Expanding the phenotypic and genetic spectrum of radioulnar synostosis associated hematological disease

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Supplementary Information – comprising 2 tables and 1 figure

Supplementary Table 1 – Characteristics of cases of radioulnar synostosis associated bone marrow failure reported in the literature

Patient	Age at diagnosis	Nationality/ ethnicity	Gene/ variant	RUS	Family history	Peripheral blood	Skeletal/ Limb abnormality	Bone marrow	Fanconi anaemia test	Transfusion dependent	Other	HSCT	Ref
Family 1 Case 1	Birth	Caucasian/ Native American	***HOXA11*** c.872delA p.N291Tfs*3	Blt	Yes	Pancytopenia	Blt clinodactyly, Hip dysplasia	Hypocellular	Normal	Yes		Unrelated BMT	1,2
Family 1 Case 2	Birth	Caucasian/ Native American	***HOXA11*** c.872delA p.N291Tfs*3	Blt	Yes	Thrombo-cytopenia	Hip dysplasia	↓ Mega-karyocytes	Normal	Yes		Unrelated CBT	1,2
Family 2 Case 3	Birth	Filipino	***HOXA11*** c.872delA p.N291Tfs*3	Blt	Yes	Thrombo-cytopenia	Blt clinodactyly	Hypercellular, no mega-karyocytes	Normal	Yes	Deafness	Related BMT	1,2
Family 2 Case 4	Birth	Filipino	***HOXA11*** c.872delA p.N291Tfs*3	Ult	Yes	Thrombo-cytopenia	Blt clinodactyly	↓ Mega-karyocytes	Normal	Yes			1,2
TRS1	Birth	Japanese	***MECOM*** c.2266A>G p.T756A	Blt	No	Pancytopenia	Bony defect 4^{th} and 5^{th} fingers	Hypocellular, no mega-karyocytes	Normal		Cleft palate	CBT	3
TRS2	Birth	Japanese	***MECOM*** c.2252A>G p.H751R	Blt	No	Thrombo-cytopenia	Blt clinodactyly	No mega-karyocytes	Normal		Dysarthria, Deafness	Unrelated BMT	3,4
TRS3	Birth	Japanese	***MECOM*** c.2248C>T p.R750W	Blt	No	Pancytopenia	Overlapping fingers	Hypocellular	Normal		Enlarged spleen	Unrelated BMT	3,5
UB004	18 months		***MECOM*** c.2248C>T p.R750W	Yes	No	Pancytopenia		Hypocellular	Normal		Tetralogy of Fallot	HSCT	6
I:1	73 years (MDS diagnosis)		***MECOM*** c.2296T>G p.C766G	Yes	Yes	Thrombo-cytopenia	Limb dysmorphisms	Myeloid malignancy			Impaired hearing		7
II:3	48 years (MDS diagnosis)		***MECOM*** c.2296T>G p.C766G	Yes	Yes	Thrombo-cytopenia	Limb dysmorphisms	Myeloid malignancy			Impaired hearing	Unrelated BMT	7
III:2	18 years		***MECOM*** c.2296T>G p.C766G	Yes	Yes	No cytopenias at 24yrs	Limb dysmorphisms	No biopsy done			Impaired hearing		7
III:3	18 years		***MECOM*** c.2296T>G p.C766G	Yes	Yes	No cytopenias at 24yrs	Limb dysmorphisms	No biopsy done			Impaired hearing, Ischemic insults		7

Female	Birth	African American	***MECOM*** c.2248C>T p.R750W	Blt	No	Amegakaryocytic thrombocytopenia	Hip dysplasia, Overlapping fingers		Normal	Yes	Premature, Facial dysmorphia	BMT	8
Male	3 years	Yemeni	***BCR-ABL*** translocation (t9:22)	Blt	No	Null B-ALL		Blast cells dominate			Enlarged spleen		9
Female	Birth		No report	Blt	Yes	Pancytopenia	Blt clinodactyly	Hypocellular	Normal	Yes		Yes	10
Male	Birth	White	No report	Blt	No	Pancytopenia	Blt clinodactyly	Hypocellular	Normal	Yes	Develop-mental delay	Related BMT	11
Family B Case 3	22 years	Portuguese	No report	Blt	Yes	Pancytopenia		Hypocellular	Normal	Yes			12

HSCT – hematopoietic stem cell transplantation; Blt – bilateral; Ult – unilateral; RUS – radioulnar synostosis; BMT – bone marrow transplantation; CBT – umbilical cord blood transplantation; MDS – myeloid dysplastic syndrome; Limb dysmorphisms – brachy, campto and clinodactyly, patella hypoplasia, metatarsus adductus, hallux valgus; B-All – B-cell acute lymphoblastic leukemia

Supplementary Table 2 – Characteristics of cases with germline *MECOM* variants and hematological defects but no radioulnar synostosis reported in the literature

Patient	**Age at diagnosis**	**Nationality /ethnicity**	**Variant**	**Family history**	**Peripheral blood**	**Skeletal/ Limb abnormality**	**Bone marrow**	**Fanconi anaemia test**	**Other**	**HSCT**	**Ref**
UB036	6 months	French	c.2334G>T p.R778S	No	Pancytopenia	Thumb abnormalities	Hypocellular	Normal	Myocardial atrophy	Yes	6
UB093	3 months	French	c.1930G>T p.E644X	No	Pancytopenia	Clubfoot	Hypocellular	Normal	Pulmonary stenosis, Facial dysmorphia	Yes	6
UB100	Birth	French	c.1302_1306del p.K434fs*10	No	Pancytopenia		Hypocellular	Normal		Yes	6
UB104	9 months	French	c.2900_2903del p.D967fs*4	No	Pancytopenia		Hypocellular	Normal		Yes	6
UB153	9 months	French	c.2208-1G>A	No	Pancytopenia	Thumb abnormalities	Hypocellular	Normal	Renal hypoplasia	Yes	6
Female	Birth	Caucasian	3q26.2 deletion	Yes	Thrombo-cytopenia	Fingernail clubbing	Hypocellular	Normal		Unrelated BMT	13
Male	Birth	Caucasian	3q26.2q26.31 deletion	No	Thrombo-cytopenia				Facial dysmorphia	Died aged 28 days	14

HSCT – hematopoietic stem cell transplantation; Blt – bilateral; BMT – bone marrow transplantation

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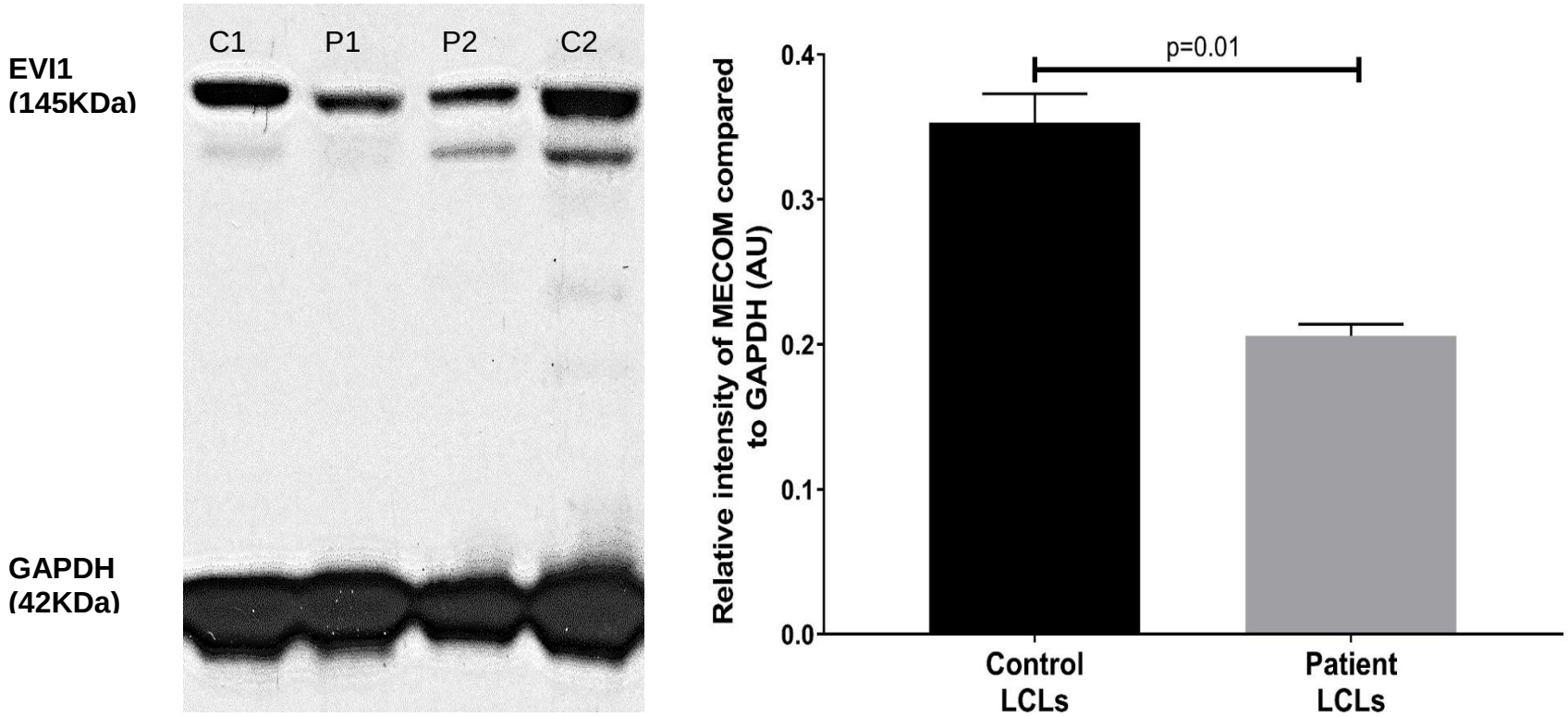
Supplementary Figure 1



Effect of p.Glu758Lys variant on the expression of MECOM from patients with RUS and hematological disease

A - Representative Western blots showing the relative amounts of MECOM protein (mouse monoclonal EVI1 antibody, Sigma) to GAPDH (rabbit monoclonal antibody, Santa Cruz) present in samples from either lymphoblastoid cell lines (LCLs) from patients (P1 and P2, Family 5 generation IV) and controls (C1 and C2). **B** – Densitometry of the MECOM and GAPDH bands show that there is a slight reduction in the relative amount of protein in the patient samples compared with controls from the LCLs (p=0.01). Each blot was performed three times. Individually the MECOM levels for each patient is significantly lower than the controls. P1 vs controls p=0.041, P2 vs controls p=0.035 (unpaired T-test).