DNAH8	c.9367C>T (p.Arg3123*)	het
DNAH8	c.644G>A (p.Gly215Glu)	het
UNC13D	c.408_414del (p.Cys136Trpfs*7)	het

Laboratory evaluation

Table 2. Immunology

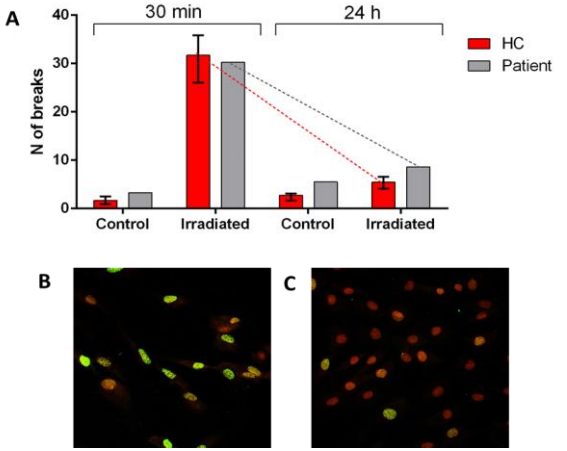
	Patient % (cells/µL)	Reference % (cells/µL)
T-cells (CD3+)	86 (808)	58-85 (600-2200)
T-helpers (CD3+CD4+)	51.1 (412)	30-56 (180-1200)
T-cytotoxic (CD3+CD8+)	34.3 (277)	18-45 (100-990)
B-cells (CD19+)	2.8 (26)	7-20 (110-550)
NK-cells	12 (113)	5-25 (75-1000)
IgG (gL/)	6.73	7-18.2
IgM (g/L)	2.47	0.4-2.93
IgA (g/L)	0.64	0.7-4.0

Immunological tests revealed decreased B-cells (2.8%,26 cells/µl), slightly reduced IgG (4.5-6.5g/L) with **normal B-mem**, **elevated CD21low B-cells (24%); naïve/memory T-cells and RTE were in normal ranges**.

Panel sequencing (Invitae immunodeficiency panel, 452 genes) revealed pathogenic variants in CDC42 (p.Arg68Gln), DNAH8 (p.Arg2123*), UNC13D (p.Cys136Trpfs*7) and one additional variant of uncertain significance in DNAH8 (p.Gly215Glu). Although patient has two HLH-associated pathogenic variants, phagocytizing macrophages was detected in bone marrow aspirate only at 7yrs, without any additional biochemical HLH sings (HLH score-160points).

Patient has an increased number of DNA double breaks in non-irradiated cells that confirmed CDC42 role in cell survival and genotoxic stress. However, DNA double-strand break repair was only slightly impaired.

Figure 1. DNA double-strand break repair evaluation



A – number of double-strand break in healthy controls (N=5) and patient on 30 min and 24 h after irradiation (dose 5 Gr); B and C - double-strand breaks in patients fibroblasts on 30m and 24h after irradiation, correspondently histone H2AX staining, confocal microscopy)

Conclusions

We describe new case of CDC42-deficiency with additional genetic events in UNC13D and DNAH8 genes.

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