

## Supplemental information

### Human inherited CCR2 deficiency underlies progressive polycystic lung disease

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**Table S1. Demographics, clinical characteristics, diagnostic tests, natural course of disease, and current status of the patients with CCR2 deficiency, related to Figure 1.**

Kindred Patient	A		B	C		D			E
	1	2	3	4	5	6	7	8	9
Sex	Female	Female	Female	Male	Male	Female	Female	Female	Female
Place of birth (parental origin)	France	France	Iran	Iran	Iran	USA	USA	USA	Iran
	(Algeria)	(Algeria)							
Year of birth	2010	2014	2010	2010	2012	2001	2006	2008	2005
Consanguinity	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Birth history/complications	Term/none	Term/none	Term/none	Term/none	Term/none	Term/none	Term/none	Term/none	Term/none
BCG vaccination in infancy, Response	Yes, Lymphadenitis (BCG-itis)	Yes, No adverse events	Yes, Lymphadenitis (BCG-itis)	Yes, No adverse events	Yes, No adverse events	No, Not applicable	No, Not applicable	No, Not applicable	Yes, dissminated BCG disease
Clinical presentation									
Digital clubbing	?	?	?	Yes	Yes	Yes	Yes	No	No
Growth pattern	Normal	Growth failure	Normal	?	?	Growth failure	Growth failure	Normal	Normal
Age at onset of symptoms, years	4	4	3	11	9	7	2.4	(19 months)	2 months
Symptoms and signs	DOE, pneumonia	Cough, DOE	NA	Cough, DOE	Cough, DOE	DOE	Cough, DOE	None	Cough, DOE
Age at evaluation (this study), years	12	8	12	12	10	21	16	14	18
Diagnostic testing, results									
SpO <sub>2</sub> , % (FiO <sub>2</sub> )	?	97	?	96	?	97 (room air)	98 (room air)	97 (room air)	96 (room air)
VO <sub>2</sub> max, % predicted	47	ND	?	?	?	?	?	?	ND
Sweat chloride test	ND	ND	?	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative
Serum LDH, U/L	ND	380	ND	425	325	ND	ND	ND	ND
Plasma GM-CSF (pg/mL)	<2.55	<2.55	<2.55	<2.55	<2.55	<2.55	<2.55	<2.55	ND
Chest CT scan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pulmonary function tests (age)	Yes (9 years)	Yes (7 years)	ND	Yes (11 years)	Yes (9 years)	Yes (20 years)	Yes (15 years)	Yes (11 years)	Yes (18 years)
FVC, % predicted	97	80	?	58.8	74.2	66	51	81	86
FEV1, % predicted	99	57	?	54	65	47	39	79	93
FEV1/FVC, % predicted	100	?	?	95	86	73	77	97	112
TLC, % predicted	97	80	?	?	?	97	126	100	93
VC, % predicted	95	71	?	?	?	71	50	78	102
RV, % predicted	102	?	?	?	?	159	384	187	129
DLCO, % predicted	ND	ND	?	?	?	80	78	116	65
Bronchoscopy and BAL	Yes	Yes	?	Yes	No	?	Yes	?	No
Lung biopsy	Yes	Yes	No	No	No	No	Yes	No	No
Genetic testing – DSP	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative
GM-CSF neutralizing antibody test, result	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	Yes, negative	ND
Genetic testing - <i>CCR2</i> allele 1, allele 2	c.640_645del, c.640_645del	c.640_645del, c.640_645del	c.182T>G, c.182T>G	c.887C>A, c.887C>A	c.887C>A, c.887C>A	c.59_60insAC, c.356T>G	c.59_60insAC, c.356T>G	c.59_60insAC, c.356T>G	c.182T>G, c.182T>G

Medical history/ infectious comorbidities	Pneumonia – no micro- organism, COVID-19, recurrent otitis	Pneumonia – RSV, EV, RhV; Pneumonia – <i>Staphylococcus</i> <i>aureus</i> , <i>Stenotrophomo- nas</i> , COVID-19, recurrent otitis	?	COVID-19, URTI	COVID-19, URTI	Pneumonia – mycoplasma, COVID-19	Pneumonia – no microorganism, COVID-19, Recurrent otitis	COVID-19	febrile seizure, asthma, pilonidal cyst, fibrocystic disease of the breasts, COVID-19
Treatment									
Antibiotics	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
WLL therapy	No	No	No	No	No	No	No	No	No
Oxygen supplementation	No	No	No	No	No	No	No	No	No
Worst respiratory status (FEV1%)	76	57	?	54	65	47	39	71	93
Clinical outcome	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive
Current age, years	12	8	12	12	10	21	16	14	18
Current respiratory status	DOE	DOE	?	DOE	DOE	DOE	DOE	Asymptomatic	DOE

AE: adverse event; BAL: bronchoalveolar lavage; CT: computed tomography; DOE: dyspnea on exertion; DLCO: diffusion capacity of the lungs for carbon monoxide; DSP: disorders of surfactant production; EV: enterovirus; FEV1: forced expiratory volume in one second; FiO<sub>2</sub>: fraction of inspired oxygen; FVC: forced vital capacity; NA: not available; ND: not done; PFTs: pulmonary function tests; RSV: respiratory syncytial virus; RhV: rhinovirus; RV: residual volume; SpO<sub>2</sub>: oxygen saturation; TLC: total lung capacity; VC: vital capacity; WLL: whole lung lavage; URTI: upper respiratory tract infection; ?: unknown.

**Table S2. Bronchoalveolar lavage cytology for CCR2-deficient patients, related to Figure 6.**

Patient	Age (years)	Cells/mL (x10 <sup>4</sup> )	Macrophages (%)	Lymphocytes (%)	Neutrophils (%)	Eosinophils (%)	BEC (%)	Culture result
Reference <sup>92</sup>	0.25-14	17.92 ± 8.12	93.33 ± 4.56	3.93 ± 3.08	2.94 ± 2.82	NR	NR	Negative
P1	9	12	54	7	38	1	0	Negative
	12	NR	42	NR	48	NR	NR	Negative
P2	7	22	62	17	20	1	0	Negative
	8	18	36	13	50	1	0	Negative
P4	11	40	5	65	30	0	0	Gram <sup>+</sup> cocci
P6	10	NR	52	10	35	0	3	Negative
P7	3	NR	67	13	19	1	0	Normal oral flora
	5	NR	68	16	13	3	0	Negative

BEC: bronchial epithelial cells; NR: not reported

**Table S3. Homozygous and compound-heterozygous variants identified by WES in eight CCR2-deficient patients, related to Figure 1.**

P1	P2	P3	P4	P5	P6	P7	P9
<i>ATRIIP</i> , p.R718H	<i>ATRIIP</i> , p.R718H	<i>AC004381.6</i> , p.K725M	<i>ABCA5</i> , p.F1102C	<i>ATN1</i> , p.Q496_Q502del	<i>AURKA</i> , c.42+2ins61	<i>AURKA</i> , c.42+2ins61	<i>ABCB9</i> , p.G248S
<b>CCR2</b> , p. <b>P214_L215del</b>	<i>CCDC117</i> , p.P28L	<i>ALOXE3</i> , p.L237M / p.I705T	<i>ATN1</i> , p.Q496_Q502del	<b>CCR2</b> , p. <b>T296N</b>	<i>C20orf132</i> , c.90+1ins29	<i>C20orf132</i> , c.90+1ins29	<i>ARID1B</i> , p.S41del / p.A460del
<i>CHPF2</i> , p.A565T	<b>CCR2</b> , p. <b>P214_L215del</b>	<i>ARHGEF17</i> , p.Q805E	<i>C1GALT1C1</i> , p.H39N	<i>CKAP5</i> , p.S1999C	<b>CCR2</b> , p. <b>T21Pfs*18 / p.L119R</b>	<b>CCR2</b> , p. <b>T21Pfs*18 / p.L119R</b>	<i>ATP1B4</i> , p.T46M
<i>CPZ</i> , p.D218E / p.R570Q	<i>CSRNP1</i> , p.R136W	<i>BRIP1</i> , p.Q944E / R1035C	<b>CCR2</b> , p. <b>T296N</b>	<i>COL21A1</i> , p.V399A	<i>FAM58A</i> , p.G3fs	<i>FAM58A</i> , p.G3fs	<i>ATXN3</i> , p.G306fs
<i>HHIPL1</i> , p.G77S	<i>DAK</i> , p.R567W	<i>C20orf27</i> , p.A48T	<i>CEP128</i> , p.F842L	<i>COL7A1</i> , p.I1597V	<i>FAM58A</i> , p.G14fs	<i>FAM58A</i> , p.G14fs	<i>CACTIN</i> , p.R689C
<i>IPCEFI</i> , p.A411V	<i>DPYD</i> , p.A721T / p.D949V	<b>CCR2</b> , p. <b>M61R</b>	<i>COL15A1</i> , p.V154G / p.R1387G	<i>CSMD1</i> , p.V895M / p.W1348C	<i>SGPP2</i> , p.I124L	<i>SGPP2</i> , p.I124L	<i>CCDC86</i> , p.L111P
<i>KIAA1217</i> , p.R46C / p.K591R	<i>EOMES</i> , p.L146F	<i>CFHR2</i> , p.R69C	<i>COL7A1</i> , p.I1597V	<i>CYP26B1</i> , p.V357I			<i>CCNT1</i> , p.G3V
<i>LAMB2</i> , p.E628Q	<i>LAMB2</i> , p.E628Q	<i>CFTR</i> , p.K68E	<i>CSMD1</i> , p.V895M / p.W1348C	<i>DBP</i> , p.G24S			<b>CCR2</b> , p. <b>M61R</b>
<i>MADCAM</i> , p.P272L / p.S310L	<i>MADCAM</i> , p.P272L / p.S310L	<i>DLEC1</i> , p.A1555V	<i>FLNB</i> , p.T1588M	<i>DFNB31</i> , p.V735I / g.117185804C>T			<i>CTNND1</i> , p.S905Y
<i>MLYCD</i> , .83945979G>A	<i>MON1A</i> , p.T486A	<i>EEF2K</i> , p.V185M	<i>G6PD</i> , p.S218F	<i>FABP1</i> , p.G32R			<i>DDX58</i> , p.D701A
<i>MON1A</i> , p.T486A	<i>NOD2</i> , p.A918D	<i>FAM81B</i> , p.Q285fs	<i>KCNH8</i> , p.S86*/p.L549*	<i>FAM231B</i> , p.W72fs			<i>EEA1</i> , p.P155S
<i>PCSK1</i> , p.P710R	<i>OTUD3</i> , p.G47_G48dup	<i>FAM81B</i> , p.D287N	<i>NKTR</i> , p.L805F	<i>FAM65C</i> , p.R239W			<i>ENDOU</i> , p.D35Y
<i>PRR12</i> , p.T774S / p.R867H	<i>PAPPA</i> , p.R180Q / p.R1087Q	<i>KCNN3</i> , p.Q78_Q80dup	<i>NUP210L</i> , p.S106G / p.Q1780R	<i>FLNB</i> , p.T1588M			<i>ENOSF1</i> , p.V406fs
<i>SIGLEC1</i> , p.Q263R	<i>PRR12</i> , p.T774S / p.R867H	<i>LGALS12</i> , p.G152*	<i>PAGE1</i> , p.E138G	<i>FRMPD3</i> , p.R659H			<i>FBLN2</i> , p.E123K
<i>TOPAZ1</i> , p.R683W	<i>SIGLEC1</i> , p.Q263R	<i>NEK4</i> g.52785947C>G	<i>PLCH2</i> , p.D23Y	<i>G6PD</i> , p.S218F			<i>HRCT1</i> , p.H102_H105dup
<i>WDR60</i> , p.E334K	<i>TAOK2</i> , p.V1129I	<i>OLFM3</i> , p.T24I / p.I111V	<i>RP11-1220K2.2</i> , p.S2197C / p.T2291I	<i>GLE1</i> , p.P2R			<i>JSRP1</i> , p.V223I
<i>WDR86</i> , p.R229Q	<i>TEKT1</i> , p.E68K	<i>OR3A1</i> , p.F34I	<i>SULT1C2</i> , p.Y128H	<i>GMIP</i> , p.G92R			<i>KIF26A</i> , p.K1450E
<i>ZNF106</i> , p.F213V / p.R926G	<i>TOPAZ1</i> , p.R683W	<i>OR5B12</i> , p.R232C	<i>WEE1</i> , p.L302V	<i>HRC</i> , p.H643Y			<i>NCKIPSD</i> , p.P625L
<i>ZNF208</i> , p.P228_K225del / p.H795R	<i>UNC93B1</i> , p.L129I / p.P209L	<i>PHF8</i> , p.E747K	<i>ZKSCAN7</i> , p.H601P	<i>LILRA2</i> , p.R165H / p.A307T			<i>NEO1</i> , p.T435R
	<i>ZNF106</i> , p.F213V / p.R926G	<i>PPAN</i> , p.E606K / p.P637L	<i>ZNF195</i> , p.A24T	<i>MYO9B</i> , p.R1148H			<i>ODF3L2</i> , p.A242T
		<i>RNASEH2C</i> , p.D115Y	<i>ZNF417</i> , p.H40fs	<i>NKTR</i> , p.L805F			<i>OGFOD3</i> , p.G237R
		<i>SAPCD2</i> , p.R253C / p.G289fs	<i>ZNF438</i> , p.Q520E / p.I810S	<i>NTN1</i> , p.M210V			<i>OR5J2</i> , p.A125V
		<i>SGSM3</i> , p.Q637*		<i>NUP210L</i> , p.S106G / p.Q1780R			<i>PEX1</i> , p.E379D / p.D1168H

		<i>STAB1</i> , p.T2395I		NYX, p.G355R			<i>PRKDC</i> , p.P764L / p.A1237T
		<i>TBC1D2</i> , p.E905K		<i>OPHN1</i> , p.A688S			<i>RING1</i> , p.A195T
		<i>TMEM123</i> , p.T125I		<i>OR7A5</i> , p.S229fs			<i>RPS6KA5</i> , p.Asp554Asn
		<i>TOB2</i> , p.S334N		<i>PIK3R6</i> , p.A736V			<i>SLC25A2</i> , p.A300T
		<i>TTC14</i> , p.S697G		<i>RABEPK</i> , p.P135fs			<i>SLC9B1P1</i> , p.I74N / p.K222*
		<i>UQCRC1</i> , p.E435K		<i>RP11-1220K2.2</i> , p.S2197C / p.T2291I			<i>SMPD1</i> , p.L47_A48del / p.V114M
		<i>UTRN</i> , p.E550D / p.T1473M		<i>WEE1</i> , p.L302V			<i>SPDEF</i> , p.R167Q
		<i>VSIG4</i> , p.M159L		<i>ZDHHC5</i> , p.R182H			<i>TYRO3</i> , c.1252+2T>C / c.1484-1G>T
		<i>XYLT1</i> , p.R694H		<i>ZKSCAN7</i> , p.H601P			<i>ZNF417</i> , p.H40fs
		<i>ZNF711</i> , p.G109A		<i>ZNF195</i> , p.A24T			
				<i>ZNF417</i> , p.H40fs			
				<i>ZPI</i> , p. D107N			

**Table S4. Levels of pro-inflammatory cytokines and chemokines in broncho-alveolar lavage samples of healthy controls ( $n = 12$ ) and two CCR2-deficient patients, related to Figure 4.**

Cytokines/chemokines (pg/mL)	Controls	P1	P2
BLC	2.73 ± 1.60	2.64	2.4
CCL-1	136.52 ± 144.92	463.32	331.21
CCL-2	21.64 ± 23.15	251.86	493.33
CCL-3	10.46 ± 24.57	62.08	N.D.
CCL-4	0.64 ± 0.4	2.106	0.547
CCL-7	7.06 ± 2.46	3.82	10.07
CCL-8	0.30 ± 0.12	0.63	2.49
CCL-11	N.D.	N.D.	N.D.
CCL-13	1.16 ± 0.57	8.25	85.346
CCL-17	1.97 ± 1.64	2.38	1.47
CCL-19	1.56 ± 1.49	N.D.	5.13
CCL-20	20.43 ± 16.22	7.87	12.46
CCL-22	1.91 ± 3.34	17.31	111.71
CCL-24	407.69 ± 281.78	327.78	393.41
CXCL-1	990.68 ± 1033.90	2818.28	1168.99
CXCL-2	58.08 ± 71.95	48.13	61.74
CXCL-5	3.19 ± 7.93	N.D.	180.31
CXCL-9	316.41 ± 268.44	320.88	411.24
CXCL-10	58.00 ± 29.39	89.82	80.92
CXCL-11	0.40 ± 0.38	0.163	0.357
CXCL-12	33.66 ± 27.03	144.54	22.29
CX3CL-1	29.48 ± 80.65	N.D.	71.6
IFN- $\alpha$ 2	0.12 ± 0.45	N.D.	N.D.
IFN- $\gamma$	0.26 ± 0.95	7.905	N.D.
IL-1 $\beta$	15.75 ± 41.44	35.82	N.D.
IL-6	42.56 ± 49.84	63.05	30.96
IL-8	106.62 ± 71.28	872.71	258.09
IL-10	1.92 ± 1.00	1.17	N.D.
IL-12p70	1.91 ± 1.60	1.32	1.01
IL-17A	3.70 ± 6.05	0.301	N.D.
IL-18	15.37 ± 21.95	161.08	16.47
IL-23	N.D.	N.D.	N.D.
IL-33	21.21 ± 23.46	N.D.	N.D.
PTX3	21.33 ± 7.33	95.55	164.32
sCD25	93.65 ± 90.48	172.64	59.28
sCD40L	173.05 ± 238.50	296.76	N.D.
sRAGE	1354.17 ± 2284.87	1111.04	1125.93
sST2	230.22 ± 85.61	303.3	194.9
sTNF-RI	110.71 ± 54.89	328.9	361.73
sTNF-RII	5.61 ± 2.81	5.36	5.8
sTREM-1	42.70 ± 26.25	80.54	85.86
TGF- $\beta$ 1	1.23 ± 4.24	N.D.	N.D.
TNF	3.86 ± 3.45	N.D.	N.D.

Mean ± SD. N.D. not detected

**Table S5. Cell counts in bone-marrow aspirate from patients with CCR2 deficiency, related to Figure 5.**

Hematopoietic lineage / cell type	P1	P2	Reference Value
Erythroblastic lineage, % of cells			
Proerythroblasts	1	1	0.5-3
Basophilic erythroblasts	1	2	1-5
Polychromatophilic erythroblasts	3	6	7-20
Acidophilic erythroblasts	8	7	4-15
Granulocytic lineage, % of cells			
Myeloblasts	1	1	0.5-5
Promyelocytes	1	1	1-6
Myelocytes	11	9	8-20
Metamyelocytes	17	16	10-23
Polymorphonuclear neutrophils	30	34	30-70
Eosinophils	0	0	0.5-4
Basophils	0	0	0-1
Lymphoid lineage, % of cells			
Lymphocytes	25	22	3-18
Lymphoblasts	0	0	-
Monocytic lineage, % of cells			
Monoblasts	0	0	-
Promonocytes	0	0	-
Monocytes	2	1	0-5
Others	0	0	-