Corneal dystrophies (CD): Misnomers and clinical classification

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„Was ist das Schwerste von allem? Was dir das Leichteste dünkt: mit den Augen zu sehen, was vor den Augen dir liegt.“

“What's hardest of all? It's what you think is easiest: to see with your eyes what's before your eyes.”
According to this wisdom from Goethe the ophthalmologist, too always has a differentialdiagnostic challenge of an ophthalmological disease.

This is also true of the various forms of corneal dystrophies. In the last 10 years there are many important and interesting DNA examinations in nearly all forms of corneal dystrophies.

I'll give you 2 examples:

1. There are several reports about many mutations of Lattice corneal dystrophy, type I

2. From Japan we recognize two papers about the homozygote forms of Granular corneal dystrophy, type I and type II
Up till today the clinical classification of the various forms of corneal dystrophies are non-uniform and mistakable.

I'll give you 1 example concerning Reis-Bücklers corneal dystrophy.

In recent years you have been able to see the following synonyms in renowned ophthalmological journals.

All this different terms require not clinical but histological consideration.
Reis-Bücklers CD

Synonyma:
- Superficial granular CD
- Atypical granular CD
- Granular CD, type III
- Anterior limiting membrane dystrophy, type I (ALMD I)
- Corneal dystrophy of Bowman's layer, type I (CDB I)
The next point is, that some misnomers still exist.

The best example is Avellino CD for Granular CD, type II.

We know, that in Japan the so-called Avellino dystrophy is more frequent than the classical granular dystrophy, type I.
Granular CD, type II
Misnomer: Avellino CD

Why:
- Bücklers (1938)
- Eastern Europe
- Japan
Why does the ophthalmologist need a clear and unmistakable classification of corneal dystrophies?

The ophthalmologist is the first, who examines a new patient with a corneal dystrophy using the slit lamp.

He must therefore have at his disposal a clear and unmistakable nomenclature for the individual corneal dystrophies.

Clinical and DNA examinations of the new patient's family will or will not confirm the clinical diagnosis. Additionally the DNA examinations provide important genetic information.

For example
Meesmann corneal dystrophy (AD, 12q13, Glu 509 Lys)
What clinical criteria are necessary to make a clinical classification of corneal dystrophies?
Clinical classification of CD

1. Opacity pattern
   unique and unmistakable landmark

   Exp.: Honeycomb CD

2. Opacity unit
   unique and unmistakable landmark

   Exp.: Granular CD,
   type 1

3. Eponym classification

   Exp.: Meesmann CD,
   Opacity Pattern: not unique
   Opacity unit: solitary microcysts
   - unique, but mistakenable
   „Epithelial solitary microcysts CD“
Briefly we'll give some comments and proposals for a clinical classification of corneal dystrophies. Of course because of the limited time some rare forms are lacking.
1. Epithelial basement membrane CD (AD, ?)
   (= histological term)

Syn.:  - Map-Dot-Dystrophy
       (= incomplete)

       - Map-Dot-Fingerprint-Cyst CD
       (= complete, but too long)

   “Cogan-Bron CD”
2. Meesmann CD  (AD, KRT3 gene, 12q13, Glu 509 Lys)
(AD, KRT12 gene, 17q12, 6 mutations)

Syn.:  Juvenile epithelial dystrophy
       (=mistakable)

       “Epithelial solitary microcysts CD”
3. Lisch CD (XD, Xp 22.3)

Syn.: Band-shaped whorled microcystic CD
(= mistakable)

“Epithelial crowded microcysts CD”
4. Granular CD, type I a

(AD, BIGH3 gene, 5qB1, Arg 555 Trp)
(= heterozygote type)
5. Granular CD, type I b (AD, BIGH3 gene, 5q31, Arg 555 Trp) (= homozygote type)

“Placoid type of CD”
6. Granular CD, type II a
(AD, BIGH3 gene, 5q31, Arg 124 His (= heterozygote type)

Syn.: Avellino CD (=mistakable)

Maybe a better term: “Star-ring CD”
7. Granular CD, type II b (AD, BIGH3 gene, 5q31, Arg 124 His) (= homozygote type)

JAPAN

“Confluent granules”
“Reticular gray-white diffuse opacity”
8. Reis-Bücklers CD (AD, BIGH3 gene, 5q31, Arg 124 Leu)
   (AD, BIGH3 gene, 5q31, Arg 555 Gln)

Syn.: Granular CD, type III
   Superficial granular CD
   Anterior limiting membrane dystrophy, type I (ALMD I)
   Corneal dystrophy of Bowman`s layer, type I (CDB I)

All terms are mistakable.

“Geographic - like CD”
9. Honeycomb CD (AD, BIGH3 gene, 5q31, Arg 555 Gln)  
(AD, BIGH3 gene, 5q31, Arg 124 Leu)

Syn.:  Thiel-Behnke CD  
       Anterior limiting membrane dystrophy, type II (ALMD II)  
       Corneal dystrophy of Bowman's layer, type II (CDB II)

Honeycomb = unique and unmistakable
10. Lattice CD, type I (AD, BL GH3, gene, 5q31, Arg 124 Cys and 6 other mutations)

Recently we found out a new mutation: Leu 509 Pro

Opacity pattern: paracentral lattice lines
11. Lattice CD, type II
Meretoja-Syndrom = is not a CD!
12. Lattice CD, type III (AR, ?)

Syn.: Hida CD

Opacity pattern:
  central and paracentral lattice lines
  = unique, but maybe mistakenable

“Lattice CD, type Hida”
13. Lattice CD, type IIIa (AD, BIGH3 gene, 5q31, Pro 501 Thr Ala 622 His His 626 Ala Ser 538 Cys)

Opacity pattern: central and paracentral lattice lines

“Lattice CD, type II”
14. Macular CD (AR, 16q21, ?)

3 different types concerning reactions to antigenic Keratan sulfate. Until now no phenotypical differences.

Opacity pattern: flecks and diffuse opacities in the whole stroma.
15. Schnyder CD
(AD, 1p34.1 - p 36, ?)

Syn.: Central crystalline dystrophy
(= mistakable)

2 Types: Cristalline type
non cristalline type (rare)
“Comma- shaped crystals CD”
16. FUCHS CD (AD, 1p 34.3. - p 3 ,COL8A2 gene)
Syn.: Endo-epithelial CD
Opacity pattern: Cornea guttata
Stromal oedema
Epithelial bullae
17. Congenital endothelial CD
   (AR, 20 tel, ?)
   (AD, 20 p, ?)

Posterior polymorphous CD
   (AD, 20q11, VSX1 gene)
Syn.: Schlichting CD

New clinical and genetical examination.
In one big family we found out all known clinical symptoms of Congenital endothelial CD and Posterior polymorphous CD!
We have summarized our first draft concerning an incomplete clinical classification of corneal dystrophies
### Clinical classification of CD (incomplete)

1. Cogan-Bron CD  
   “Map-Dot-Fingerprint-Cysts CD”

2. Meesmann CD  
   “Epithelial solitary microcysts CD”

3. Lisch CD  
   “Epithelial crowded microcysts CD”

4. Granular CD, type I a

5. Granular CD, type I b

6. Granular CD, type II a  
   “Star-ring CD”

7. Granular CD, type II b  
   a = heterozygote  
   b = homozygote

8. Reis-Bücklers CD  
   “Geographic-like CD”

9. Honeycomb CD

10. Lattice CD, type I (AD)

11. Lattice CD, type II (AD)

12. Lattice CD, type Hida (AR)

13. Macular CD

14. Schnyder CD  
   “Comma-shaped cristals CD”

15. Fuchs CD

16. Congenital endothelial CD
We propose to constitute an international commission under the auspices of ISGED to elaborate an international accepted clinical classification of corneal dystrophies.

We propose the following colleagues alphabetically:
ISGED

COMMISSION for a clinical classification of corneal dystrophies

Dr. Bron (Oxford)          Dr. Munier (Lausanne)
Dr. Dighiero (Paris)        Dr. Okada (Osaka)
Dr. Héon (Toronto)          Dr. Stone (Iowa)
Dr. Klintworth (Durham)     Dr. Traboulsi (Cleveland)
Dr. Mashima (Tokyo)
Every 2 years the commission has to update the classification of corneal dystrophies.

It would be desirable if finally in the future in the renowned international ophthalmologic and genetic journals a uniform and unmistakable nomenclature for corneal dystrophies could be used incorporating the proposal of the ISGED commission for corneal dystrophies classification.