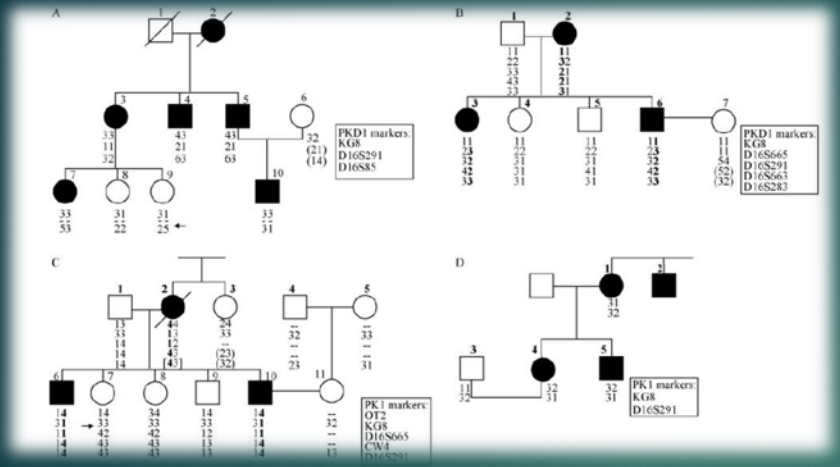

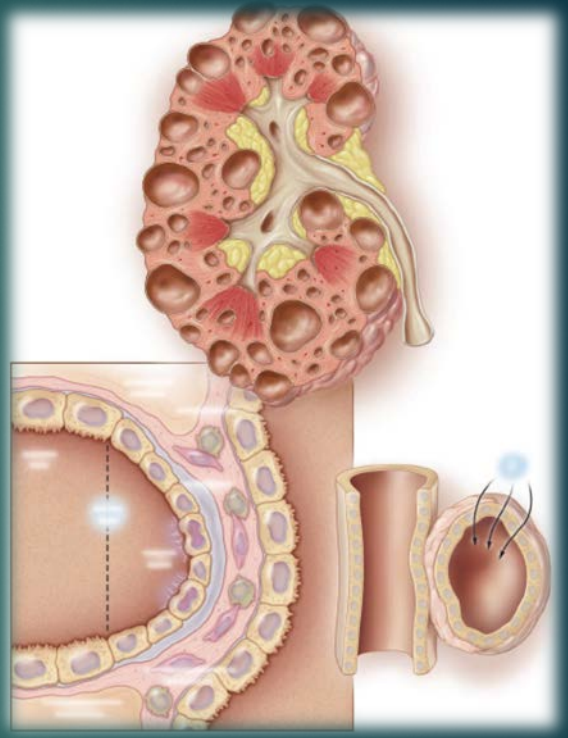

Familienplanung bei Polyzystischer Nierenerkrankung

PROF. DR. CH. BREYMANN

INSTITUT PERINATAL ZÜRICH/HIRSLANDEN

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Familienplanung Warum ?

- FAPLA bei betroffenen Frauen/ Eltern vor einer Schwangerschaft
- FAPLA betreffend eigener Erkrankung der Mutter
  - Beratung bei Hochrisiko Schwangerschaft
- FAPLA im Bezug auf das werdende Kind
  - Pränatale Diagnostik
    - Während der Schwangerschaft
      - Natürlich oder nach Therapie
      - Chorionbiopsie / Fruchtwasserpunktion
    - Vor einer Schwangerschaft
      - PID (Präimplantationsdiagnostik)
      - Immer künstliche Befruchtung (!)

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Frauen und PKD

- Schwangerschaft ist möglich
- Idealerweise keine Niereninsuffizienz/ Hypertension
- Höheres Risiko für
  - Bluthochdruck in der SS
  - Präeklampsie/ Gestose
  - Bei vorbestehenden Komplikationen
- Cave: Lebervergrösserung
  - Durch Oestrogene (?)
  - Schwangerschaften (?)

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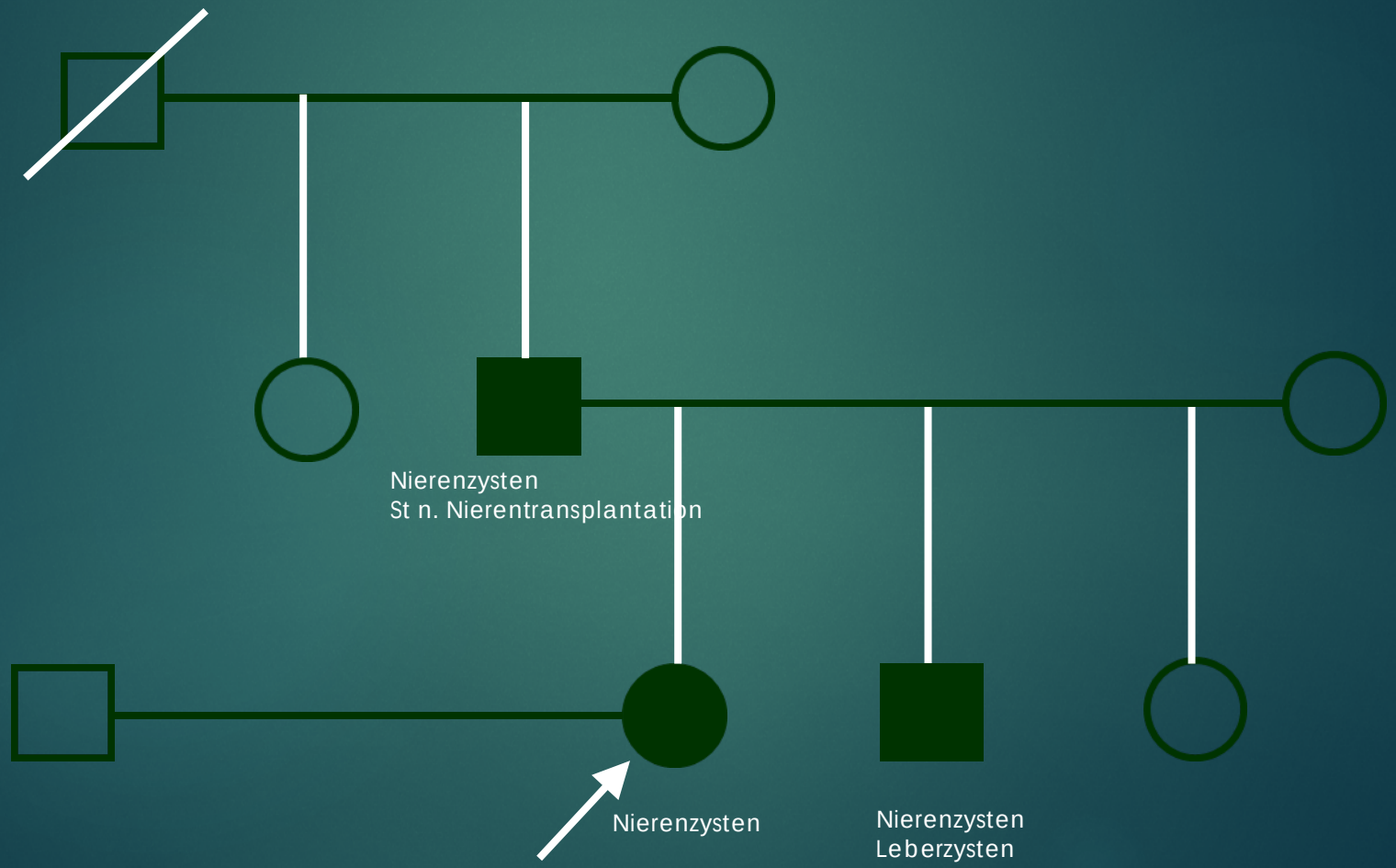
Ref.: Prof. A. Rauch USZ Inst. F. Genetik

ADPKD I



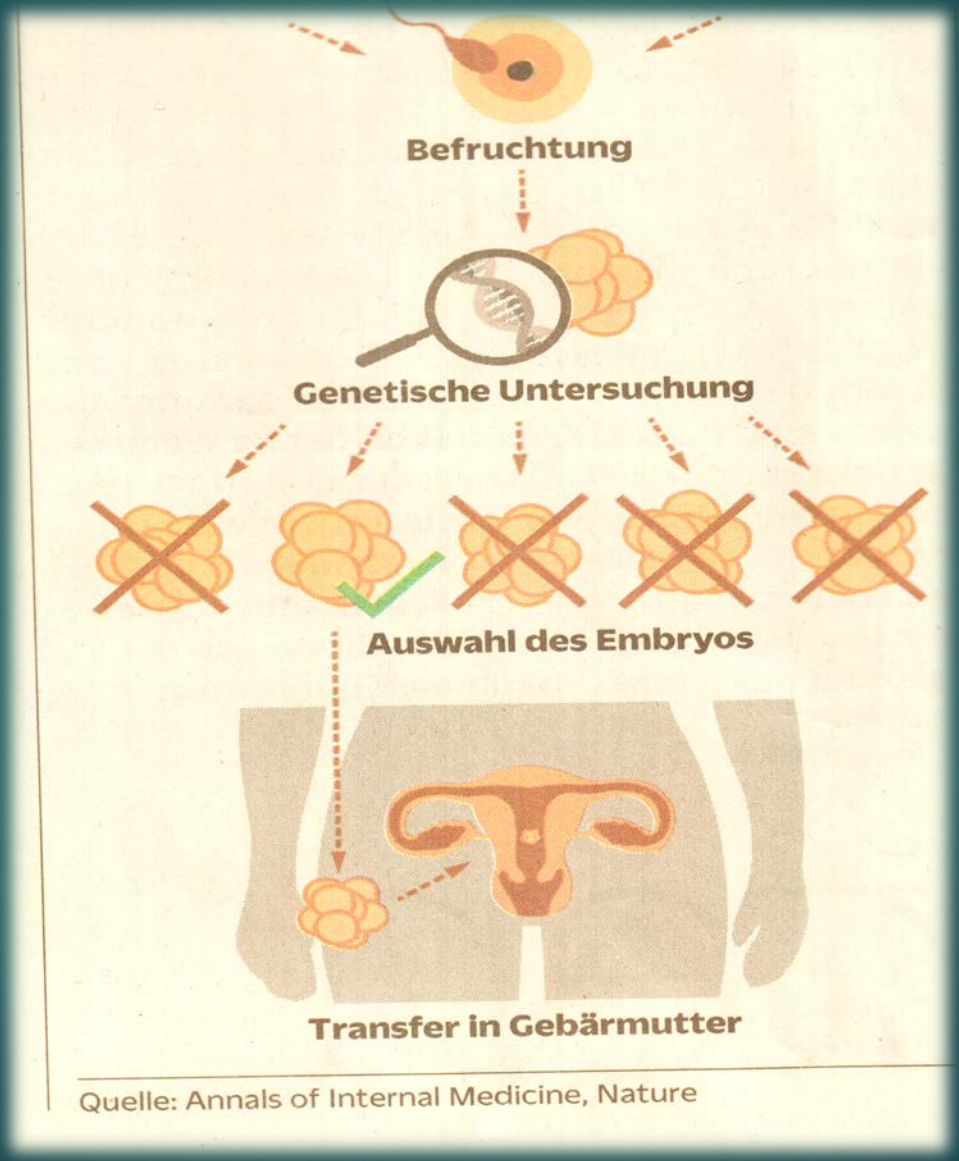
ADPKD II

Kinderwunsch bei Patientin mit klinisch autosomal-dominanter polyzystischer Nierenerkrankung:

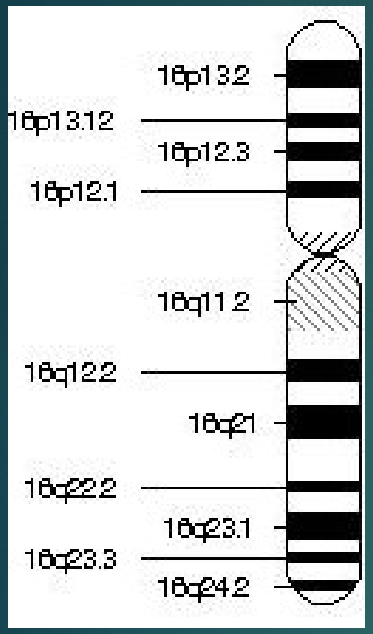
- Wiederholungsrisiko von 50%
- Wunsch nach Polkörperchendiagnostik
- Für PKD/PID oder auch PD vorherige Identifikation der Mutation im PKD1 oder PKD2-Gen notwendig

Ref.: Prof. A. Rauch USZ Inst. F. Genetik

Präimplantationsdiagnostik am Embryo vor Transfer in die Gebärmutter



ADPKD III



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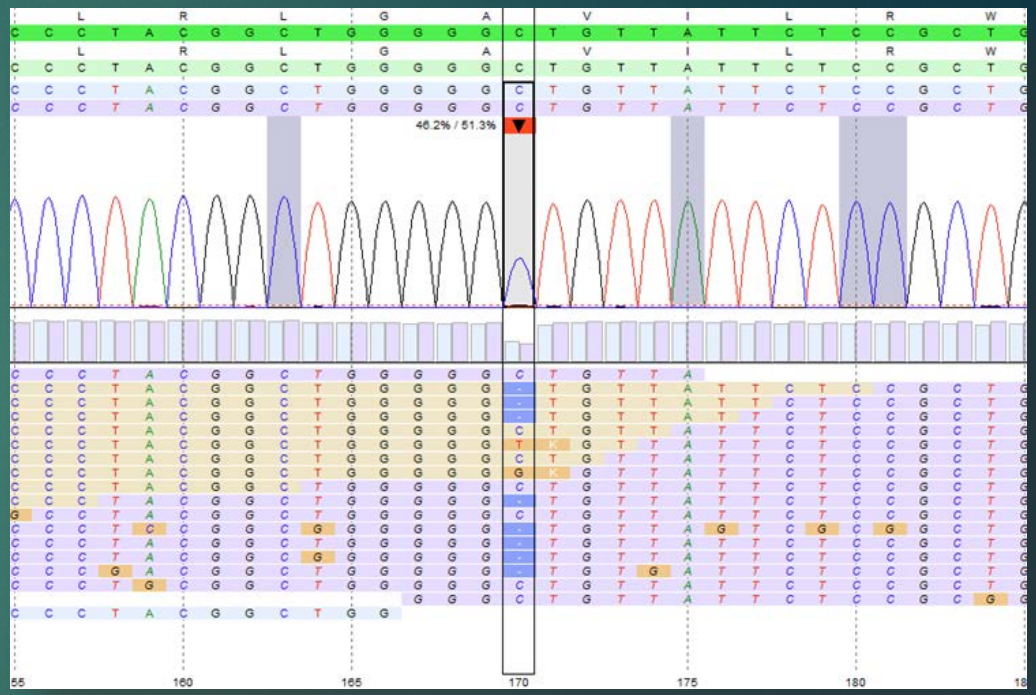
PKD1-Gen



Next Generation Sequencing:
PKD1-Mutation mit Verlust eines C-Bausteins in ca. 50% der Sequenzen, d.h. in einer der beiden Genkopien

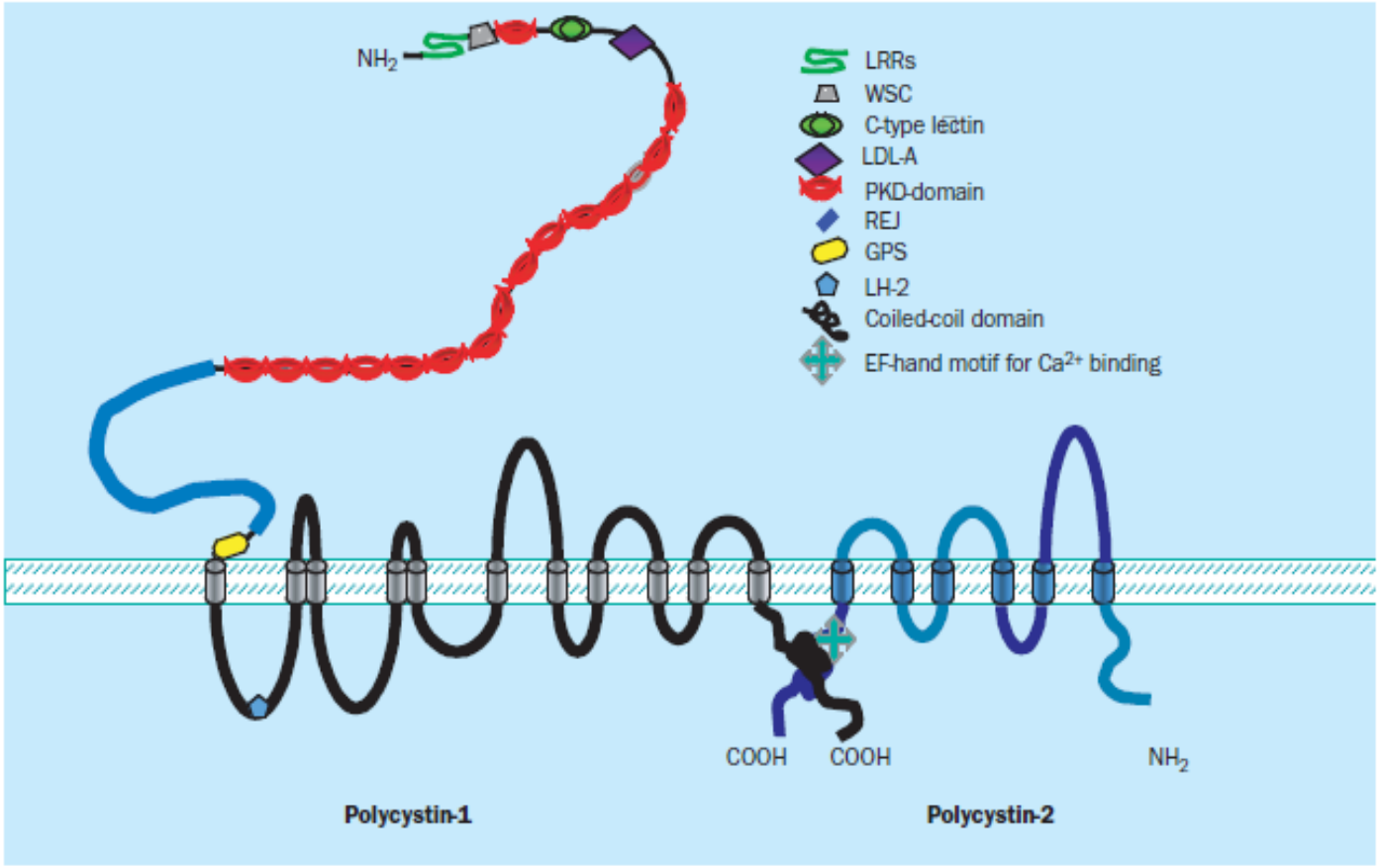


Figure 2: **Possible interaction between polycystin-1 and polycystin-2**
LLRs=leucine-rich repeats plus flanking sequences; WSC=cell-wall integrity and stress-response component domain; C-type lectin domain: homology to a specific Ca^{2+}-dependent binding domain for carbohydrates; LDL-A=low density lipoprotein receptor LDL-A module like domain; REJ=receptor for egg jelly module; GPS=G-protein coupled receptor proteolytic site domain; LH-2=lipoxygenase homology-2 domain.

Lancet 2001

Das Gen PKD1 kodiert das Protein Polycystin-1. Dieses Protein bildet zusammen mit Polycystin-2 einen Komplex, welcher multiple Signalwege reguliert um die normale renale tubuläre Struktur und Funktion zu gewährleisten.

Probleme/ Grenzen

- Zuordnung Genotyp >> Phenotyp PKD Mutation
- Intrafamiliäre Variabilität
  - Jede Familie mit «eigener» Mutation
- PKD 1 Gen Mutationen (schwerer Verlauf)
  - Early onset Disease (PKD1/TSC2 Gen)
  - Manchmal schwer zu detektieren
  - Hohe Zahl an Zuordnungen nötig (GT > PT)
- PKD 2 Gen Mutationen (oft milderer Verlauf)
  - Einfacher Detektierbar
  - Hohe Variabilität Genotyp / Phänotyp
  - Hohe Variabilität der Proteinfunktion Polycystin 1/2

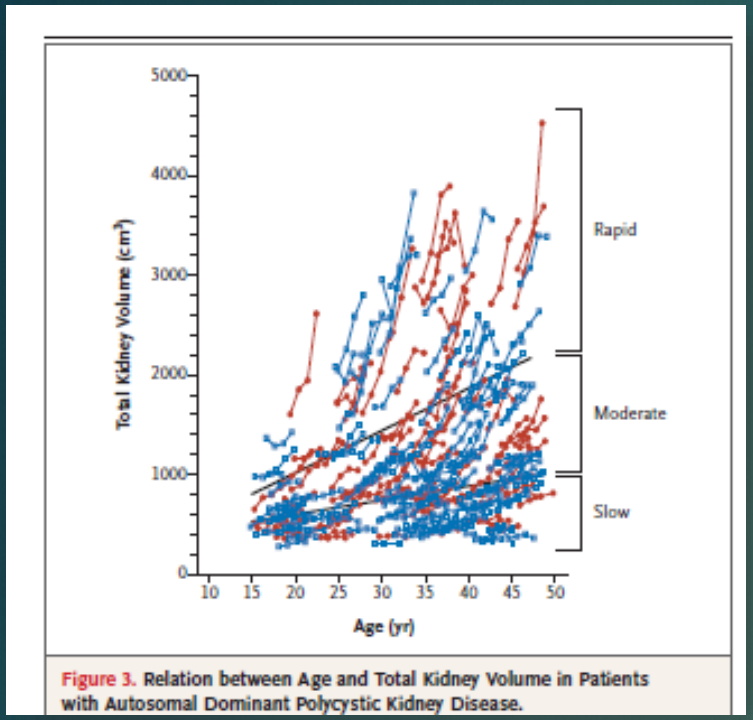
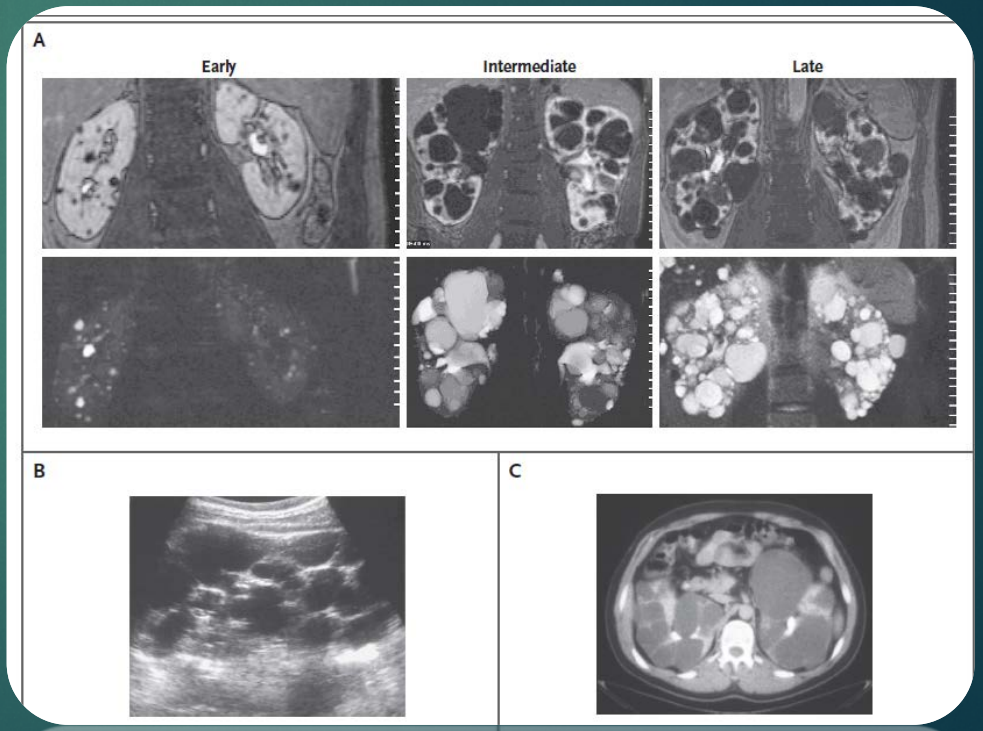


Figure 3. Relation between Age and Total Kidney Volume in Patients with Autosomal Dominant Polycystic Kidney Disease.



NEJM 2008

PKD ist keine «Einzelgenerkrankung» !

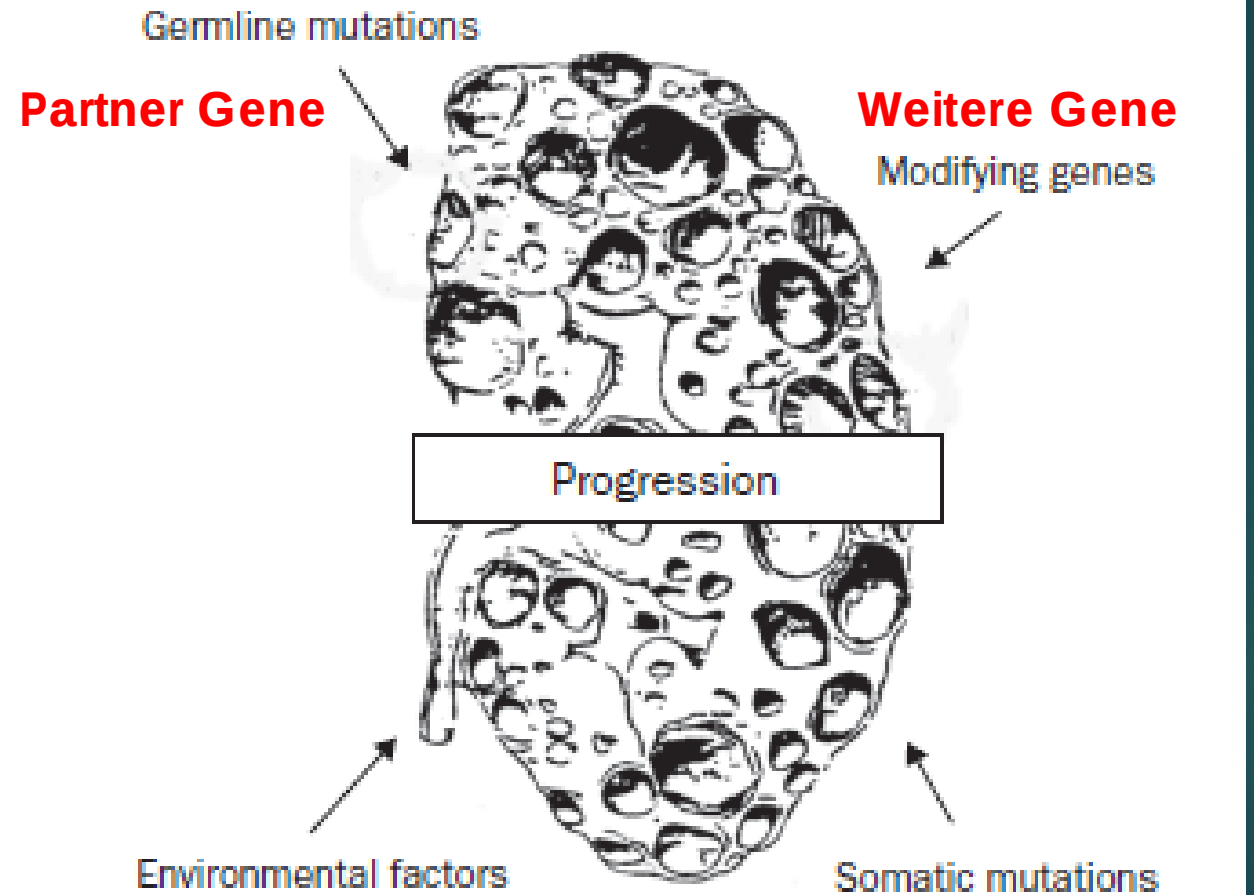


Figure 3: **Factors affecting progression of polycystic kidney disease**

American Journal of Medical Genetics 35:510–515 (1990)

Attitudes of At-Risk and Affected Individuals Regarding Presymptomatic Testing for Autosomal Dominant Polycystic Kidney Disease

Eva Sujansky, Susan Beeler Kreutzer, Ann M. Johnson, Dennis C. Lezotte, Robert W. Schrier, and Patricia A. Gabow

Departments of Pediatrics (E.S., S.B.K.), Medicine (R.W.S., A.M.J.), and Preventive Medicine and Biometrics (D.C.L.), University of Colorado Health Sciences Center, and Department of Medicine, Denver General Hospital (P.A.G.) Denver

TABLE III. Effect of ADPKD On Family Planning

	%		
	Affected	At-risk	*P* value
All participants			
Did not have children after diagnosis because of recurrence risk	11	—	—
Would not have had children if had known were at-risk for ADPKD	18	10	NS
Participants 18–40 years of age			
Diagnosis would affect family planning	44	30	NS
Will not have more children out of concern for the recurrence risk	18	8	NS

TABLE IV. Utilization Of Gene Testing

	%				
	Test self, at-risk	Test children[a]		Test fetus[b]	
		Affected	At-risk	Affected	At-risk
Yes	97	88	89	65	50
Uncertain	2	6	9	20	22
No	1	6	2	15	28
P value	—	NS		NS	

[a] All participants.
[b] Participants 18–40 yr of age.

TABLE V. Decision to Terminate a Pregnancy for ADPKD or Very Serious Medical Problem (VSMP)

	Participants 18–40 years of age, %*			
	Affected		At-risk	
	ADPKD (a)	VSMP (b)	ADPKD (c)	VSMP (d)
Yes	4	25	8	16
Uncertain	41	59	30	56
No	55	16	62	28

* a vs. c (NS); b vs. d (NS); a vs. b ($P<0.001$); c vs. d ($P<0.001$).

Molecular Human Reproduction Vol.11, No.1 pp.65–71, 2004
Advance Access publication December 10, 2004 doi:10.1093/molehr/gah128

PGD for autosomal dominant polycystic kidney disease type 1

M.De Rycke[1,4], I.Georgiou[3], K.Sermon[1], W.Lissens[1], P.Henderix[2], H.Joris[2], P.Platteau[2], A.Van Steirteghem[2] and I.Liebaers[1]

[1]Centre for Medical Genetics and [2]Centre for Reproductive Medicine, University Hospital and Medical School, Dutch-speaking Brussels Free University, Laarbeeklaan, Brussels, Belgium and [3]Laboratory of Reproductive Genetics, Department of Obstetrics and Gynecology, Medical School, University of Ioannina, Ioannina, Greece

Table I. Relevant clinical information for four couples requesting PGD for ADPKD type 1

Couple	Patient	Age of female at first PGD	Reproductive history pre-PGD	PGD results
1	Male	30	G1P2A1, post 4 ICSI cycles: 1 miscarriage, 1 pregnancy; PND: affected fetus; no TOP: affected child	PGD1: pregnancy no PND; healthy boy now 2 years
2	Male	37	G0P0A0	PGD2: pregnancy PND, healthy girl now 5 months
3	Male	32	G2P0A2 A1–2: spontaneous abortions	PGD1–2: no pregnancy; future: undecided
4	Female	26	G0P0A0	PGD1 planned

G = gestation; P = paritus; A = abortion; TOP = termination of pregnancy; PND = prenatal diagnosis.

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Table III. Results of PGD cycles for ADPKD type 1 using duplex-PCR of markers KG8 and D16S291

Couple	Cycle	COC (*n*)	ICSI (*n*)	2PN (*n*)	Embryos biopsied (*n*)	Blastomeres analysed (*n*)	Blastomeres amplified (*n*)	Blastomeres with ADO (*n*)	Unaffected embryos (*n*)	Affected embryos (*n*)	Embryos without diagnosis (*n*)	Embryos transferred (*n*)	Embryos frozen (*n*)	Embryos implanted (*n*)
1	1	15	15	12	7	14	14	0/12	3	3	1	2	0	1
2	2	9	9	6	2	4	3	0/1	1	0	1	1	0	0
	3	15	15	11	9	18	18	1/18	7	2	0	2	2	1
3	4	14	8	5	5	10	8	0/8	0	4	1	0	0	0
	5	11	11	5	1	2	2	1/2	0	1	0	0	0	0
Total	5	64	59	39	24	48	45 93.8%	2/41 4.9%	11	10	3			

COC = cumulus–oocyte complexes; 2 PN = two pronuclei (normal fertilization).
The ADO is calculated per heterozygous cell.

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affected, will not lead to embryo transfer, but will diminish the number of healthy embryos available for transfer and reduce the chances for pregnancy. Patients are advised to have a control prenatal diagnosis, which relies on flanking polymorphic markers. The second couple opted for prenatal diagnosis as they were primarily interested in karyotype analysis (the female partner was 37) and secondly, as a control for ADPKD. Three informative markers linked to *PKD1* were used during prenatal testing; however, since all three markers were proximal, the risk for misdiagnosis remained unchanged.

A drawback of the marker-based approach, specifically for ADPKD, is the need for several affected family members in order to establish which of the two possible genes underlies the disease in the family. In case of diseases caused by defects in a single gene, the availability of at least one first-degree relative of the patient is sufficient to set up marker-based PGD protocols.

Merkepunkte

- Die genetische Diagnostik der PKD 1 & 2 Genmutationen ist möglich
- Pränatal (während der SS)
- Präimplantation (PID)
- PID setzt die künstliche Befruchtung voraus
- PID = Embryoselektion
- PID ersetzt nicht immer die Diagnostik in der SS !
- Genaue Kentniss der familiären Mutation wichtig
- In vielen Fällen Aussage über Verlauf und Schwere der Erkrankung bei der Heterogenität schwierig
- Individuelle Beratung in Abhängigkeit der Schwere der Erkrankung nötig

PRENATAL AND PREIMPLANTATION GENETIC TESTING — Prenatal testing for autosomal dominant polycystic kidney disease (ADPKD) is rarely considered for adult-onset conditions, such as ADPKD, that do not affect intellect and have some effective therapies [38]. A possible exception may be in rare families where severe, early-onset disease in one child suggests a significant risk of recurrence of severe disease in a sibling. Preimplantation genetic testing has been performed in some cases; it is available in some countries and should be included in the discussion of reproductive choices with patients with ADPKD [8,39].

Quelle: UpToDate 2016

Danke
Für die
Aufmerksamkeit !!

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