Thursdays Webinars

EuroBloodNet

Pathophysiology, clinical presentation and management of congenital erythrocytosis

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Speaker, Center for Rare Hematopoietic Disorders and Immunodeficiencies (ZSHI Ulm)
Center for Rare Diseases (ZSE Ulm), Ulm University Medical Center, Germany

ERN-EuroBloodNet subnetworks: RBC defects, BMF & hematopoietic defects

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the Health Programme
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European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

No COI to declare in the context of the topic of this webinar.

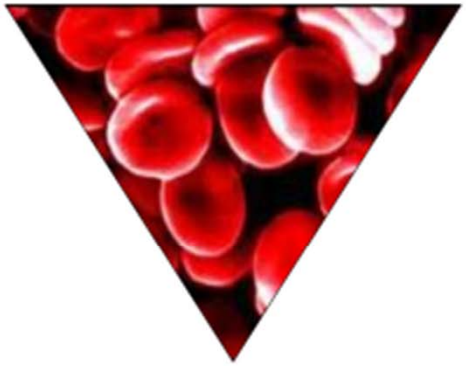
Learning objectives of the webinar

1. To understand the classification of CE according to pathogenesis
2. To know diagnostic parameters in CE and its use in the diagnostic pathway
3. To use the diagnostic pathway in an individual patient
4. To know the clinical and pathogenic background in distinct types of CE
5. To get an overview on some useful and and other more questionable treatment approaches in CE

Regulation of erythropoiesis

„Apparent" erythrocytosis
= red cell mass (↑)
+ plasma volume (↓)

Relative erythrocytosis
= plasma volume ↓



Absolute erythrocytosis
= red cell mass ↑

- **Primary erythrocytosis**
  = Epo-independent, intrinsic defect of erythroid progenitor cells
- **Secondary erythrocytosis**
  = Epo-dependent, normal sensitivity of the Epo receptor

Erythrocytosis

- Absolute erythrocytosis
  - Primary erythrocytosis
    - Congenital
      - Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)
    - Acquired
      - Polycythemia vera
  - Secondary erythrocytosis
    - Congenital
      - Defective O2-Sensing
        - Familial Erythrocytosis Type 2; *VHL*
        - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
        - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
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        - Familial Erythrocytosis Type 6; *HBB*
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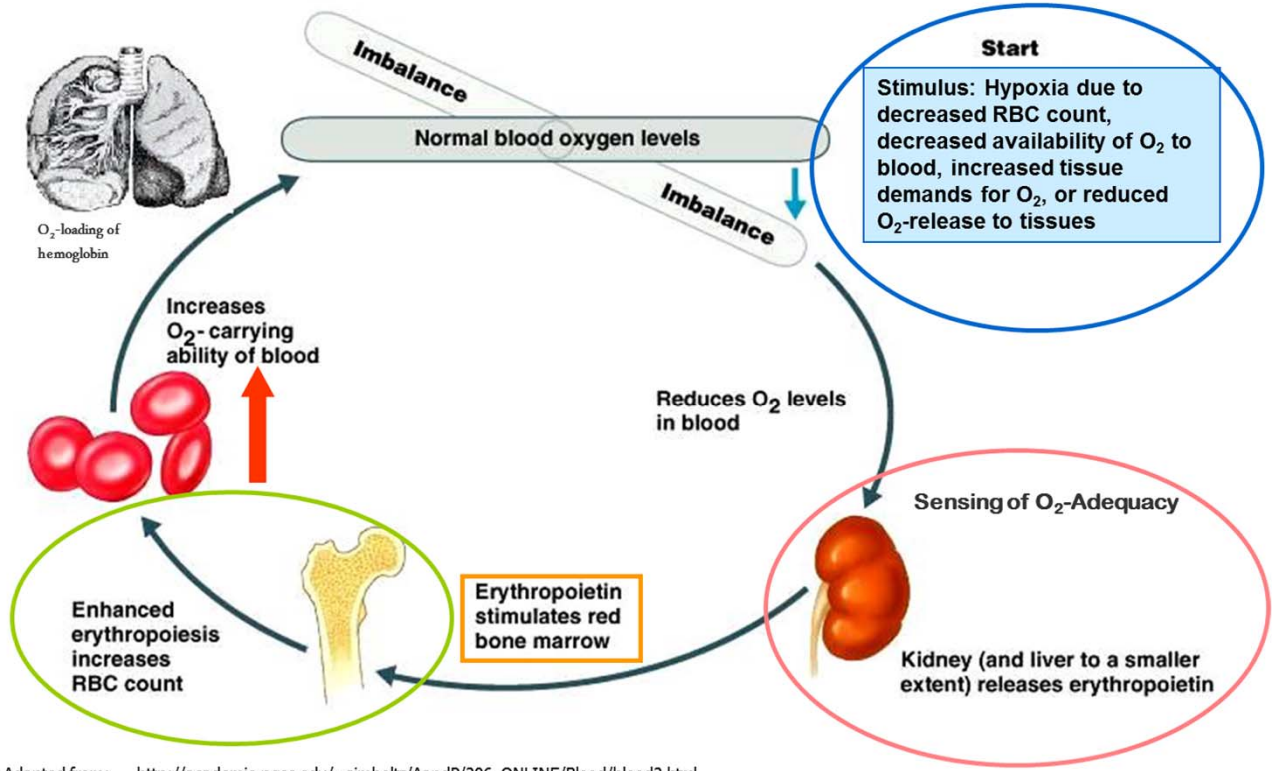
        - Familial Erythrocytosis Type „x"; *PKLR*
    - Acquired
      - Physiological EPO elevation due to
        - pulmonary
        - cardiac
        - renal
        - hepatic diseases
      - Autonomous EPO synthesis
        - Kidney: nephroblastoma, RCC
        - Liver: hepatoma, HCC
        - CNS: e.g. hemangioblastoma
        - Endocrine tumor (e.g. pheoc.)

Regulation of erythropoiesis



Adapted from: http://academic.pgcc.edu/~aimholtz/AandP/206_ONLINE/Blood/blood2.html
http://links.nephron.com/issues/anemia

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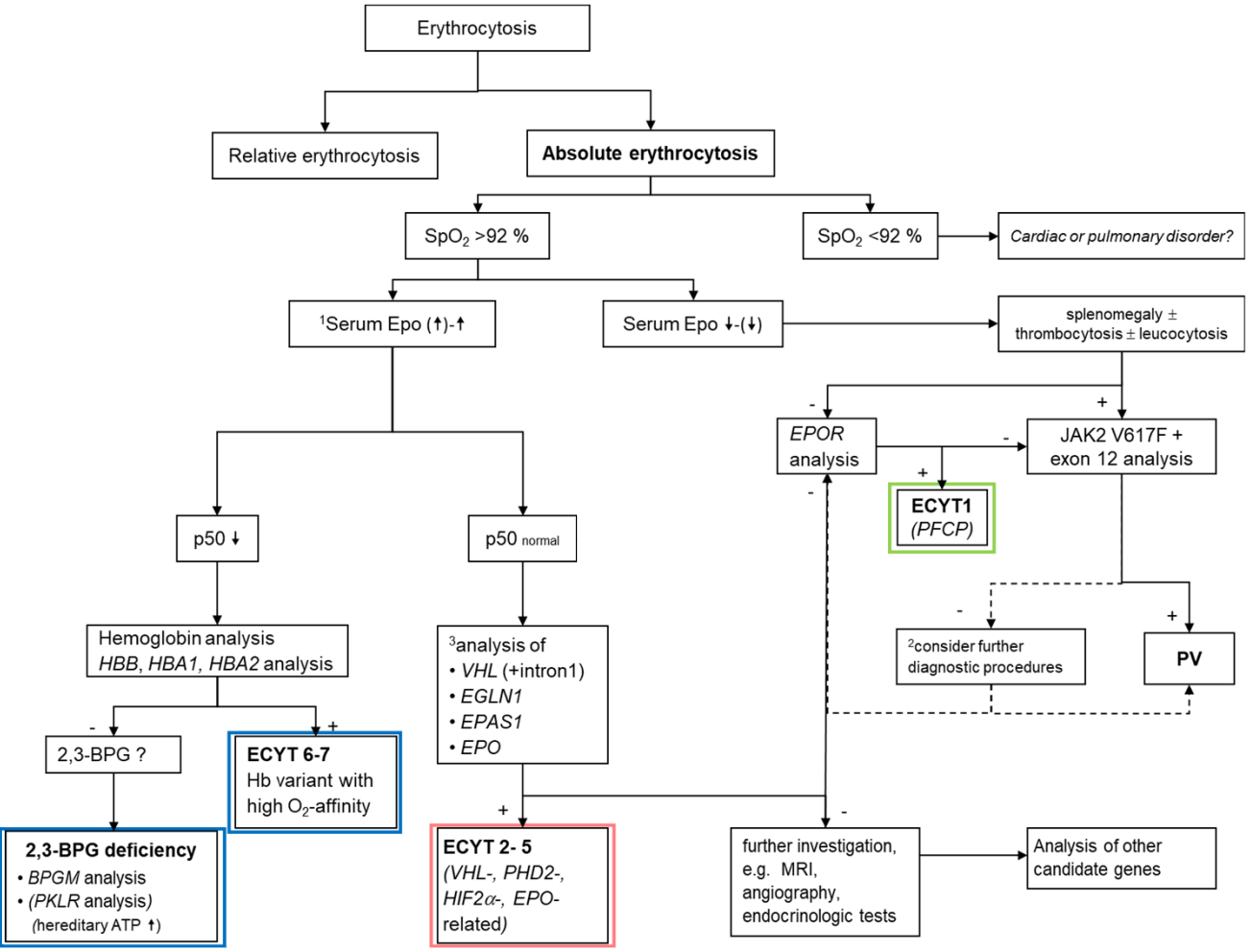

modified acc. Cario et al, PBC 2013

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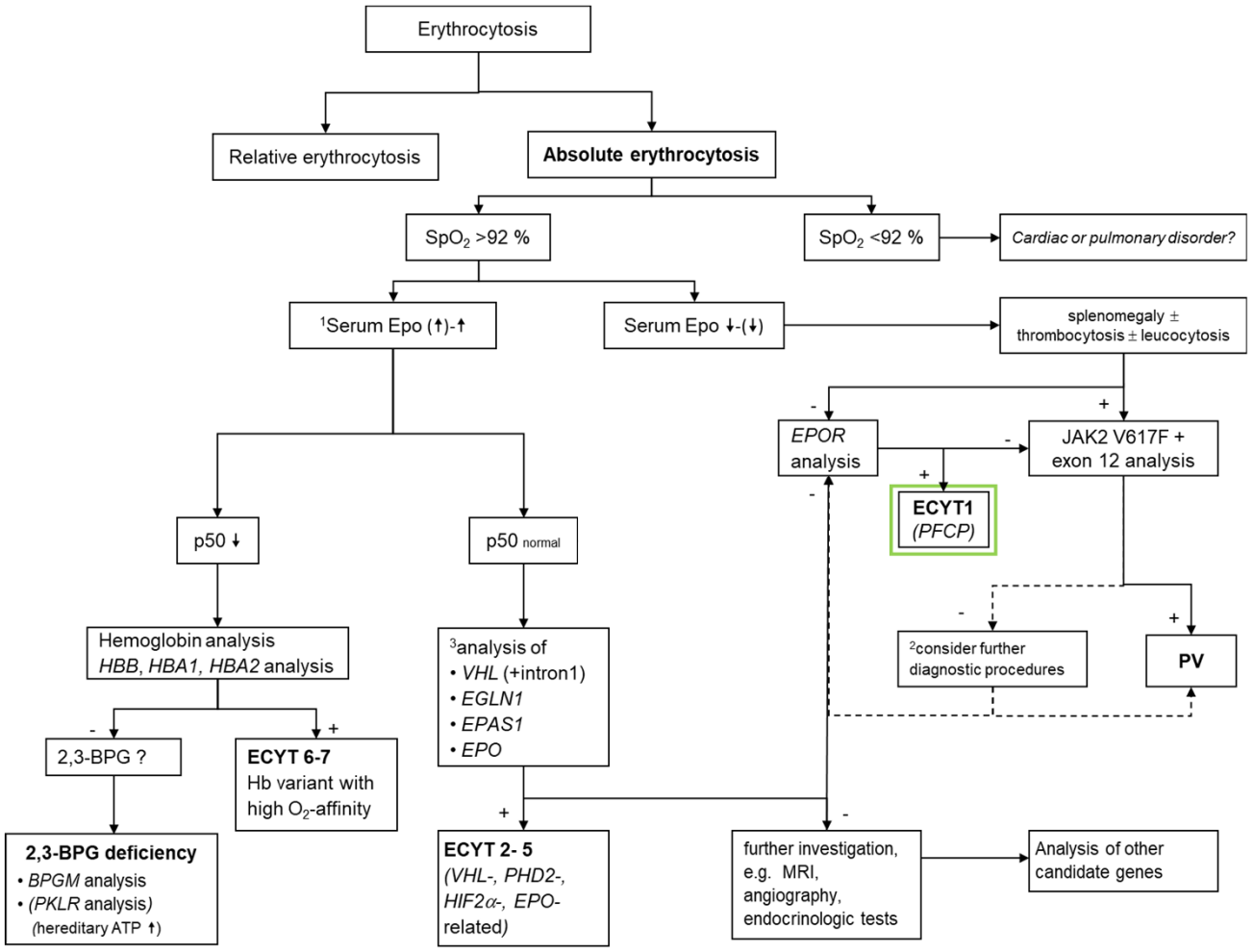

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Familial erythrocytosis Type I

Eero Mäntyranta

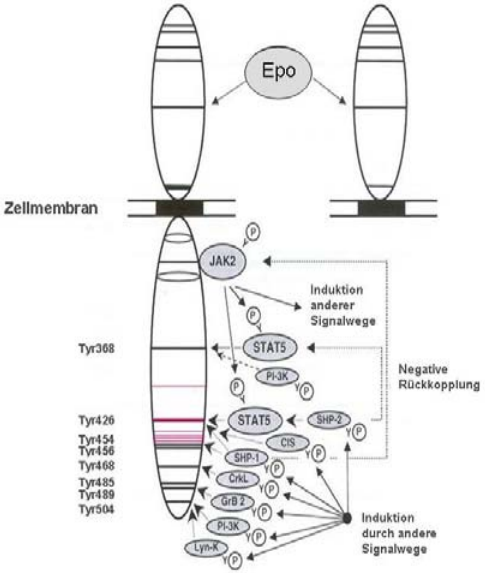
* 20.11.1937

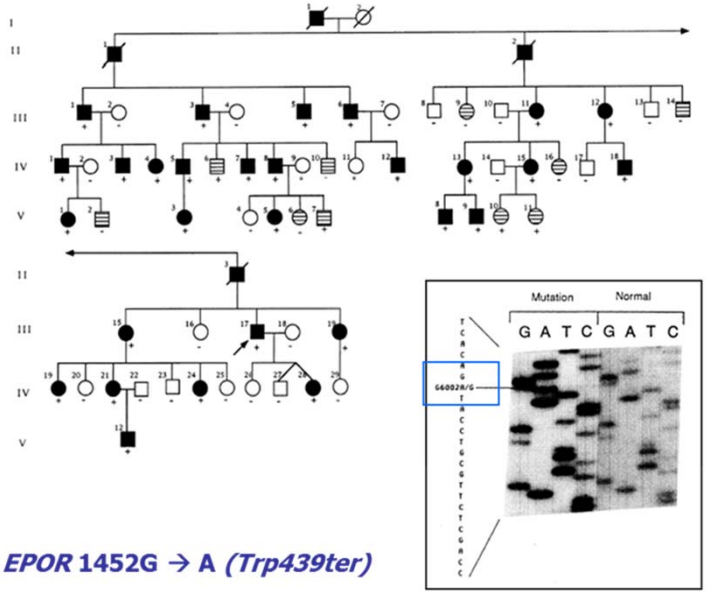
† 30.12.2013

Finnish cross-country skier

World championship and medals 1962, 1966

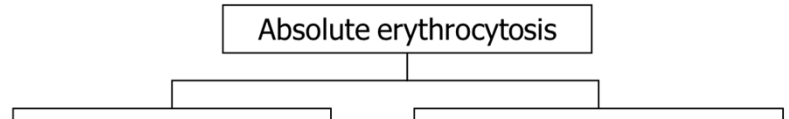
Olympic championship and medals 1960, 1964, 1968





EPOR* 1452G → A *(Trp439ter)

de la Chapelle A, et al. *PNAS* 1993



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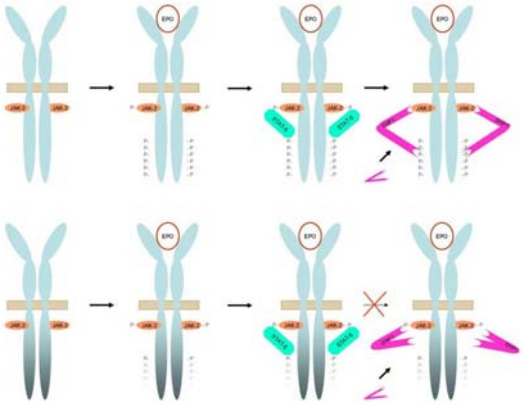
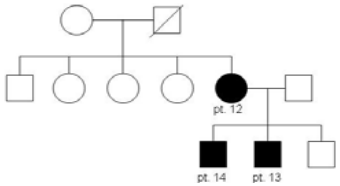
Familial erythrocytosis Type I

Erythrocytosis

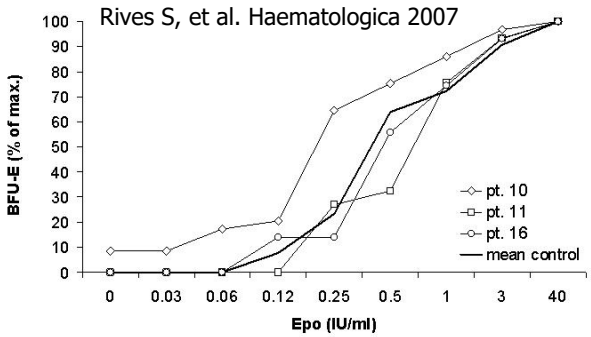
Epo receptor – Activation and down-regulation



! Heterogeneous phenotype !



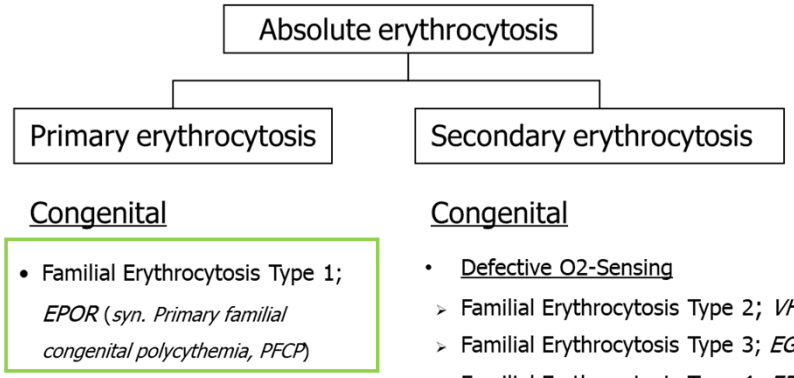
		Pt. 12	Pt. 13	Pt. 14
Age	[years]	40	14	22
Gender	[m/f]	f	m	m
Hemoglobin	[g/dl]	12.9	22.8	19.7
Erythropoietin	[mU/ml]	2.3	< 7.8	n.d.



Previously described and novel *EPOR* gene mutations

Protein effect	References
p.Pro380Ala	Almeida (this report)
p.Pro381Glnfs*2	Al-Sheikh et al. (2008)
p.Glu399*	Arcasoy et al. (2002)
p.Ser412Argfs*41	O'Rourke et al. (2011)
p.Ser412*	Bento et al. (2013a)
p.Ser415Hisfs*18	Minkov M (this report)
p.Glu417*	Perrotta et al. (2010)
p.Gly418Profs*34	Petersen et al. (2004)
p.Phe424*	Al-Sheikh et al. (2008)
p.Glu425*	Kralovics and Prchal (2001)
p.Tyr426*	Kralovics et al. (1998); Rives et al. (2007)
p.Ile428Tyrfs*17	Kralovics et al. (1997a)
p.Leu429Trpfs*24	Al-Sheikh et al. (2008)
p.Asp430Glyfs*15	Sokol et al. (1995)
p.Asp430Glufs*26	Watowich et al. (1999)
p.Gln434*	Furukawa et al. (1997)
p.Gln434Cysfs*17	Arcasoy et al. (1997); Kravolics et al. (1997a)
p.Arg437His	Bento C (this report)
p.Pro438Metfs*6	Bento et al. (2013a)
p.Trp439*	la Chapelle et al. (1993); Percy et al. (1998) Rives et al. (2007)
p.Asn487Ser	Le Couedic et al. (1996); Al-Sheikh et al. (2008)
p.Pro488Ser	Sokol et al. (1994); Kralovics et al. (1997b)

Bento C, et al. Hum Mut 2013



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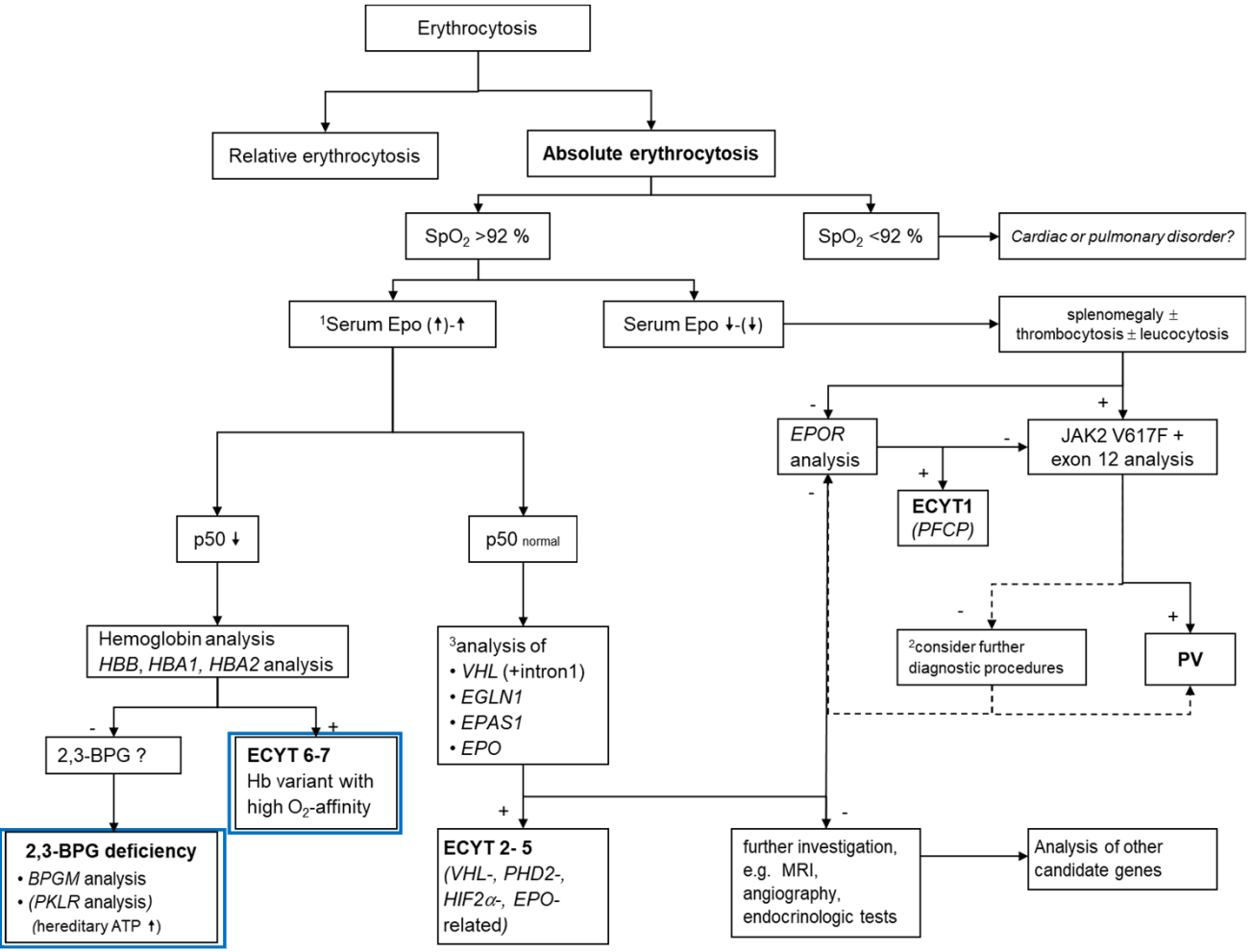

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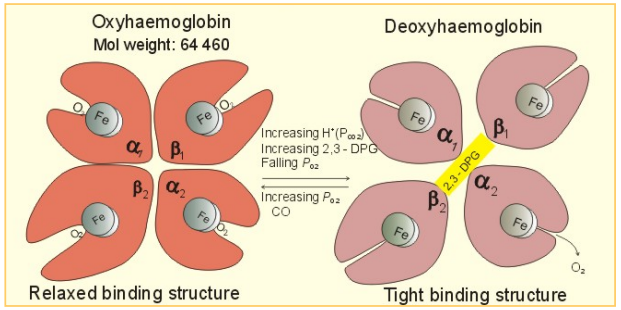
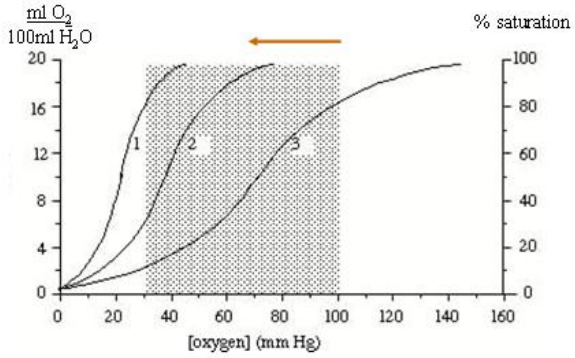
Hemoglobin variants with increased O_2-affinity

- Charache, S., et al. *J Clin Invest* 1966 → Hb Chesapeake
- > 200 Hb-variants with increased O_2-affinity, 1/3 associated with erythrocytosis

1. mutations within the α_1/β_2-interface → ↗ quaternary confirmation
2. mutations in the 2,3-BPG binding site
3. C-terminal substitutions in the β-chain → reduced Bohr-effect
4. mutations interfering with heme binding

	1	2	3
P50	LOW	intermediate	HIGH
O_2 – affinity	HIGH	intermediate	LOW
O_2 – uptake in the lung	increased	intermediate	decreased
O_2 – release to the tissues	decreased	intermediate	increased





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2,3 – Bisphosphoglycerate (2,3 BPG) deficiency

Erythrocytosis

Rosa R, et al. The First Case of a Complete Deficiency of Diphosphoglycerate Mutase in Human Erythrocytes.

J Clin Invest 1978; 62: 907-15

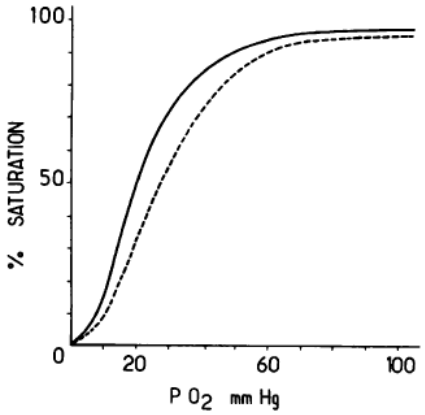
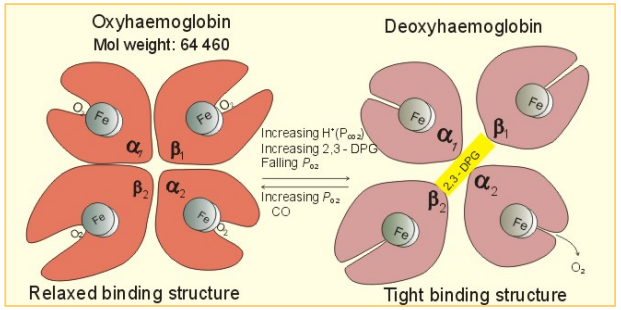
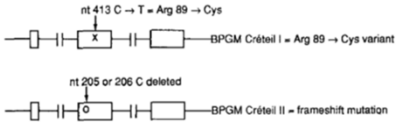


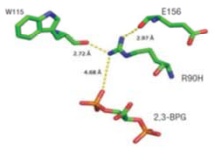
TABLE II
Family Study of the Correlation between 2,3-DPG and P_{50} Values

	2,3-DPG	P_{50}
	μmol/g/Hb	*mm Hg*
Propositus	0.4	17.3
Son	9.2	19.5
Daughter	10.6	22.5
Normal adult values	15±2	26.5±1



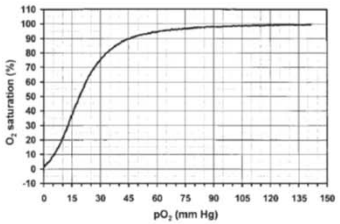


Lemarchandel V et al. Blood 1992



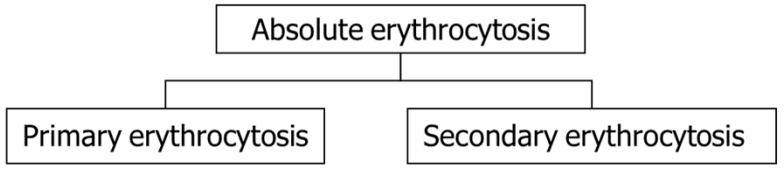
Arg90His

Petousi N et al. BJH 2014



Arg62Gln

Hoyer JD et al. AJH 2004



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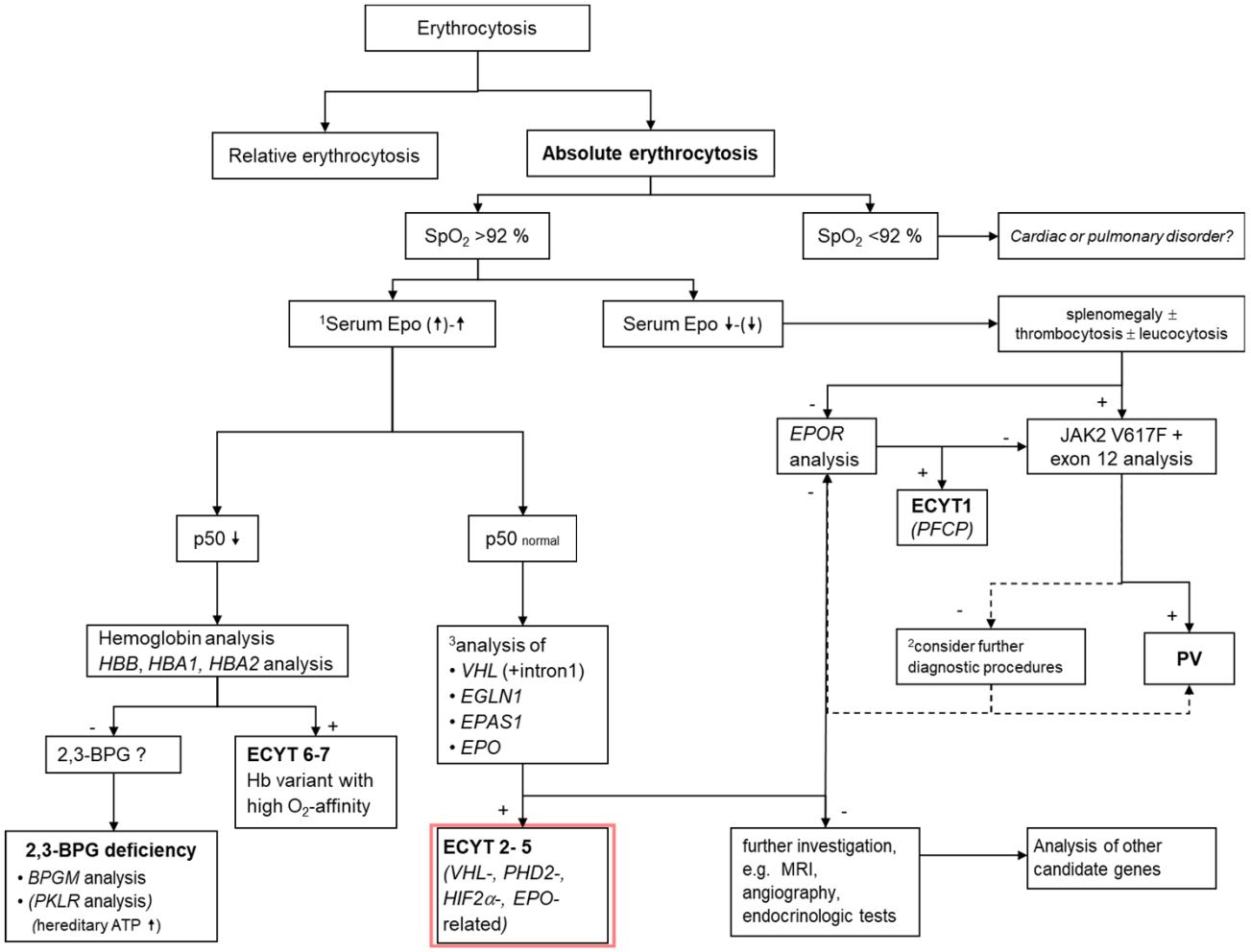

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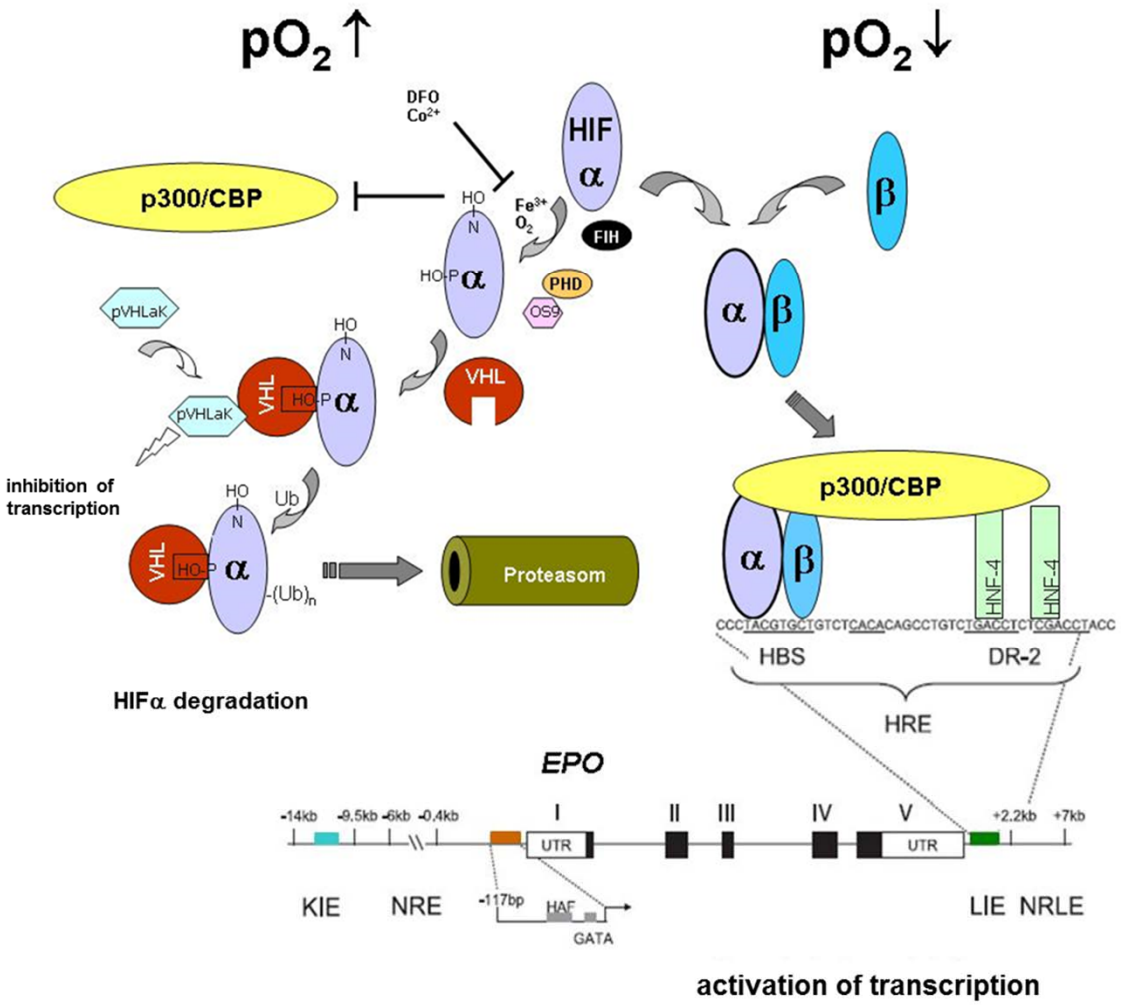

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  - Familial Erythrocytosis Type 8; *BPGM*
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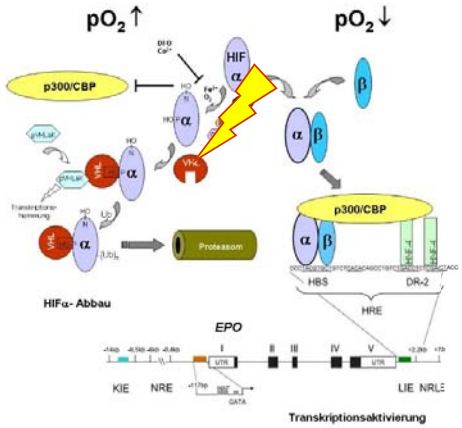
Acquired

- Physiological EPO elevation due to
  - pulmonary
  - cardiac
  - renal
  - hepatic diseases
- Autonomous EPO synthesis
  - Kidney: nephroblastoma, RCC
  - Liver: hepatoma, HCC
  - CNS: e.g. hemangioblastoma
  - Endocrine tumor (e.g. pheoc.)

Familial erythrocytosis Type II *Chuvash polycythemia* Erythrocytosis



Polyakova LA.
Familial erythrocytosis among inhabitants of the Chuvash ASSR.
Problemi gematologii i perilivaniya krovi 1974; 10: 30-36

Sergeyeva A, Gordeuk VR, Tokarev YN, et al.
Congenital polycythemia in Chuvashia.
Blood 1997; 89: 2148-54

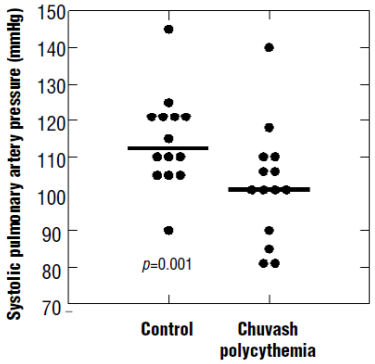
Ang SO, Chen H, Hirota K, et al.
Disruption of oxygen homeostasis underlies congenital Chuvash polycythemia.
Nature Genetics 2002; 32(4): 614-621

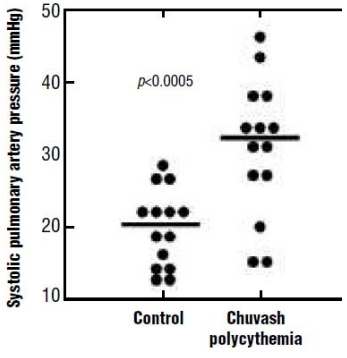
- Absolute erythrocytosis
  - Primary erythrocytosis
    - Congenital
      - Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)
  - Secondary erythrocytosis
    - Congenital
      - Defective O2-Sensing
        - Familial Erythrocytosis Type 2; *VHL*
        - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
        - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
        - Familial Erythrocytosis Type 5; *EPO*
      - Altered Hb oxygen affinity
        - Familial Erythrocytosis Type 6; *HBB*
        - Familial Erythrocytosis Type 7; *HBA1, HBA2*
        - Familial Erythrocytosis Type 8; *BPGM*
        - Familial Erythrocytosis Type „x"; *PKLR*

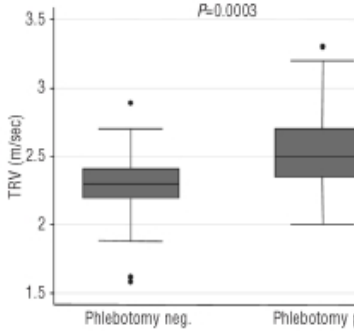
Morbidity

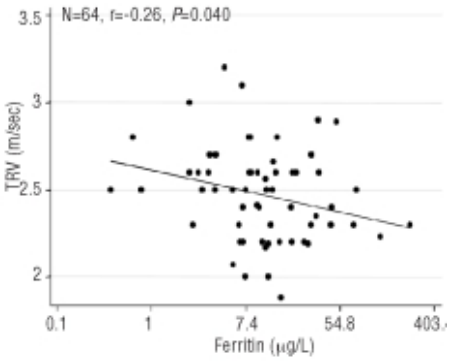
History of thrombosis	26 %
History of bleeding	33 %
Peptic ulcer disease	30 %
Dyspnea on exertion	56 %
Varicose veins	74 %
Previous silent infarction	45 %
Vertebral body hemangioma	55 %

Pulmonary hypertension







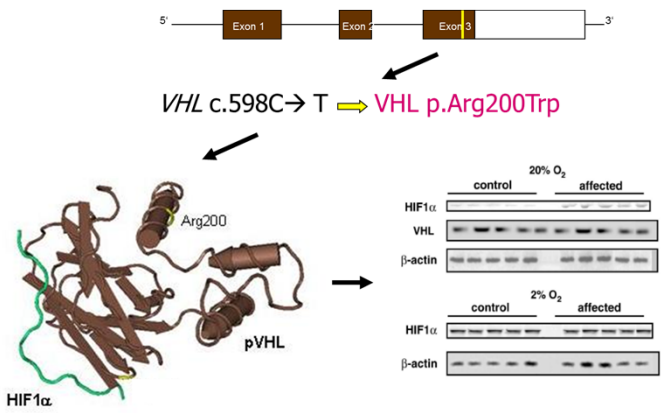


Gordeuk VR, et al. Blood 2004

Bushuev VI et al. Haematologica 2006

Sable Ca et al. Haematologica 2012

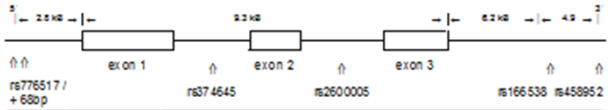
Familial erythrocytosis Type II *Chuvash polycythemia* Erythrocytosis



Ang SO, et al. Nature Genetics 2002

Liu E, Percy MJ, Amos CI, et al.
The worldwide distribution of the VHL 598C>T mutation indicates a single founding event.
Blood 2004; 103: 1937-1940

VHL haplotype analysis



		Haplotype					
Patients	VHL-gene mutation	rs776517	rs776517 + 68bp	rs374645	rs2600005	rs166538	rs458952
#02	C598T/C598T	G	C	T	A	C	A
#03	C598T/C598T	G	C	T	A	C	A
#15	C598T/C598T	G	C	T	A	C	A
#46	C598T/C598T	A	A	C	G	C	G
#20	C598T/wt	G/A	C/A	T/C	A/G	C/T	A/G
#09	G311T/wt	A	A	C	G	C/T	G
n=16	wt/wt	A	A	C	G (#26: A/G)	T (n=10) C/T (n=6)	G (#26: A/G)

Carlo H, et al. Haematologica 2005

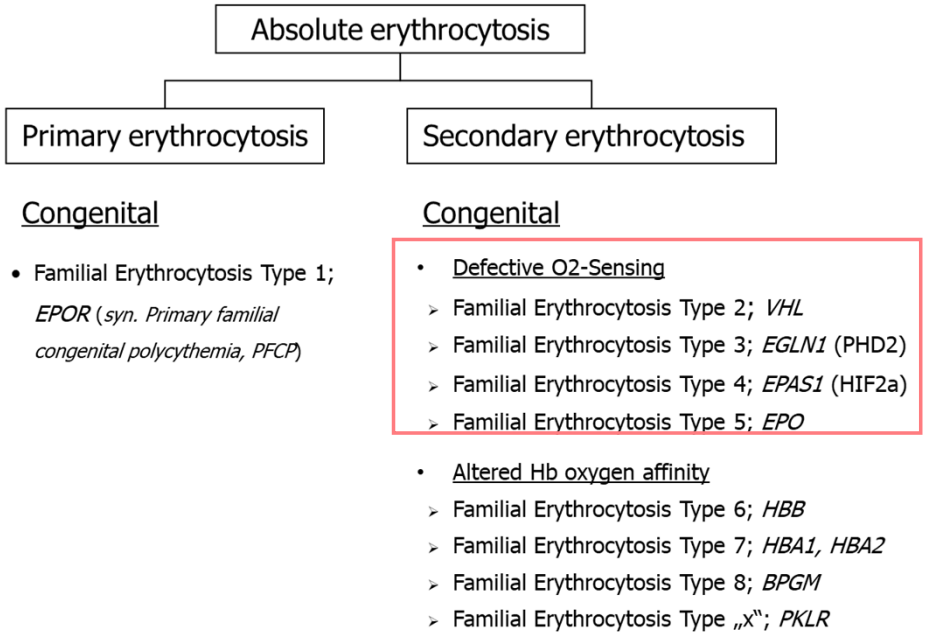
VHL mutations in ECYT II

Protein effect	References
p.Glu10*	Vainchenker (this report)
p.Arg79Cys	Bento et al. (2005)
p.Pro81Ala	Casadevall (this report)
p.Gly104Val	Cario et al. (2005)
p.Thr124Lys	Lorenzo et al. (2013)
p.Asp126Asn	Bond et al. (2011)
p.Asp126Tyr	Pastore et al. (2003a)
p.Val130Leu	Pastore et al. (2003a)
p.Pro138Leu	Lanikova et al. (2013)
p.Gly144Arg	Randi et al. (2005)
p.Tyr175Cys	Bento et al. (2005)
p.Ser183Leu	Bond et al. (2011)
p.Leu188Val	Pastore et al. (2003b)
p.His191Asp	Pastore et al. (2003b)
p.Pro192Thr	Percy et al. (2007)
p.Pro192Ser	Pastore et al. (2003b)
p.Lys196Glu	Bento et al. (2013b)
p.Arg200Trp	Ang et al. (2002a)

Bento C, et al. Hum Mut 2013

Perrotta S, et al.
Von Hippel-Lindau-dependent polycythemia is endemic on the island of Ischia: identification of a novel cluster.
Blood 2006; 107: 514-9

Tomasic NL, et al.
The phenotype of polycythemia due to Croatian homozygous VHL (571C>G:H191D) mutation is different from that of Chuvash polycythemia (VHL 598C>T:R200W).
Haematologica 2013; 98:560-7



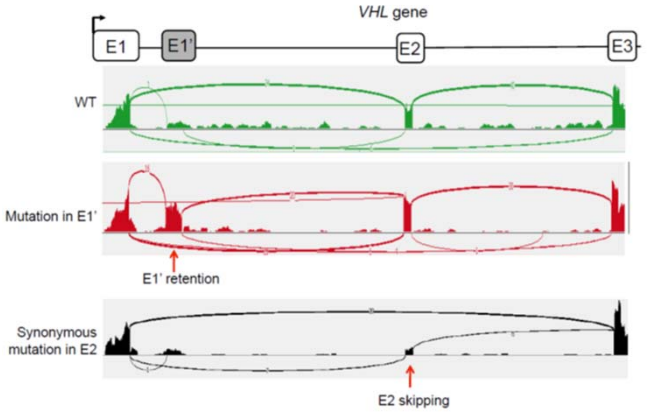
Familial erythrocytosis Type II *Chuvash polycythemia* Erythrocytosis

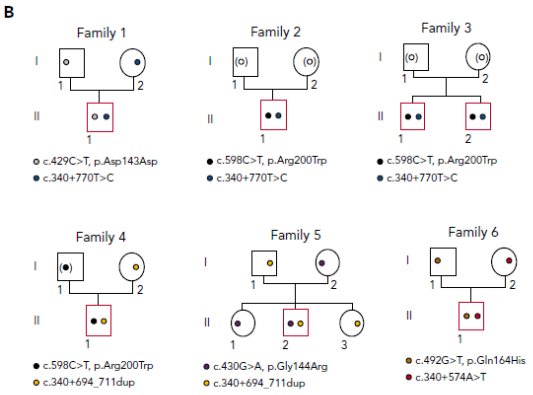
RED CELLS, IRON, AND ERYTHROPOIESIS

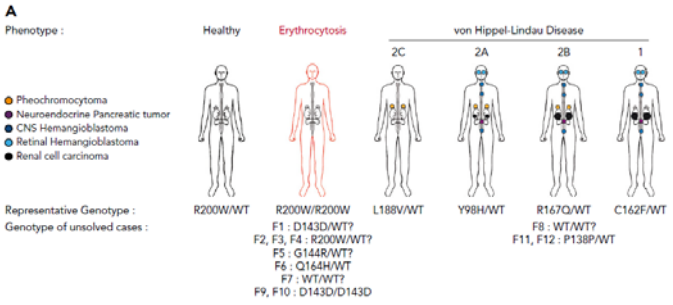
Identification of a new *VHL* exon and complex splicing alterations in familial erythrocytosis or von Hippel-Lindau disease

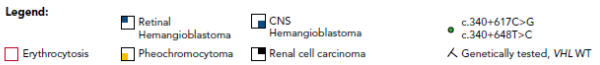
Marion Lenglet,[1-3,*] Florence Robriquet,[2,3,*] Klaus Schwarz,[4,5] Carme Camps,[6,7] Anne Couturier,[8] David Hoogewijs,[9] Alexandre Buffet,[10-12] Samantha J. L. Knight,[6,7] Sophie Gad,[1,13] Sophie Couvé,[1,13] Franck Chesnel,[8] Mathilde Pacault,[2,14] Pierre Lindenbaum,[3] Sylvie Job,[15] Solenne Dumont,[2] Thomas Besnard,[3,14] Marine Cornec,[2] Helene Dreau,[16] Melissa Pentony,[6,7] Erika Kvikstad,[6,7] Sophie Deveaux,[17-20] Nelly Burnichon,[10-12,18,19,21] Sophie Ferlicot,[17,22] Mathias Vilaine,[2] Jean-Michaël Mazzella,[10-12,18,19,21] Fabrice Airaud,[14] Céline Garrec,[14] Laurence Heidet,[23] Sabine Irtan,[24] Elpis Mantadakis,[25] Karim Bouchireb,[23] Klaus-Michael Debatin,[26] Richard Redon,[3] Stéphane Bezieau,[3,16] Brigitte Bressac-de Paillerets,[13,27] Bin Tean Teh,[28] François Girodon,[29-31] Maria-Luigia Randi,[32] Maria Caterina Putti,[33] Vincent Bours,[34] Richard Van Wijk,[35] Joachim R. Göthert,[36] Antonis Kattamis,[37] Nicolas Janin,[38] Celeste Bento,[39] Jenny C. Taylor,[6,7] Yannick Arlot-Bonnemains,[8] Stéphane Richard,[1,13,17-20,†] Anne-Paule Gimenez-Roqueplo,[10-12,18,19,21,†] Holger Cario,[26,†] and Betty Gardie[1-3,31,‡]

Lenglet M, et al. Blood 2018









Primary erythrocytosis

Congenital

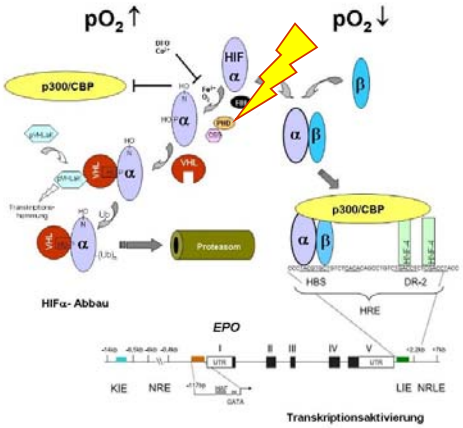
- Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)

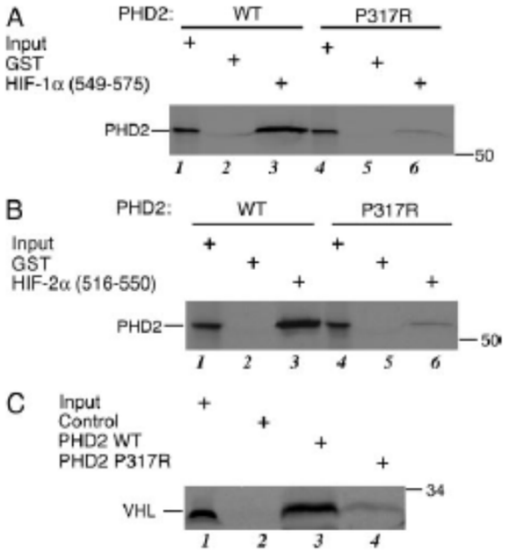
Secondary erythrocytosis

Congenital

- Defective O2-Sensing
  - Familial Erythrocytosis Type 2; *VHL*
  - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
  - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
  - Familial Erythrocytosis Type 5; *EPO*
- Altered Hb oxygen affinity
  - Familial Erythrocytosis Type 6; *HBB*
  - Familial Erythrocytosis Type 7; *HBA1, HBA2*
  - Familial Erythrocytosis Type 8; *BPGM*
  - Familial Erythrocytosis Type „x"; *PKLR*

Familial erythrocytosis Type III





Percy MJ, et al. *PNAS* 2006

Heterozygous mutation *EGLN1* c.950C→G = PHD2 Pro317Arg

- AA change in the active site of PHD2
- Reduced HIF-binding and HIF hydroxylase activity
- Defective inhibition of a HRE reporter gene activity
- "Normal" serum Epo

Erythrocytosis

Absolute erythrocytosis

Primary erythrocytosis

Congenital

- Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)

Secondary erythrocytosis

Congenital

- Defective O2-Sensing
  - Familial Erythrocytosis Type 2; *VHL*
  - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
  - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
  - Familial Erythrocytosis Type 5; *EPO*
- Altered Hb oxygen affinity
  - Familial Erythrocytosis Type 6; *HBB*
  - Familial Erythrocytosis Type 7; *HBA1, HBA2*
  - Familial Erythrocytosis Type 8; *BPGM*
  - Familial Erythrocytosis Type „x"; *PKLR*

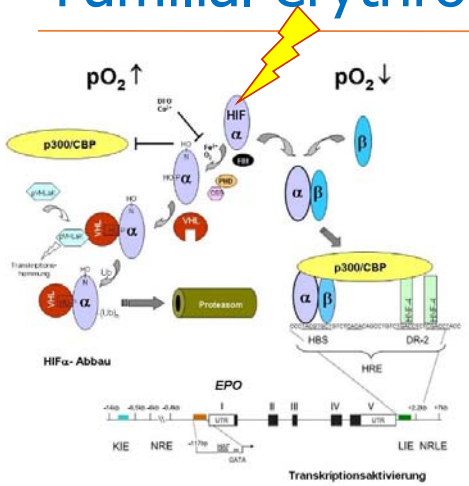
EGLN1 mutations in ECYT III

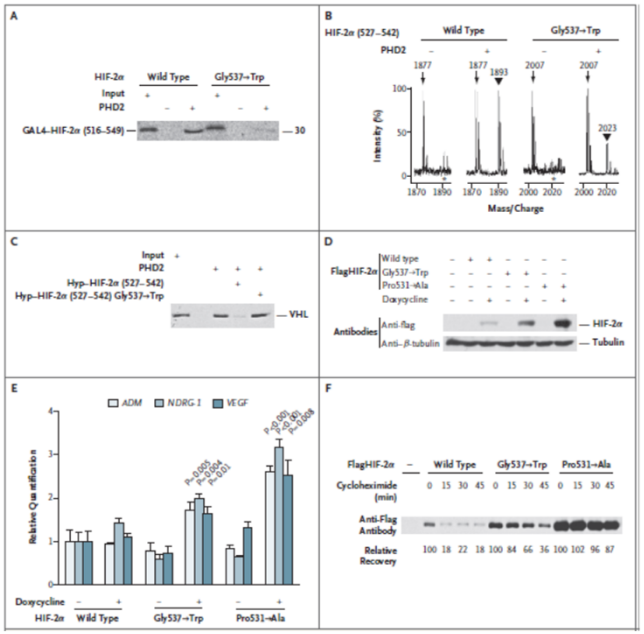
Protein effect	References
p.Asp4Glu#	Lorenzo et al. (2010)
p.Cys127Ser#	Lorenzo et al. (2010)
p.Gln157His#	Albiero et al. (2011); Ladroue et al. (2012)
p.Pro200Gln	Ladroue et al. (2012)
p.Met202Ilefs*72	Al-Sheikh et al. (2008)
p.Asn203Lys	Albiero et al. (2012)
p.Lys204Glu	McMullin (this report)
p.Asp254His	Ladroue et al. (2012)
p.Arg281Thrfs*4	Al-Sheikh et al. (2008)
p.Gly285Arg	McMullin (this report)
p.Lys291Ile	Albiero et al. (2012)
p.Pro317Arg	Percy et al. (2006)
p.Trp334Arg	Bento et al. (2013b)
p.Val338Glyfs*18	McMullin (this report)
p.Arg371His	Percy et al. (2007); Ladroue et al. (2012)
p.His374Arg	Ladroue et al. (2008)
p.Gln377*	Al-Sheikh et al. (2008)
p.Arg398*	Ladroue et al. (2012)
p.Lys423Glu	Albiero et al., (2012)

+ paraganglioma

Bento C, et al. Hum Mut 2013

Familial erythrocytosis Type IV





Percy MJ, et al. *NEJM* 2008

Heterozygous mutation *EPAS1* c.1609G→T = HIF2α Gly537Trp

- AA change close to Pro531
- Reduced PHD2-binding and proline hydroxylation
- Reduced VHL-binding to hyp-HIF2a
- Increased HIF2a-stability

Erythrocytosis

Absolute erythrocytosis

Primary erythrocytosis

Congenital

- Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)

Secondary erythrocytosis

Congenital

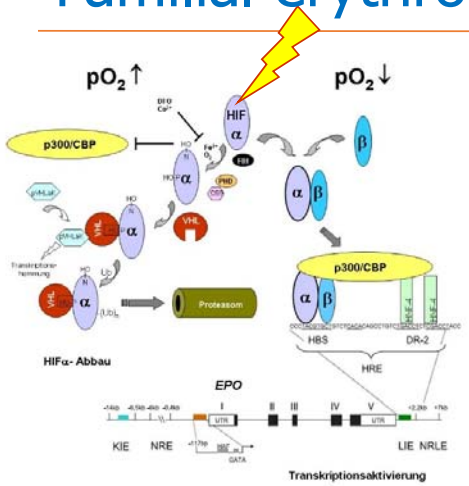
- Defective O2-Sensing
  - Familial Erythrocytosis Type 2; *VHL*
  - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
  - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
  - Familial Erythrocytosis Type 5; *EPO*
- Altered Hb oxygen affinity
  - Familial Erythrocytosis Type 6; *HBB*
  - Familial Erythrocytosis Type 7; *HBA1, HBA2*
  - Familial Erythrocytosis Type 8; *BPGM*
  - Familial Erythrocytosis Type „x"; *PKLR*

EPAS1 mutations in ECYT IV

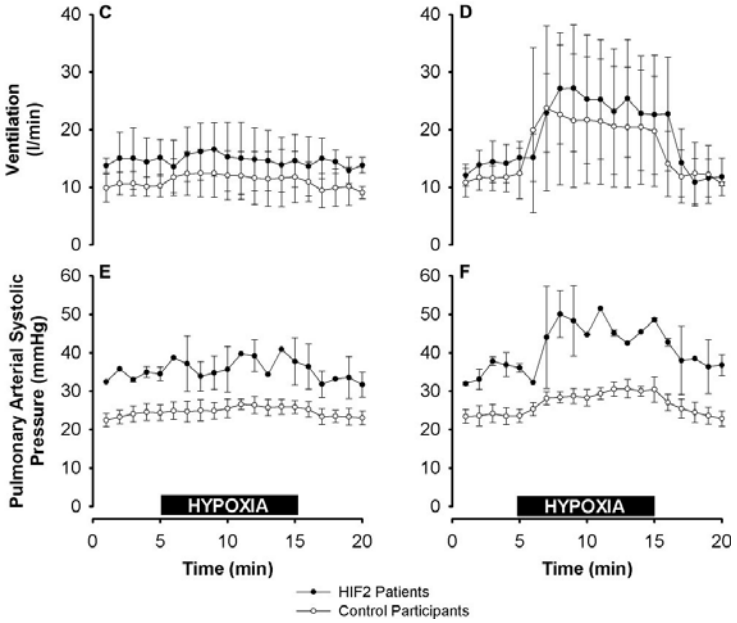
Protein effect	References
p.Phe374Tyr	Lorenzo et al. (2012)
p.Ile533Val	Perrotta et al. (2013)
p.Pro534Leu	Percy et al. (2008)
p.Met535Ile	Martini et al. (2008)
p.Met535Val	Percy et al. (2012)
p.Met535Thr	Percy et al. (2008)
p.Gly537Arg	Percy et al. (2008); Gale et al. (2008)
p.Gly537Trp	Percy et al. (2008)
p.Asp539Glu	van Wijk et al. (2010)
p.Phe540Leu	Percy et al. (2012)

Bento C, et al. Hum Mut 2013

Familial erythrocytosis Type IV



Pulmonary hypertension



Formenti F, et al. FASEB J 2011

Erythrocytosis

Absolute erythrocytosis

Primary erythrocytosis

Congenital

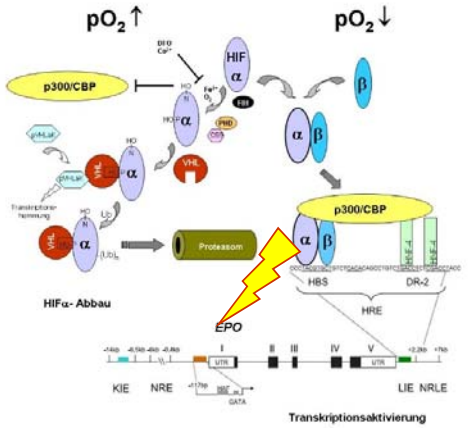
- Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)

Secondary erythrocytosis

Congenital

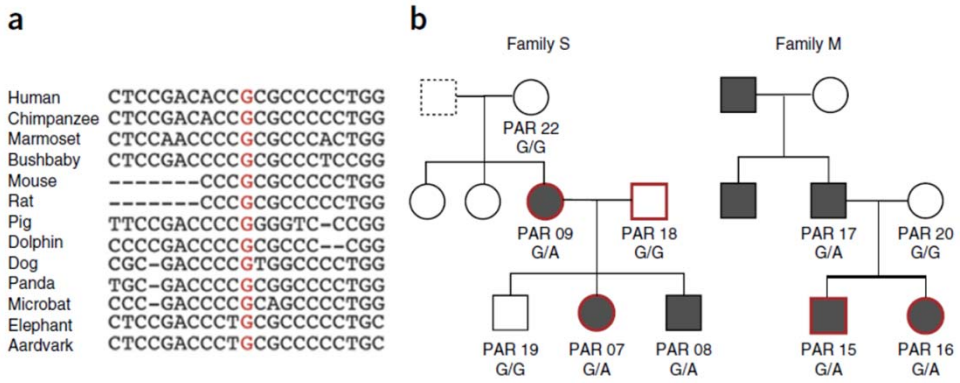
- Defective O2-Sensing
  - Familial Erythrocytosis Type 2; *VHL*
  - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
  - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
  - Familial Erythrocytosis Type 5; *EPO*
- Altered Hb oxygen affinity
  - Familial Erythrocytosis Type 6; *HBB*
  - Familial Erythrocytosis Type 7; *HBA1, HBA2*
  - Familial Erythrocytosis Type 8; *BPGM*
  - Familial Erythrocytosis Type „x"; *PKLR*

Familial erythrocytosis Type V



CBC	PAR07 at 10 yrs.	PAR08 at 12 yrs.
WBC [Giga/l]	4.7	4.8
RBC [Tera/l]	6.1+	7.3+
Hb [g/dl]	17.6+	20.6+
Hct [l/l]	0.51+	0.58+
Plt [Giga/l]	251	166
Epo [mIU/ml]	4.6	5.9

EPO g.100318468G>A (in 5' UTR)



Taylor JC, et al. Nature Genet 2015

Erythrocytosis

- Absolute erythrocytosis
  - Primary erythrocytosis
    - Congenital
      - Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)
  - Secondary erythrocytosis
    - Congenital
      - Defective O2-Sensing
        - Familial Erythrocytosis Type 2; *VHL*
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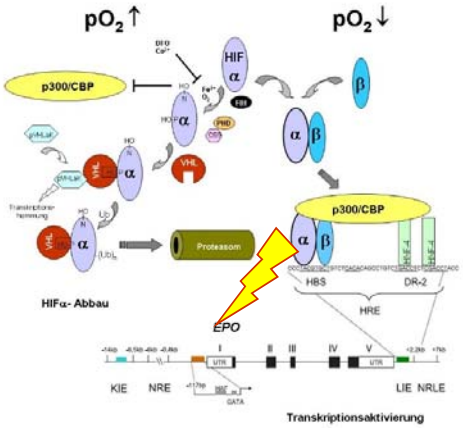
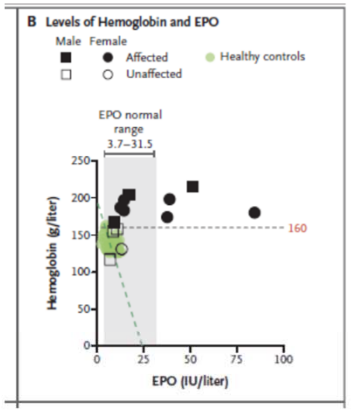
      - Altered Hb oxygen affinity
        - Familial Erythrocytosis Type 6; *HBB*
        - Familial Erythrocytosis Type 7; *HBA1, HBA2*
        - Familial Erythrocytosis Type 8; *BPGM*
        - Familial Erythrocytosis Type „x"; *PKLR*

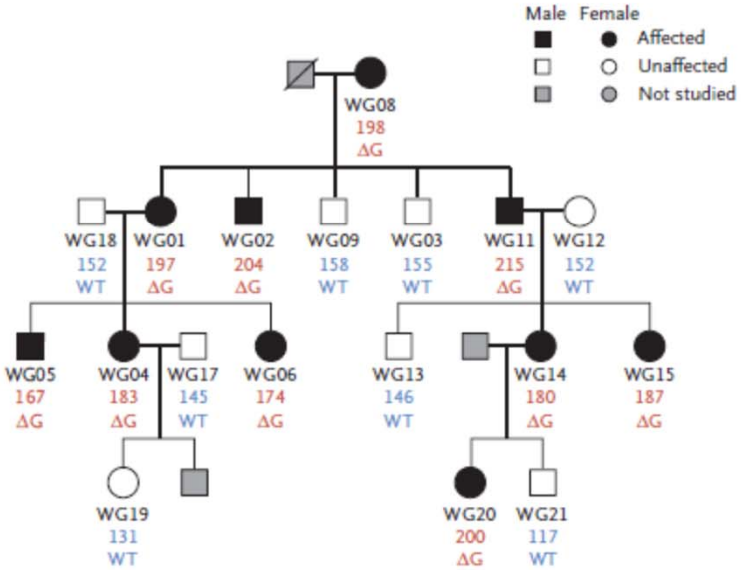
Familial erythrocytosis Type V



Zmajkovic J, et al.
NEJM 2018

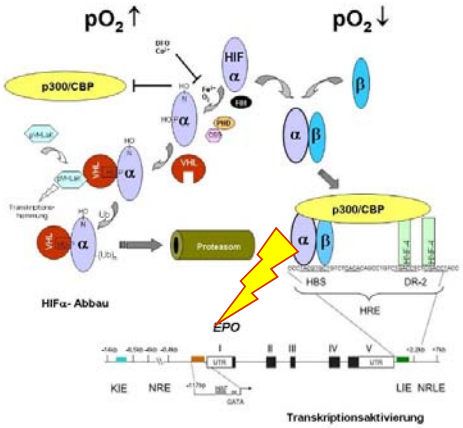
EPO c.32delG





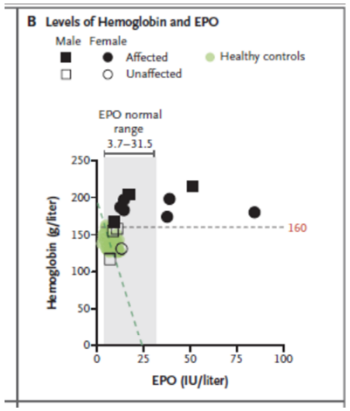
- Absolute erythrocytosis
  - Primary erythrocytosis
    - Congenital
      - Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)
  - Secondary erythrocytosis
    - Congenital
      - Defective O2-Sensing
        - Familial Erythrocytosis Type 2; *VHL*
        - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
        - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
        - Familial Erythrocytosis Type 5; *EPO*
      - Altered Hb oxygen affinity
        - Familial Erythrocytosis Type 6; *HBB*
        - Familial Erythrocytosis Type 7; *HBA1, HBA2*
        - Familial Erythrocytosis Type 8; *BPGM*
        - Familial Erythrocytosis Type „x"; *PKLR*

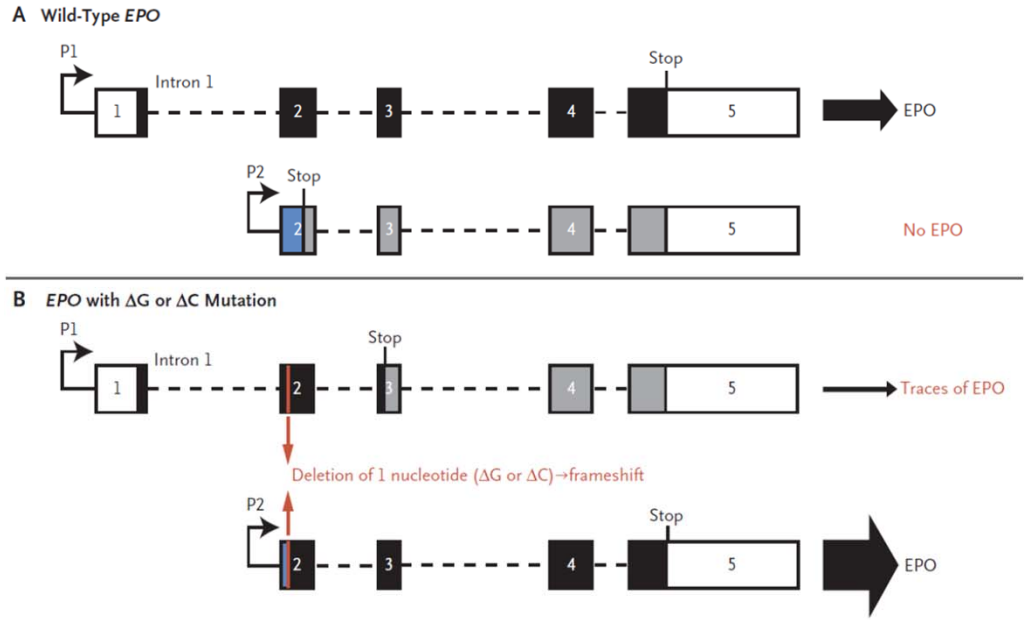
Familial erythrocytosis Type V



Zmajkovic J, et al.
NEJM 2018

EPO c.32delG





+ *EPO* c.19delC

(Camps C, et al. Haematologica 2016)

Absolute erythrocytosis

Primary erythrocytosis

Congenital

- Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)

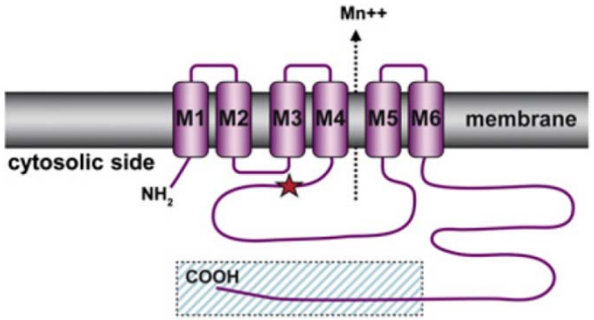
Secondary erythrocytosis

Congenital

- Defective O2-Sensing
  - Familial Erythrocytosis Type 2; *VHL*
  - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
  - Familial Erythrocytosis Type 4; *EPAS1* (HIF2a)
  - Familial Erythrocytosis Type 5; *EPO*
- Altered Hb oxygen affinity
  - Familial Erythrocytosis Type 6; *HBB*
  - Familial Erythrocytosis Type 7; *HBA1, HBA2*
  - Familial Erythrocytosis Type 8; *BPGM*
  - Familial Erythrocytosis Type „x"; *PKLR*

SLC30A10

= human manganese transporter



Quadri M, et al. AJHG 2012

J Inherit Metab Dis (2008) 31:151–163
DOI 10.1007/s10545-008-0813-1

SSIEM SYMPOSIUM 2007

Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia—A new metabolic disorder

Karin Tuschl · Philippa B. Mills · Howard Parsons · Marian Malone · Darren Fowler · Maria Bitner-Glindzicz · Peter T. Clayton

Hypermanganesemia syndrome (HMDPC)

ARTICLE

Syndrome of Hepatic Cirrhosis, Dystonia, Polycythemia, and Hypermanganesemia Caused by Mutations in *SLC30A10*, a Manganese Transporter in Man

Karin Tuschl,[1,*] Peter T. Clayton,[1] Sidney M. Gospe, Jr.,[2] Shamshad Gulab,[3] Shahnaz Ibrahim,[3] Pratibha Singhi,[4] Roosy Aulakh,[5] Reinaldo T. Ribeiro,[6] Orlando G. Barsottini,[6] Maha S. Zaki,[7] Maria Luz Del Rosario,[8] Sarah Dyack,[9] Victoria Price,[9] Andrea Rideout,[9] Kevin Gordon,[9] Ron A. Wevers,[10] W.K. "Kling" Chong,[11] and Philippa B. Mills[1]

The American Journal of Human Genetics *90*, 457–466, March 9, 2012 457

ARTICLE

Mutations in *SLC30A10* Cause Parkinsonism and Dystonia with Hypermanganesemia, Polycythemia, and Chronic Liver Disease

Marialuisa Quadri,[1] Antonio Federico,[2] Tianna Zhao,[1] Guido J. Breedveld,[1] Carla Battisti,[2] Cathérine Delnooz,[3] Lies-Anne Severijnen,[1] Iara Di Toro Mammarella,[2] Andrea Mignarri,[2] Lucia Monti,[4] Antioco Sanna,[4] Peng Lu,[5] Francesca Punzo,[1,6] Giovanni Cossu,[7] Rob Willemsen,[1] Fabrizio Rasi,[8] Ben A. Oostra,[1] Bart P. van de Warrenburg,[3] and Vincenzo Bonifati[1,*]

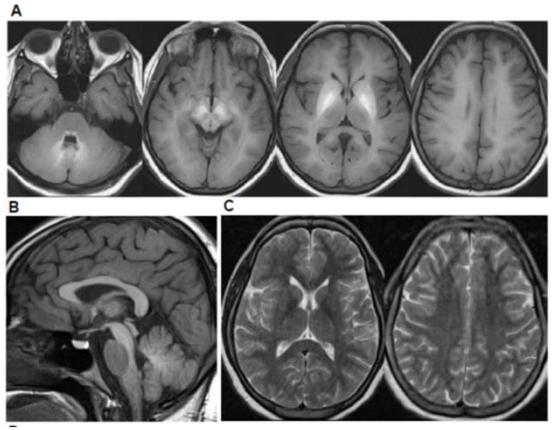
The American Journal of Human Genetics *90*, 467–477, March 9, 2012 467

Homozygosity mapping → *SLC30A10* mutations in all affected individuals

Lab results

Mn	1600 - 6370 nmol/l (<320)
Hb	15.9 - 22.5 g/dl
Ferr.	6 - 30 µg/l
Epo	20.4 - 473 U/l

- Neurologic symptoms:
  - Dystonia
  - Dysarthria
  - Fine tremor
  - Bradykinesia
  - Spastic paraparesis (1pt.)
  - No cognitive impairment
- Erythrocytosis
- Iron deficiency
- Liver: steatosis, cirrhosis, failure



cMRI: Hyperintensities in T1

Treatment

Chelation with

1. disodium calcium edetate ($CaNa_2$[EDTA])
2. 2,3 dimercaptosuccinic acid (DMSA)
3. (D-Penicillamin p.o.)

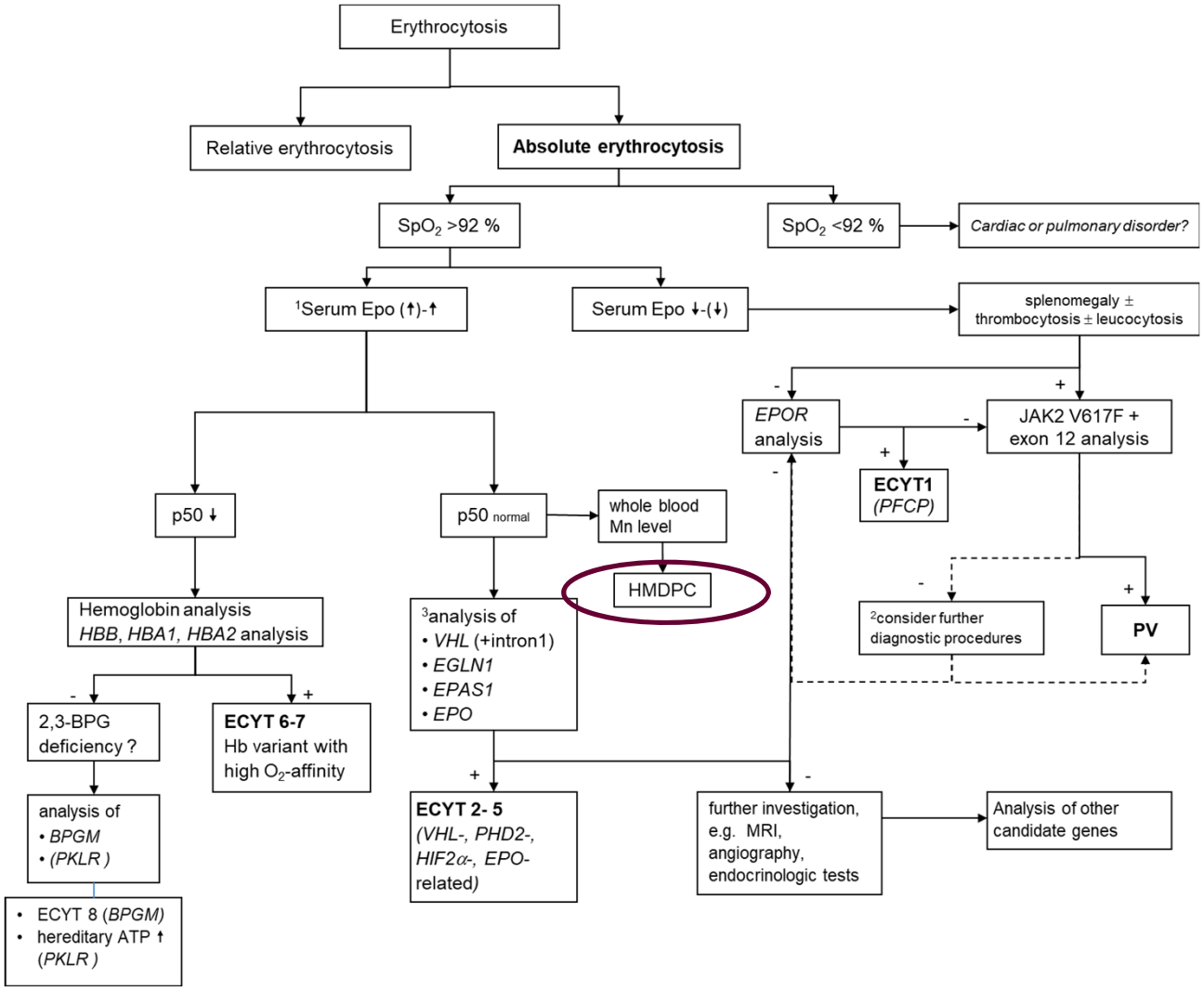
Additional treatment:
Iron supplementation with e.g. ferrous sulfate

Table 1. Agents That Affect *Epo* Gene Expression

Induction in vivo and in vitro
Hypoxia
Transition metals: Co^{2+}, Ni^{2+}, Mn^{2+}[118,192]
Iron chelators: desferrioxamine[120]
Abrogation of induction in Hep3B and HepG2 cells
Carbon monoxide[91,118,193]
Nitric oxide, nitroprusside[91]
Hydrogen peroxide[86,194]
Inflammatory cytokines: TNF-α, IL-1[181,182]
Phorbol esters: Forskolin[193,195-197]
Protein synthesis inhibitors: cycloheximide[83,118]

Ebert J, Bunn F, Blood 1999

Diagnostic algorithm



modified acc. Cario et al, PBC 2013

Erythrocytosis

Absolute erythrocytosis

Primary erythrocytosis

Congenital

- Familial Erythrocytosis Type 1; *EPOR* (*syn. Primary familial congenital polycythemia, PFCP*)

Acquired

- Polycythemia vera

HMDPC = hypermanganesemia, dystonia, polycythemia, cirrhosis

Secondary erythrocytosis

Congenital

- Defective O2-Sensing
  - Familial Erythrocytosis Type 2; *VHL*
  - Familial Erythrocytosis Type 3; *EGLN1* (PHD2)
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  - Familial Erythrocytosis Type 5; *EPO*
- Altered Hb oxygen affinity
  - Familial Erythrocytosis Type 6; *HBB*
  - Familial Erythrocytosis Type 7; *HBA1, HBA2*
  - Familial Erythrocytosis Type 8; *BPGM*
  - Familial Erythrocytosis Type „x"; *PKLR*
- Syndromal
  - e.g. Hypermanganesemia (HMDPC, SLC30A10)

Acquired

- Physiological EPO elevation due to
  - pulmonary
  - cardiac
  - renal
  - hepatic diseases
- Autonomous EPO synthesis
  - Kidney: nephroblastoma, RCC
  - Liver: hepatoma, HCC
  - CNS: e.g. hemangioblastoma
  - Endocrine tumor (e.g. pheoc.)

Treatment

1. Phlebotomy:

2. Interferon-alpha, peg-IFNα, hydroxycarbamide :

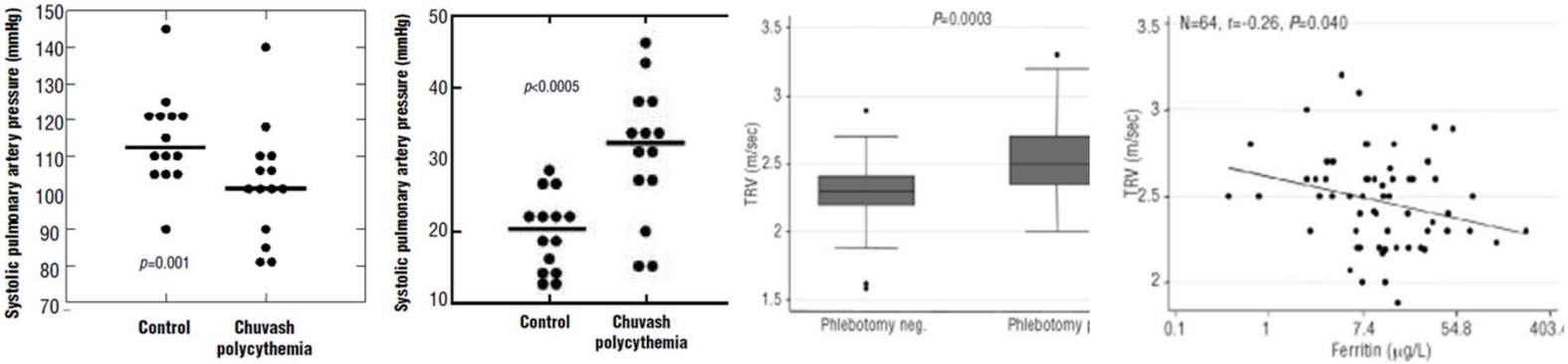
3. Ruxolitinib:

4. others:

Treatment

1. Phlebotomy:
   - standard treatment for PV (± ASA), certainly o.k. in ECYT1 (*EPOR*)
   - no change (worsening?) of prognosis in *VHL*, *EPAS1 (+EGLN1?)* –related Ecyt
     - CAVE: pulmonary arterial hypertension ?
   - in *HBB* variants: only for short term intervention (alternative: exchange Tx)

Pulmonary hypertension in Chuvash Polycythemia



Bushuev VI et al. Haematologica 2006

Sable Ca et al. Haematologica 2012

Treatment

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   - no change (worsening?) of prognosis in *VHL*, *EPAS1 (+EGLN1?)* –related Ecyt
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   - in *HBB* variants: only for short term intervention (alternative: exchange Tx)

2. Interferon-alpha, peg-IFNα, hydroxycarbamide :
   - peg-IFNa and HC: well established in adult PV
   - Hydroxycarbamide in erythrocytosis other than PV?

Hydroxycarbamide for CE ??

Reiss U, et al. Hydroxyurea therapy for management of secondary erythrocytosis in cyanotic congenital heart disease. AJH 2007

TABLE I. Patient Characteristics and Laboratory Parameters Before and During Hydroxyurea Therapy

	Patient 1		Patient 2		Patient 3		Patient 4	
Age (years)	16		18		22		42	
Diagnosis	Tetralogy of Fallot		Tricuspid atresia		Single right ventricle		Atrio-ventricular canal	
O_2 saturation	85%		85%		61%		48%	
Previous therapy	None		Aspirin		Aspirin, occasional phlebotomy		Phlebotomy every 2 weeks	
Hyperviscosity symptoms	Easy fatigue, dyspnea		Recurrent stroke		Recurrent TIA, headaches		Exhaustion, weakness after phlebotomy	
HU therapy	Start	Steady state (6 months)	Start	Steady state (24 months)	Start[a]	Steady state (19 months)	Start	Steady state (10 months)
HU (mg/kg/day)		16		15		25		7
Hb (g/dL)	21.8	19.8	24.6	21.8	23.3	21.3	21.0	17.2
Hct (%)	64	59	76	67	74	65	68	59
RBC (10^{12}/L)	7.84	5.77	8.20	4.55	10.90	5.45	7.37	5.90
MCV (fL)	90	102	93	147	71	120	93	99
MCH (pg)	27.9	34.2	30.4	47.9	19.4	39.1	28.5	34.3
MCHC (g/dL)	34.3	33.6	32.8	32.5	27.4	32.6	30.7	29.4
Hb F (%)	0.7	1.4	1.4	9.3	0.2	1.7	–	1.9
Ferritin (ng/mL)	71	–	77	–	<1	21	40	–

- Lower hematocrit → lower viscosity
- Higher MCV and MCH → macrocytes with better deformability?
- Avoidance of iron deficient → less rigid microcytes increasing viscosity
- Only slightly lower hemoglobin

→ well tolerated
→ relieve of hyperviscosity symptoms

Treatment

1. Phlebotomy:
   - standard treatment for PV (± ASA), certainly o.k. in ECYT1 (*EPOR*)
   - no change (worsening?) of prognosis in *VHL*, *EPAS1 (+EGLN1?)* –related Ecyt
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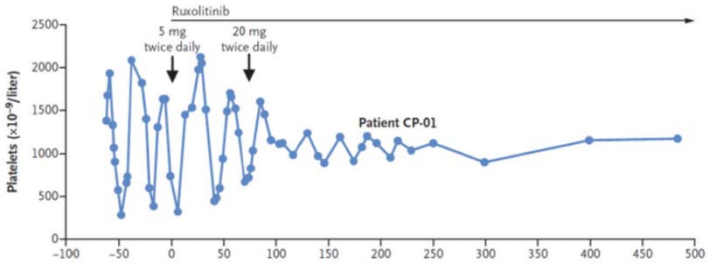
   - Hydroxycarbamide in erythrocytosis other than PV?

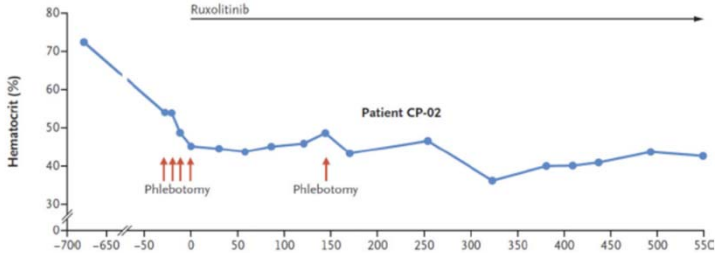
3. Ruxolitinib:
   - accepted second-line treatment in adult PV
   - option for *EPOR*- or *VHL*- related erythrocytosis?

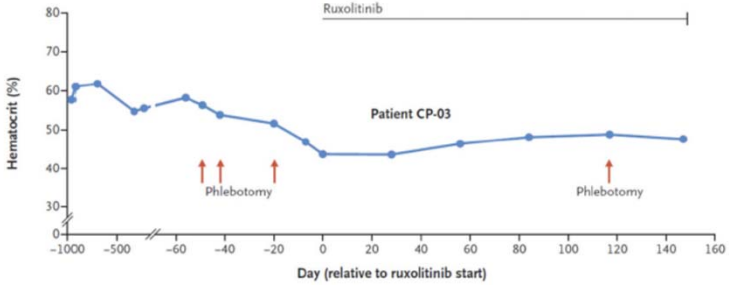
Ruxolitinib for *VHL*- related erythrocytosis ?

Zhou AW, et al. Clinical Improvement with JAK2 Inhibition in Chuvash Polycythemia. NEJM 2016

	Patient CP-01		Patient CP-02		Patient CP-03	
	33 yr of age		23 yr of age		28 yr of age	
	Before treatment	During treatment (69 wk)	Before treatment	During treatment (78 wk)	Before treatment	During treatment (21 wk)
White cells ($\times 10^{-9}$/liter)	8.5	4.8	10.8	15.4	8.1	8.5
Hemoglobin (g/dl)	13.8	16.5	12.6	11.8	13.7	15.0
Hematocrit (%)	46.0	55.9	45.2	42.6	43.7	47.6
Platelets ($\times 10^{-9}$/liter)	1500	1037	380	736	228	302
Erythropoietin (IU/liter)	1707	1081 (36 wk)	133	968 (54 wk)	32	ND
Phlebotomy frequency	Weekly	Less than 1×/mo	4× in 4 wk before ruxolitinib	1× in 78 wk with ruxolitinib	3× in 7 wk before ruxolitinib	1× in 21 wk with ruxolitinib
Symptoms	Headaches, back pain	Markedly improved	Episodic, severe abdominal pain	Markedly improved	Fatigue, aquagenic pruritus	Markedly improved







- hematologic and symptomatic improvement
- no major safety issues or serious side effects
- clinical responses associated with decreases in erythroid-colony formation and inflammatory cytokine levels

Treatment

1. Phlebotomy:
   - standard treatment for PV (± ASA), certainly o.k. in ECYT1 (*EPOR*)
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   - Hydroxycarbamide in erythrocytosis other than PV?

3. Ruxolitinib:
   - accepted second-line treatment in adult PV
   - option for VHL-related erythrocytosis?

4. others:
   - ACE-inhibitors ?, AT1R-antagonists ?
   - Digoxin ?
   - new options? → HIF 2α-inhibitors
   - symptomatic treatment in PAH (sildenafil, bosentan, macicentan)

ACE-/ AT1R- inhibitors or theophylline for CE ?

Vishnu, et al.
A Post-transplant erythrocytosis refractory to ACE inhibitors and angiotensin receptor blockers. BMC Case Rep 2018

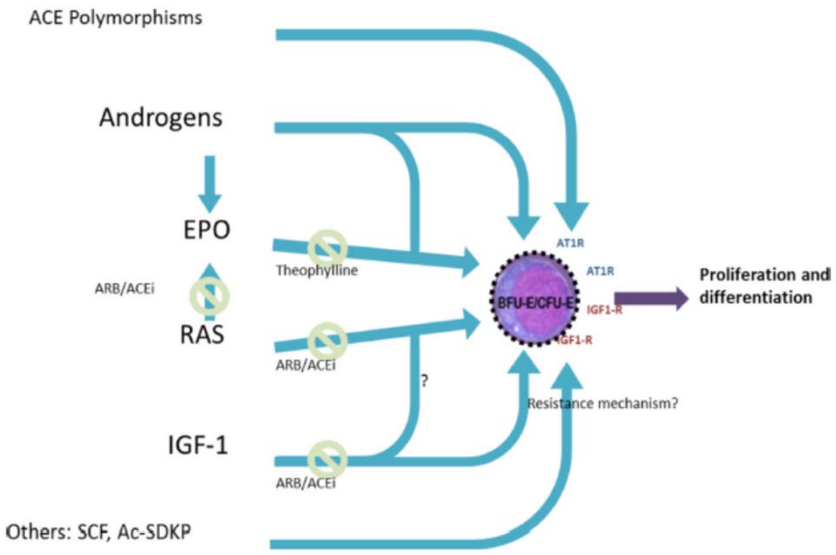


Table 1 Patients with PTE who are refractory to ACE inhibitors/ARB: literature review

Author	Year	Study type	Sample size	Refractory patients	Mean hct (%) or mean hgb level (mg/dL)	Mean EPO (mIU/L) at diagnosis	Treatment strategy
Brouhard *et al*	1992	Case report	1	0	19.1±0.6	Not specified	Enalapril 5 mg
Rell *et al*	1994	Prospective	17	3	51.1	12.2	Enalapril 2.5–20 mg/day
Torregosa *et al*	1994	Prospective	19	0	56.2±1.9	13.5±9.48	Captopril 25 mg/day
Mulhern *et al*	1995	Prospective trial	8	1	53.7±0.6	22.8±8.4	Different ACE inhibitors
Perazella *et al*	1995	Prospective trial	10	0	52±2	20±11	Enalapril 2.5–5 mg/day
Rostaing *et al*	1995	Prospective trial	12	2	51.14±2	17.41±13.5	Enalapril 5–20 mg/day
Midtveddt *et al*	1996	Case report	1	0	52	<12	Lisinopril 2.5 mg/day
MacGregor *et al*	1996	Prospective	52	3	16.7±0.8	Not specified	Lisinopril or enalapril 2.5–5 mg/day
Ducloux *et al*	1997	Case series	3	0	49	15.6	Losartan 100 mg/day
Ducloux *et al*	1998	Case series	4	0	52±0.01	17±3.7	Losartan 100 mg/day
Tsang *et al*	1998	Prospective trial	11	0	52.5±1.5	Not specified	Losartan 12.5–25 mg/day
Iñigo *et al*	1999	Prospective trial	20	0	54.6±3.5	Not specified	Losartan 50 mg/day
Javid *et al*	1999	Case series	20	2	Not specified	Not specified	Enalapril 15 mg/day
Colak *et al*	2001	Case series	23	3	41%	Not specified	Losartan 50 mg/day
Singh *et al*	2002	Prospective trial	11	1	57.7±5.4	Not specified	Losartan 25 mg/day
Wang *et al*	2002	Prospective trial	8	2	52.1±1.1	10.49±7.64	Losartan 50 mg/day and enalapril 5 mg/day
Jimeno *et al*	2005	Prospective trial	21	0	Not specified	Not specified	Enalapril 2.5–5 mg/day
Basri *et al*	2007	Retrospective cohort	29	0	Not specified	Not specified	Different ACE inhibitors
Kiberd	2009	Retrospective cohort	59	37	18.1±9	Not specified	Different ACE inhibitors and ARB
Ahmed *et al*	2012	Retrospective cohort	40	28	54.78±1.96	Not specified	Different ACE inhibitors
Moreno *et al* (this article)	2017	Case report	1	1	59.35	8.1	Enalapril and losartan
Total			370	83			

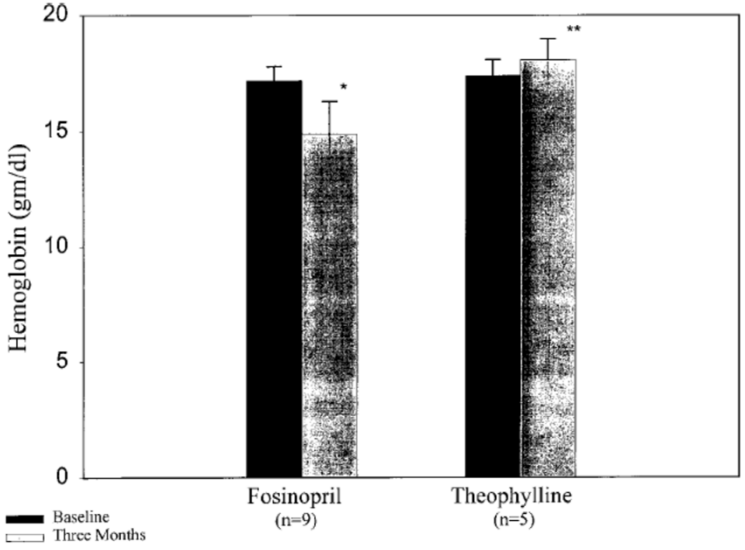
ARB, angiotensin II receptor blocker; EPO, erythropoietin; hct, haematocrit; hgb, haemoglobin; PTE, post-transplant erythrocytosis.

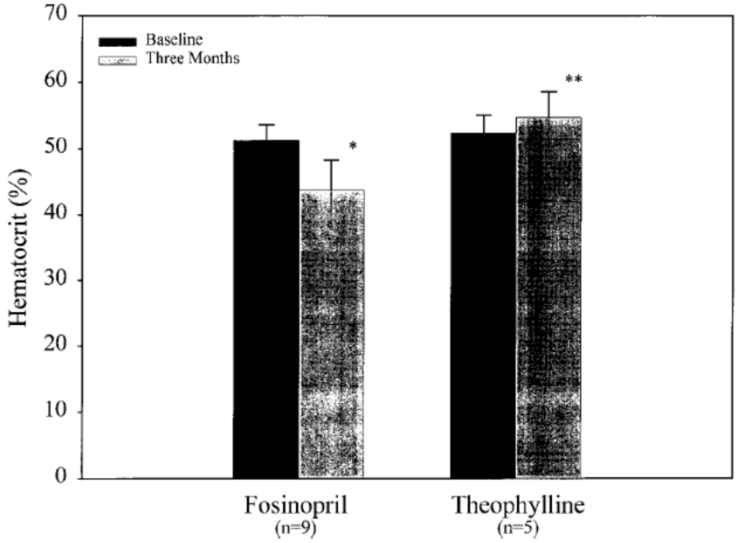
ACE-/ AT1R- inhibitors or theophylline for CE ?

Trivedi H, et al.
A Prospective, Randomized, Open Labelled Crossover Trial of Fosinopril and Theophylline in Post Renal Transplant Erythrocytosis.
Ren Fail 2003

Table 2. Mean (±SD) values before and after fosinopril and theophylline therapy.

	Hgb (gm/dL)[a]	Hct (%)[b]	BUN (mg/dL)[d]	Creatinine (mg/dL)[d]	Potassium (Meq/L)[d]	Mean BP (mmHg)[d]
Pre-fosinopril ($n=9$)	17.2 ± 0.6	51.3 ± 2.4	24.4 ± 10.2	1.6 ± 0.5	4.5 ± 0.4	102 ± 7.2
Post-fosinopril ($n=9$)	14.9 ± 1.4[a]	43.7 ± 4.6[b]	27.4 ± 12.2	1.6 ± 0.4	4.4 ± 0.6	100.4 ± 8.2
Pre-theophylline ($n=5$)	17.4 ± 0.7	52.4 ± 2.7	20 ± 11.5	1.4 ± 0.6	4.4 ± 0.2	106.3 ± 9.4
Post-theophylline ($n=5$)	18.1 ± 0.9[c]	54.7 ± 3.9[c]	23.5 ± 10.4	1.6 ± 0.7	4.2 ± 0.2	111 ± 6.1





Digoxin for CE due to O_2-sensing defects ?

PNAS

Digoxin and other cardiac glycosides inhibit HIF-1α synthesis and block tumor growth

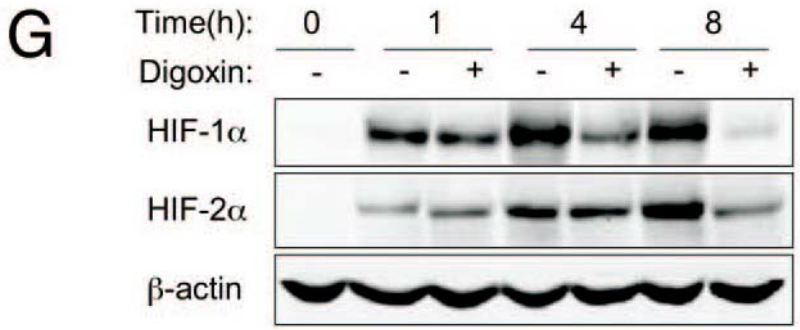
Huafeng Zhang[a,b], David Z. Qian[a,b], Yee Sun Tan[a,c], KangAe Lee[a,c], Ping Gao[d], Yunzhao R. Ren[e], Sergio Rey[a,c], Hans Hammers[b], Daniel Chang[a], Roberto Pili[b], Chi V. Dang[b,d], Jun O. Liu[e], and Gregg L. Semenza[a,b,c,d,f,g,1]

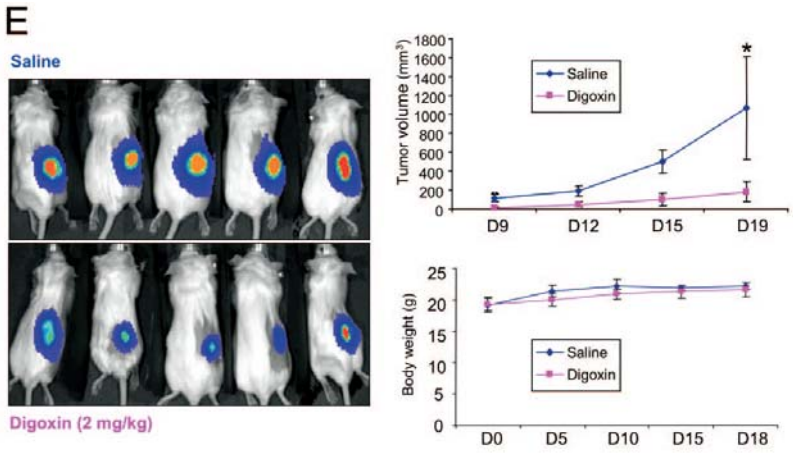
[a]Vascular Program, Institute for Cell Engineering, [b]Department of Oncology, [c]McKusick-Nathans Institute of Genetic Medicine, [d]Department of Medicine, [e]Department of Pharmacology, [f]Department of Pediatrics, and [g]Department of Radiation Oncology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected in 2008.

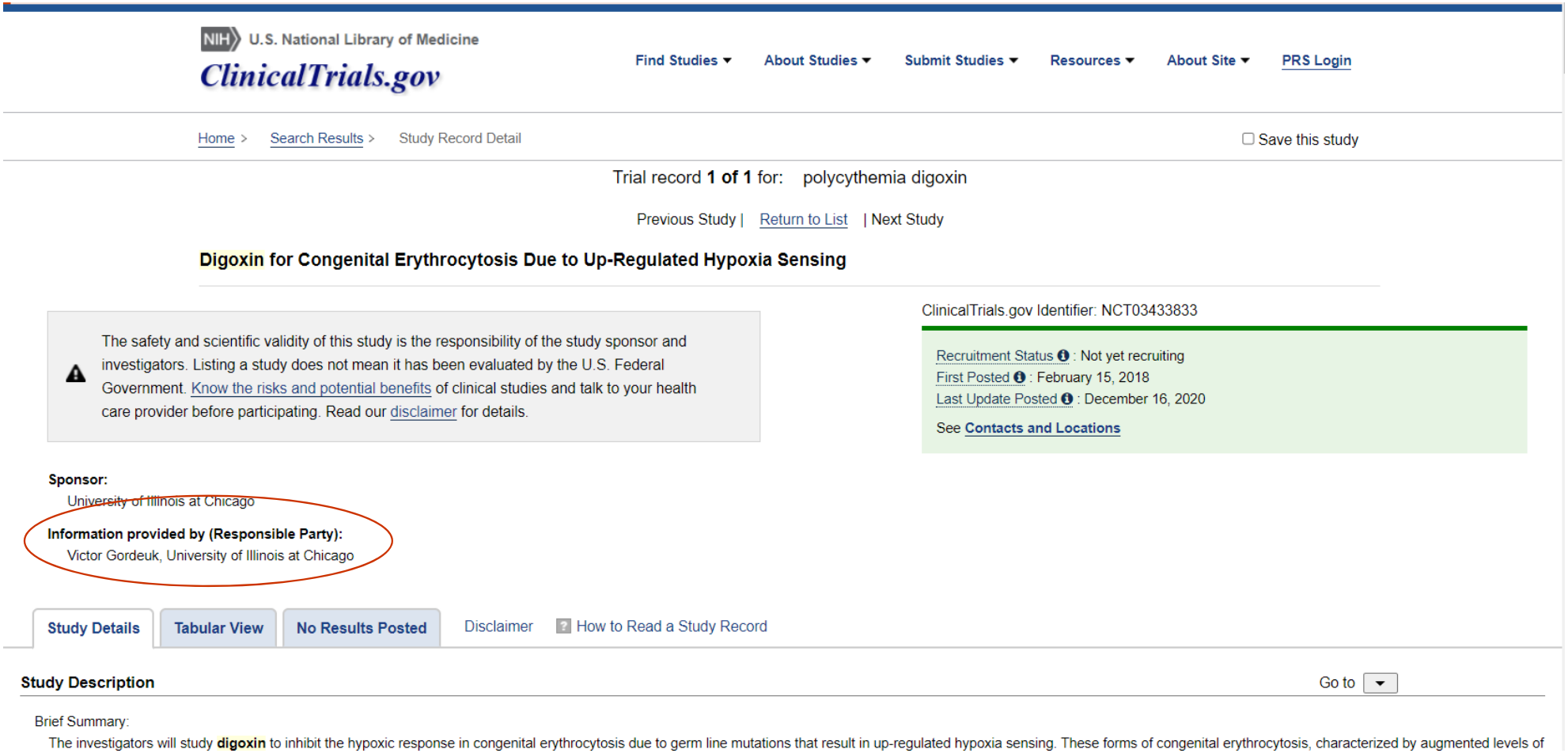
Contributed by Gregg L. Semenza, September 30, 2008 (sent for review August 21, 2008)

Zhang H, et al. PNAS 2008





Digoxin for CE due to O_2-sensing defects ?



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Trial record **1 of 1** for: polycythemia digoxin

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Digoxin for Congenital Erythrocytosis Due to Up-Regulated Hypoxia Sensing

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03433833

Recruitment Status : Not yet recruiting
First Posted : February 15, 2018
Last Update Posted : December 16, 2020

See **Contacts and Locations**

Sponsor:
University of Illinois at Chicago

Information provided by (Responsible Party):
Victor Gordeuk, University of Illinois at Chicago

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description Go to

Brief Summary:
The investigators will study **digoxin** to inhibit the hypoxic response in congenital erythrocytosis due to germ line mutations that result in up-regulated hypoxia sensing. These forms of congenital erythrocytosis, characterized by augmented levels of

HIF2a- inhibitors for CE due to O_2-sensing defects ?

Published in final edited form as:
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Targeting Renal Cell Carcinoma with a HIF-2 antagonist

Wenfang Chen[1,2,3,†], Haley Hill[1,2,†], Alana Christie[1,†], Min Soo Kim[1,4,†], Eboni Holloman[1,2], Andrea Pavia-Jimenez[1,2], Farrah Homayoun[1,2], Yuanqing Ma[1,2], Nirav Patel[1,2], Paul Yell[5], Guiyang Hao[6], Qurratulain Yousuf[1,2], Allison Joyce[1,2], Ivan Pedrosa[1,6], Heather Geiger[7], He Zhang[1,4], Jenny Chang[1], Kevin H. Gardner[8], Richard K. Bruick[1,9], Catherine Reeves[7], Tae Hyun Hwang[1,4], Kevin Courtney[1,2], Eugene Frenkel[1,2], Xiankai Sun[1,6], Naseem Zojwalla[10], Tai Wong[10], James P. Rizzi[10], Eli M. Wallace[10], John A. Josey[10], Yang Xie[1,4], Xian-Jin Xie[1,4], Payal Kapur[1,11], Renée M. McKay[1,2], and James Brugarolas[1,2,*]

Chen W, et al. Nature 2016

blood® Regular Article

RED CELLS, IRON, AND ERYTHROPOIESIS

Therapeutic inhibition of HIF-2α reverses polycythemia and pulmonary hypertension in murine models of human diseases

Manik C. Ghosh,[1] De-Liang Zhang,[1] Wade H. Ollivierre,[1] Audrey Noguchi,[2] Danielle A. Springer,[2] W. Marston Linehan,[3] and Tracey A. Rouault[1]

Ghosh MC, et al. Blood 2021

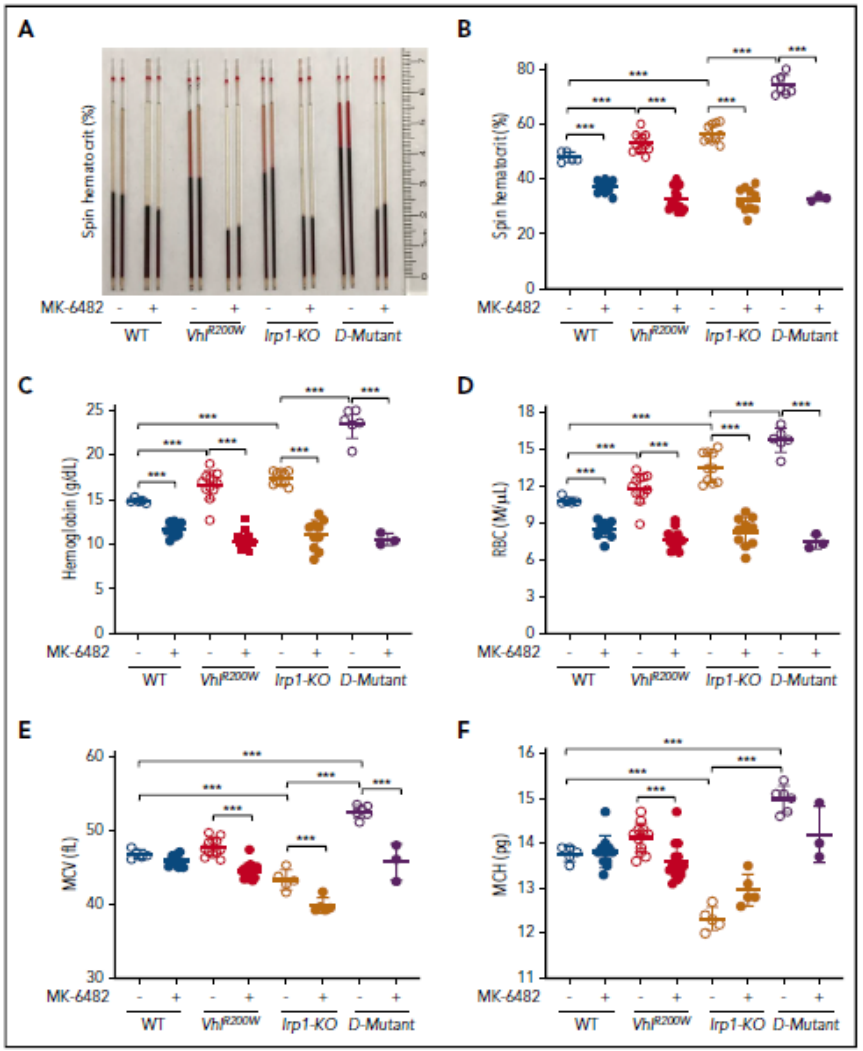

Figure 2. MK-6482 reversed polycythemia in *Vhl*^{R200W}, *Irp1-KO*, and double-mutant *Vhl*^{R200W};*Irp1-KO* mice.

HIF2a- inhibitors for CE due to O_2-sensing defects ?

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FDA approves belzutifan for cancers associated with von Hippel-Lindau disease

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Oncology (Cancer) / Hematologic Malignancies Approval Notifications

On August 13, 2021, the Food and Drug Administration approved belzutifan (Welireg, Merck), a hypoxia-inducible factor inhibitor for adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Content current as of:
08/13/2021

Regulated Product(s)
Drugs

⇨ Probably high potential to represent an efficient treatment option in all types CE to O_2-sensing defects (not in the case of EPO mutation)

Anything else ?

Walterspiel JN, et al. J Pediatr 1985

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Number 4

Erythropoietin-induced congenital erythrocytosis: Treatment with myelosuppressive agents and hookworm infestation

Juan N. Walterspiel, M.D., George R. Buchanan, M.D., Gerhard A. Schad, Ph.D., and Ugo Carpentieri, M.D.
Dallas and Galveston, Texas, and Philadelphia, Pennsylvania

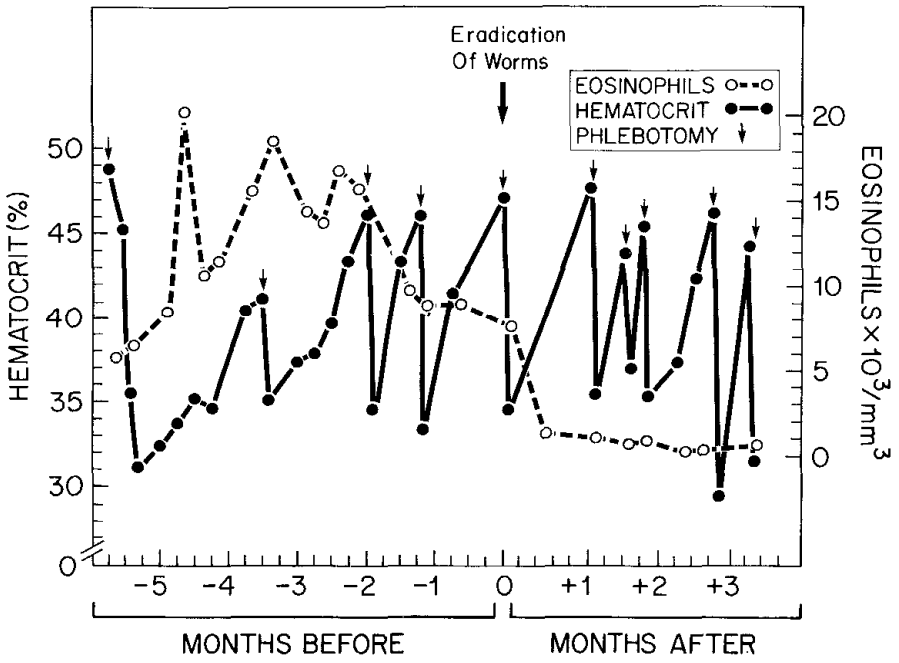

Figure. Hematocrit and eosinophil count from time of final *Ancylostoma duodenale* transfer (beginning of curve) until 3½ months after eradication of worms.

Summary

Pathogenesis

1. Increasing knowledge on etiology and pathophysiology of CE
2. Etiology in the majority of cases with presumed CE still unexplored
3. Polygenic pathogenesis may play a role

Clinical data

1. Extremely rare → clinical data extremely sparse → collaborative approaches needed
2. No systematic treatment data available.
3. Clinical trials difficult to establish

Treatment

1. Phlebotomy easily performed, but
   - Thresholds unknown
   - May even worsen the clinical course in some types of CE
2. Among new options, HIF2a- inhibitors most promising