

Supplementary information

Material and methods

Patients and Samples

A total of 68 samples, including 66 cases with CMML were analyzed. Bone marrow samples were obtained at diagnosis or after diagnosis free of disease progression. All patients signed an informed consent for research and the study was approved by our institutional review board (“Comité d’Orientation Scientifique” of the Institut Paoli-Calmettes). The main clinical and biological data of the 68 samples are presented in Supplementary Tables S1 & S2.

Nucleic acid extraction was done as previously described.¹

Gene sequencing

Genes were selected for their known involvement in leukemogenesis. DNA Sanger-sequencing of exon-coding sequences of *CBL* (exons 8, 9), *JAK2* (exon 14), *NRAS* (exons 1, 2), *KRAS* (exons 1, 2), *DOK1* (exons 1-5), *DOK2* (exons 1-5), *FLT3* (exons 14,15,20), *NF1* (all exons), *PTPN11* (exons 3,11), *RUNX1* (exons 1-8), *TET2* (exons 3-11), *IDH1/2* (exon 4), *DNMT3A* (exons 15-23), *ASXL1* (exon 12), *EZH2* (all exons), *SUZ12* (exons 14-18), *SRSF2* (exon 2), *SF3B1* (exons 12-16), *U2AF1* (exons 2-6) and *ZRSR2* (exon 2) as previously described^{2, 3}. The transcript IDs (Ensembl) for *DOK1* and *DOK2* are ENSG00000115325 and ENSG00000147443, respectively.

Primers were previously described.^{1, 4} The *DOK1* and *DOK2* primers used for amplified DNA sequencing are described in Supplementary Table S3. DNA were amplified in a total volume of 25 μ L PCR mix containing at least 5 ng template DNA, Taq buffer, 200 μ mol of each deoxynucleotide triphosphate, 20 pmol of each primer, and 1 U of Hot Star Taq (Qiagen). PCR conditions were 95°C 10 min; 95°C 30 sec, variable temperature 30 sec, 72°C 30 sec to 1 min depending on PCR product length for 35 cycles, 72°C 10 min. PCR products were purified using Millipore plate MSNU030. Two μ L of the purified PCR products were used for sequencing using the Big Dye terminator v1.1 kit (Applied Biosystems) including the forward or reverse primer. After G50 purification, sequences were loaded on ABI 3130xl and 3730 automats (Applied Biosystems). The sequence data files were analyzed using SeqScape software. The genetic alterations identified were cross-referenced to information from the Ensembl Genome Browser (<http://www.ensembl.org>) and all mutations were confirmed on an independent PCR product.

Molecular Modeling

We generated a 3D model of the *DOK2* PTB – EMLLENLpY phospho-peptide complex by 3D homology. We used the 1UEF (PDB code) structure of the *DOK1* PTB – RET complex as representative 3D structure of the complex. Chains B and D from the 1UEF structure were deleted (with their water molecules associated) using SYBYL X1.3 and the resulting *DOK1* PTB - RET structure was aligned with the 2DLW structure of the PTB *DOK2* protein (rmsd of 4.7Å for the two monomers). We then mutated the RET sequence TWIENKLPY by the *DOK1* PH-PTB phospho-peptide EMLLENLpY sequence and energy minimize the resulting model (using the torsion module from SYBYL X1.3).

Plasmid constructs

The constructs encoding GFP-tagged full-length DOK2 were described previously.⁵

⁶ Standard site-directed mutagenesis techniques (QuickChange Site Directed Mutagenesis Kit, Stratagene) were used to generate *DOK2* RR200-201AA (*DOK2* RR) and *DOK2* L238P from plasmid constructs coding for GFP- or HA-tagged wild-type (WT) *DOK2*. We generated *DOK2* RR200-201AA introducing base pair changes: c860g, g861c, c863g and g964c coding for two Alanine (A) codons (GCG-GCC) instead of the two Arginine (R) codons (CGG-CGC) in the *DOK2* open reading frame (ORF). *DOK2* L238P was constructed by introducing a t972c change in the *DOK2* ORF. HA-tagged *DOK2* WT and mutant sequences were then subcloned into the *EcoRI* and the *BamHI* restriction sites of pMSCV-IRES-GFP (pMIG) vector for retroviral infections also known as pFBMoSALF⁷ containing the *env* gene (kindly provided by Dr. Estelle Duprez, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France). All sequences were confirmed by direct sequencing before expression in Cos-1 cells and retrovirus generation.

Cell culture

KG-1 myeloid cells were cultured in IMDM (Iscove's Modified Dulbecco's Medium; Gibco) with 20% heat-inactivated fetal bovine serum (Eurobio) supplemented with 100U/ml penicillin (Gibco), 100µg/ml streptomycin (Gibco).

Preparation of Mouse embryonic fibroblasts (MEF): *Dok1*^{-/-} *Dok2*^{-/-} double knockout (DKO) mouse strain in 129/Sv genetic background was described previously^{8,9} and wild-type 129/Sv mouse strain is purchased from Charles River Laboratories France (L'Arbresle, France). Pregnant mice were sacrificed at 13.5 days post-coitus.

Embryos were dissected from the uterus, and extra embryonic membranes and viscera were subsequently removed. Embryos were washed in PBS, and then head and liver were removed. Tissue were dissociated on a 70 μ m filter, cells were then washed and seed on culture dishes. MEF were cultured in DMEM (Dulbecco's modified Eagles's medium; Gibco) with 10% heat-inactivated fetal bovine serum (Eurobio) supplemented with 50 nM β 2-mercapto ethanol (Gibco), 1mM sodium pyruvate, 100 U/ml penicillin (Gibco), 100 μ g/ml streptomycin (Gibco), and 2mM L-Glutamine (Gibco) and non-essential amino acids (Gibco).

Transfection

For overexpression of DOK proteins (Dok2wt-GFP, Dok2RR-GFP and Dok2L238P-GFP), 2×10^6 KG-1 cells were transfected with 2 μ g of the previously described plasmids by nucleofection using the Amaxa Technology (Solution R, program V-001; Lonza Cologne AG). Transfection efficiency was quantified by flow cytometry (>50% GFP positive cells for all constructs, data not shown).

Retroviral infection

293T cells were cultured in DMEM (Dulbecco's modified Eagles's medium; Invitrogen) with 10% fetal bovine serum (Eurobio) were used for expression of HA-tagged wild-type DOK2 and mutants (Dok2 RR, Dok2 L238P) in pMIG vectors. Cells were transfected with Lipofectamine 2000 (Invitrogen™, Life Technologies) according to the manufacturer's instructions. For generation of *DOK2* constructs retrovirus, supernatants from 293T cells transfected with previously described pMIG-*DOK2* constructs were collected after 24 and 48 h, filtered and applied to MEFs by 2 rounds of centrifugation. MEFs subsequently infected were at passage 2 to passage

4. For generating MEF cell lines with stable expression of DOK2 WT or mutants (Dok2 RR, Dok2 L238P), cells were grown for 7 to 14 days following retroviral transduction and GFP positive cells were sorted by Cell Sorter.

Stable expression of HA-tagged Dok2 WT and mutants (Dok2 RR, Dok2 L238P) was confirmed by Western blot analysis.

Proliferation Assays

MEFs expressing wild-type or DOK2 mutants were seeded in triplicate and each day trypsinized, washed and counted with CountBright™ absolute counting beads (Life Technologies), by flow cytometry during 6 days.

Flow cytometry analysis and cell sorting

Flow cytometry analysis was performed on a BD LSR II flow cytometer and cell sorting was executed on a BD FACS Aria III or a BD FACS Aria II. FACS data were analyzed with BD-DIVA Version 6.1.2 software (BD Biosciences).

Cell stimulation, immunoprecipitation and immunoblotting

KG-1 cells were starved in IMDM containing 5% FCS during 2h. Then KG-1 cells were treated by 50 μ M (see Figure 1c) or 1 μ M (see Figure 1d) of sodium pervanadate as previously described¹⁰ for 5 min at 37°C. After stimulation, cells were lysed. For immunoprecipitation, post-nuclear lysates were incubated 10 μ g of anti-Dok-1 Ab (Ab8112, Abcam) coupled to protein A-Sepharose for 2 h at 4°C. Western Blots were performed as previously described¹¹. Detections were performed with following the antibodies: anti-phospho ERK1/2 (Thr202/Thr204) (#4377, Cell Signaling Technology), anti-ERK1/2 (#9101, Cell Signaling

Technology), anti-GFP (#11814450001, Roche), anti- β -tubulin (#2128, Cell Signaling Technology) and anti-Dok1 (Ab8112, Abcam).

Statistical Analyses

Results were expressed as mean values \pm SEM. Statistical significance of differences between the results was assessed using a two-way ANOVA test, performed using Prism (GraphPad software, version 5.03). *P* values < 0.05 were considered statistically significant and the degree of significance is indicated as follows: *, *P* < 0.05 ; **, *P* < 0.01 ; ***, *P* < 0.001 .

References

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Supplementary tables

Table S1. Clinical and biological data of the 68 samples

Case	Sex/Age (years)	Diagnosis	Karyotype	RUNX1 (exons 1-8)	TET2 (exons 3-11)	IDH1/2 (exons 4)	DNMT3A (exons 15-23)	ASXL1 (exon 12)	EZH2 (all exons)	SUZ12 (exons 14-16)	SRSF2 (exon 2)	SF3B1 (exons 12-16)	U2AF1 (exons 2,6)	ZRSR2 (exons 1-11)	CBL (exons 8-9)	DDK1 (exons 1-5)	DOK2 (exons 1-5)	FLT3 ITD(TKD) (exons 14,15,20)	JAK2 (exon 14)	KRAS (exons 1-2)	NRAS (exons 1-2)	NFI (all exons)	PTPN11 (exons 3,11)
HD-0178	M85	MD-CMML1	46,XY,del(20)(q11q13)[20]			R140Q					P95H												
HD-0197	M59	MD-CMML1	46,XY[20]	R320X							Del												
HD-0206	M73	MD-CMML2	46,XY[20]		Del	R172K	R882	D879EfsX7					S35F										
HD-0254	F/83	MD-CMML2	46,XX[20]							Del	P95H					D263E						Del	
HD-0230	M83	MD-CMML1	46,XY[20]					H630PfsX86						P350GfsX140				R201H					
HD-0242	F/82	MD-CMML1	46,XX[25]								P95H												
HD-0271	F/62	MD-CMML1	46,XX[20]					P1263QfsX17			P95H												
HD-0280	M78	MD-CMML1	45,X,-Y[19]/46,XY[1]		S1189WfsX37																		
HD-0328	M73	MD-CMML1	46,XY[20]		G355D			G646WfsX12			P95H				C404Y								
HD-0340	M73	MD-CMML1	46,XY[20]																				
HD-0355	M65	MD-CMML1	46,XY[20]		C1289F						P95R												
HD-0372	M60	MD-CMML1	46,XY[20]				R882																
HD-0380	F/82	MD-CMML1	46,XX[20]		Q1414X																		
HD-0388	F/71	MD-CMML1	46,XX[20]	M133I	L1721PfsX8						P95H												
HD-0396	M70	MD-CMML1	46,XY[20]		S354X						P95H												
HD-0400	M62	MD-CMML1	46,XY[20]									K666N											
HD-0638	F/68	MD-CMML1	46,XX[20]		L1394WfsX54						P95H												
HD-0660	M80	MD-CMML1	46,XY[20]					R693X			P95H												
HD-0703	M74	MD-CMML1	46,XY[20]																				
HD-0711	M79	MD-CMML1	46,XY[20]		Q649X																		
HD-0712	M41	MD-CMML1	46,XY[20]																				
HD-0743	M68	MD-CMML1	46,XY[20]								P95H												
HD-0755	M46	MD-CMML1	46,XY[20]		R1359C			T622NfsX11	nd	nd	R639PfsX153												
HD-0877	M74	MD-CMML1	46,XX[20]																				
HD-0895	M68	MD-CMML1	46,XY[20]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-0938	F/74	MD-CMML1	46,XX[20]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-0979	M74	MD-CMML1	46,XY[20]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-0991	M66	MD-CMML1	46,XY[22]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-1159	F/68	MD-CMML1	46,XX[20]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-1292	F/87	MD-CMML1	46,XX,del(20)(q11q13)[2]/46,XX[18]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-0176	M42	MP-CMML1	46,XY[20]																				
HD-0229	M87	MP-CMML2	46,XY[20]		Q1191X																		
HD-0257	F71	MP-CMML1	46,XX[20]			R140Q																	
HD-0318	M69	MP-CMML1	46,XY,del(20)(q11q13)[20]	R166X				Q768X			P95L												
HD-0320	F74	MP-CMML2	47,XX,+8[20]	splicing defect	R1404X			G646WfsX12	L660F														A72T
HD-0321	M55	MP-CMML2	46,XY[20]	R166X				H630PfsX86			P95H												
HD-0322	F/61	MP-CMML1	46,XX[20]															R201H					
HD-0327	F72	MP-CMML1	47,XX,+8[20]	Y377LfsX223	C1193W			G646WfsX12															G12D
HD-0366	M78	MP-CMML1	46,XY[20]					S846QfsX5 (nc)															
HD-0367	F70	MP-CMML2	46,XX,inv(11)(p15q22)[20]															ITD					
HD-0370	M70	MP-CMML2	46,XY[20]					T1271KfsX10 (nc)			P95H												
HD-0376	F/65	MP-CMML2	46,XX,(1-3)(p36;q21)[20]									K700E											
HD-0397	F71	MP-CMML1	46,XX[20]																				
HD-0398	M62	MP-CMML1	47,XY,+19[17]/46,XY[3]					G646WfsX12			P95H												
HD-0399	M74	MP-CMML1	46,XY[20]		S141L			G646WfsX12			P95H				C396Y								
HD-0404	M88	MP-CMML2	47,XY,+21[20]	R201X	N1581HfsX17			H630PfsX86			P95L												
HD-0426	M47	MP-CMML1	46,XY[20]																				
HD-0485	M63	MP-CMML2	46,XY[20]	R320X	L1252P						P95H												
HD-0627	F/87	MP-CMML1	46,XX,del(20)(q11q13)[6]/46,XX[19]					G646WfsX12															
HD-0669	M88	MP-CMML1	46,XY[20]					A611DfsX8			P95H												
HD-0671	F71	MP-CMML1	47,XX,+19[8]/46,XX[12]	K110R				Y591X		Del													Del
HD-0702	M82	MP-CMML2	47,XY,+8[20]																				G12D
HD-0707	M85	MP-CMML1	46,XY[20]															Y371H					
HD-0715	M69	MP-CMML1	46,XY[20]																				
HD-0723	M83	MP-CMML1	46,XY[20]			R140Q		L1213HfsX3			R839PfsX153												G12V
HD-0853	M86	MP-CMML1	46,XX[20]																				
HD-0861	M78	MP-CMML2	5,X,-Y[24]/46,XY[1]																				
HD-0864	F72	MD-CMML1	46,XX,del(20)(q11q13)[2]/46,XX[18]																				
HD-0967	F/68	MP-CMML2	46,XX,(1-3)(p36;q21)[20]								K700E												G13V
HD-0988*	M61	MP-CMML2	46,XY[20]															L60Q					G12S
HD-1025	M69	MP-CMML1	46,XY,del(11)(q21 or q14q25)[9]/46,XY[16]												C381R								G13D
HD-1030	F/82	MP-CMML1	46,XX[11]																				
HD-1039	F70	MP-CMML1	46,XX[20]																				
HD-1054	M77	MP-CMML1	45,X,-Y[20]																				
HD-1056	F/64	MD-CMML1	46,XX[20]																				
HD-1236	M64	MP-CMML2	46,XY[20]		R1216X			G646WfsX12			P95H							L238P (nc)					
HD-0978	M67	J-MPN/MDS	46,XY,del(5)(q15q23)[12]/46,XY[8]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	V617F				nd
HD-2054	M64	J-MPN/MDS	46,XY[20]	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	R215H					nd

nd: not done

nc: verified as not constitutional

del: deleted

HD-0988* : relapse after allograft

MD-CMML1: myelodysplastic form of chronic myelomonocytic leukemia type 1 defined by white blood cell count inferior to 13 giga per liter

MD-CMML2: myelodysplastic form of chronic myelomonocytic leukemia type 2 defined by white blood cell count superior to 13 giga per liter

MP-CMML1: myeloproliferative form of chronic myelomonocytic leukemia type 1

MP-CMML2: myeloproliferative form of chronic myelomonocytic leukemia type 2

U-MPN/MDS: unclassified-myeloproliferative myelodysplastic neoplasm

Table S2. HGVS (human genome variation society) nomenclature and clinical course of the 6 *DOK* mutated patients

Case	<i>DOK1</i> or <i>DOK2</i> allelic variant (HGVS nomenclature)	Sex/Age (years) - Diagnosis	Clinical course									
			treatments						transformation into AML	allograft	status	
			AZA	HYDREA	IDA/ARAC	IFN	REV	TRISENOX				
HD-0254	<i>DOK1</i> c.789T>A (p.Asp263Glu)	F/83 - MD-CMML2	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-0230	<i>DOK2</i> c.602G>A (p.Arg201His)	M/83 - MD-CMML1	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd
HD-0322	<i>DOK2</i> c.602G>A (p.Arg201His)	F/61 - MP-CMML1	no	no	no	no	no	no	yes	no	no	dead
HD-0988*	<i>DOK1</i> c.179T>A (p.Leu60Gln)	M/61 - MP-CMML2	yes	yes	no	no	yes	no	no	yes (refractory AML)	no	dead
HD-1236	<i>DOK2</i> c.713T>C (p.Leu238Pro)	M/64 - MP-CMML2	yes	no	no	no	no	no	no	yes (refractory AML)	no	dead
HD-2054	<i>DOK2</i> c.644G>A (p.Arg215His)	M/64 - U-MPN/MDS	no	yes	yes	yes	no	no	no	no	yes	alive

HD-0988* : relapse after allograft

MD-CMML1: myelodysplastic form of chronic myelomonocytic leukemia type 1 defined by white blood cell count inferior to 13 giga per liter

MD-CMML2: myelodysplastic form of chronic myelomonocytic leukemia type 2 defined by white blood cell count superior to 13 giga per liter

MP-CMML1: myeloproliferative form of chronic myelomonocytic leukemia type 1

MP-CMML2: myeloproliferative form of chronic myelomonocytic leukemia type 2

U-MPN/MDS: unclassified-myeloproliferative myelodysplastic neoplasm

AML: Acute myeloid leukemia

AZA: Azacytidine

IDA/ARAC: Idarubicine/ Aracytine

IFN: Interferon

REV: Revlimid

nd: no data available

Table S3. Primers used for *DOK1* and *DOK2* gene sequencing

DOK1

DOK1_ex1F	5'-GCGGAAACTCCTCCAGGGAA-3'
DOK1_ex1R	5'-TCACGGGAAAGTCACAGGCT-3'
DOK1_ex2F	5'-GTGGCATCGTCCTTGGGAAACTT-3'
DOK1_ex2R	5'-AGAGTCCAGCTGCCTTTCTGTAGT-3'
DOK1_ex3F	5'-GCAGTTACAGAGGCAGAGAAATGGG-3'
DOK1_ex3R	5'-TAGTGTCCAAGCACTCACTCGGAA-3'
DOK1_ex4F	5'-TTCCGAGTGAGTGCTTGGACACTA-3'
DOK1_ex4R	5'-TCAGAGCTTCCCCTTTCTGTCT-3'
DOK1_ex5-1F	5'-TCCTCTGATGGCTCCTGGTAATGT-3'
DOK1_ex5-1R	5'-GGCTCCCGAGGCAGATCATAAA-3'
DOK1_ex5-2F	5'-TCCCTATACTCAGACCCCTTGGACA-3'
DOK1_ex5-2R	5'-CTGGCTTCTGCTGGTTCTAACCAT-3'

DOK2

DOK2_ex1F	5'-AGAGGCAAGGGCAGGAGTGAA-3'
DOK2_ex1R	5'-AAAGAGCCCTCCCAAAGTTGAGC-3'
DOK2_ex2F	5'-TTCTCCCCTTGGCTCACGATCT-3'
DOK2_ex2R	5'-TCACCCTGACCTTGACACCTGTAA-3'
DOK2_ex3F	5'-CAGGTTGAGGTGGCCTGAAAGAA-3'
DOK2_ex3R	5'-TGGGGATAACCACAAGGCAGGAA-3'
DOK2_ex4F	5'-CAGGCCAGCTGTTTCCCATTA-3'
DOK2_ex4R	5'-ACTCCACTTCTGCCATCTTGTCACT-3'
DOK2_ex5-1F	5'-CCTGGCCAATAACCTGCTTTCT-3'
DOK2_ex5-1R	5'-TCCTGCGGGCTGTCATAGA-3'
DOK2_ex5-2F	5'-AGTATGCCGTGCCCTTCGATG-3'
DOK2_ex5-2R	5'-AGGCCCTGGGAGAGGCAATTTAT-3'