Is Genetic the new Black ?

22 YEARS OLD KURDISH WOMAN
+CONSANGUINITY

- Consults for alopecia areata and hyperkeratosis
- Lab tests show hypogammaglobulinemia
- IgG 4.03g/L <8
- IgA 0.3g/L <0.9
- IgM 0.29g/L <0.6

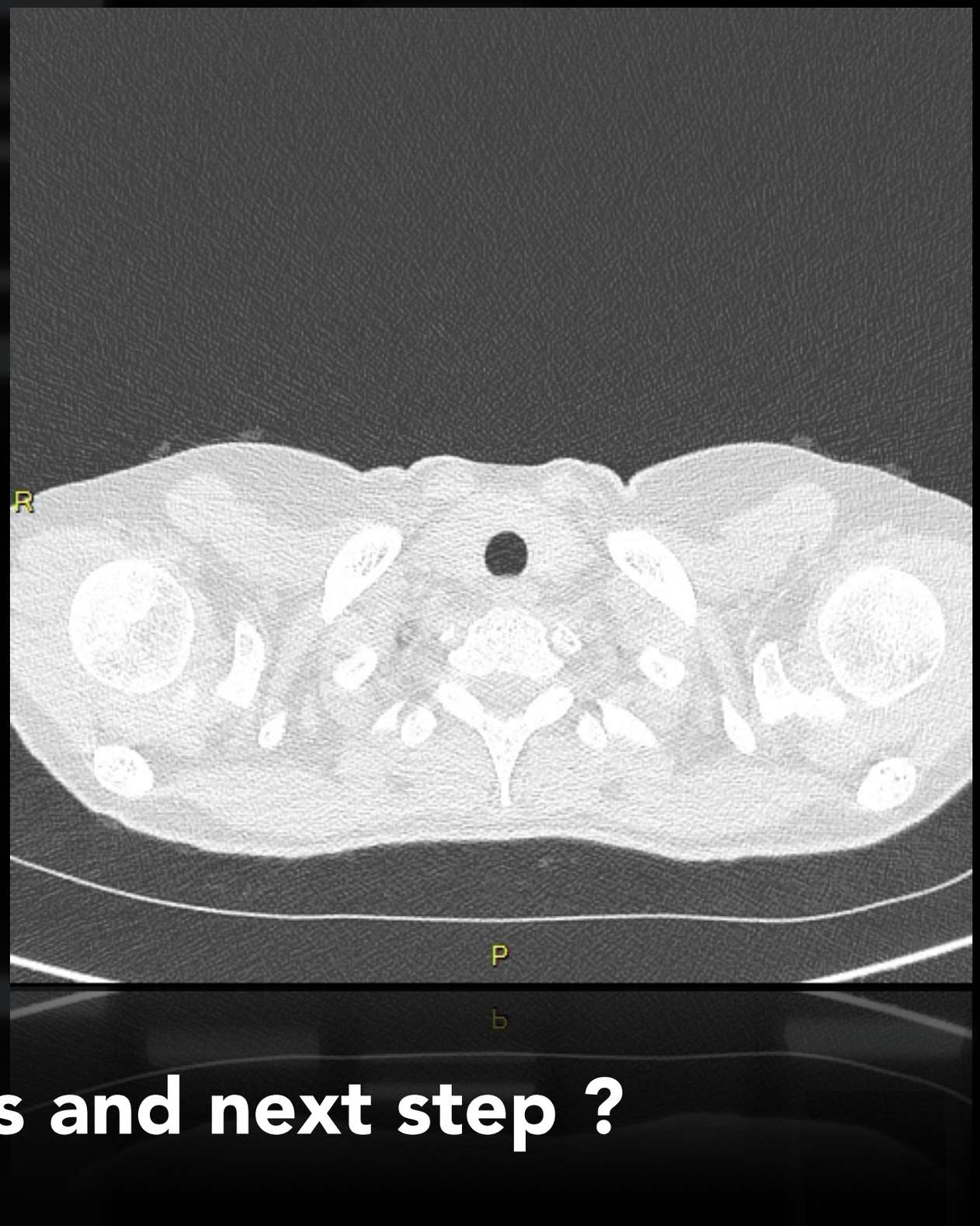
Hypothesis and next steps ?

CVID

- No monoclonal gammapathy, nephrotic syndrome or diarrhea
- Immunophenotyping :
  - Global T lymphopenia
  - Low B cells count & No Memory Switched B cells
- Skin biopsy : Cutaneous T lymphoma

NEW INFORMATIONS

- Microcephaly
- Arched Palate
- Radio-induced genomic instability



Hypothesis and next step ?

GENETIC STUDIES

- **Telomeres length study : <1% percentile**
- **Telomerase proteins' genes study**

NEW DKC1 MUTATION

All other telomerase and DNA repair genes are normal
(exome wide sequencing)

TELOMERASE ACTION

OK ! BUT IT DOESN'T WORK !

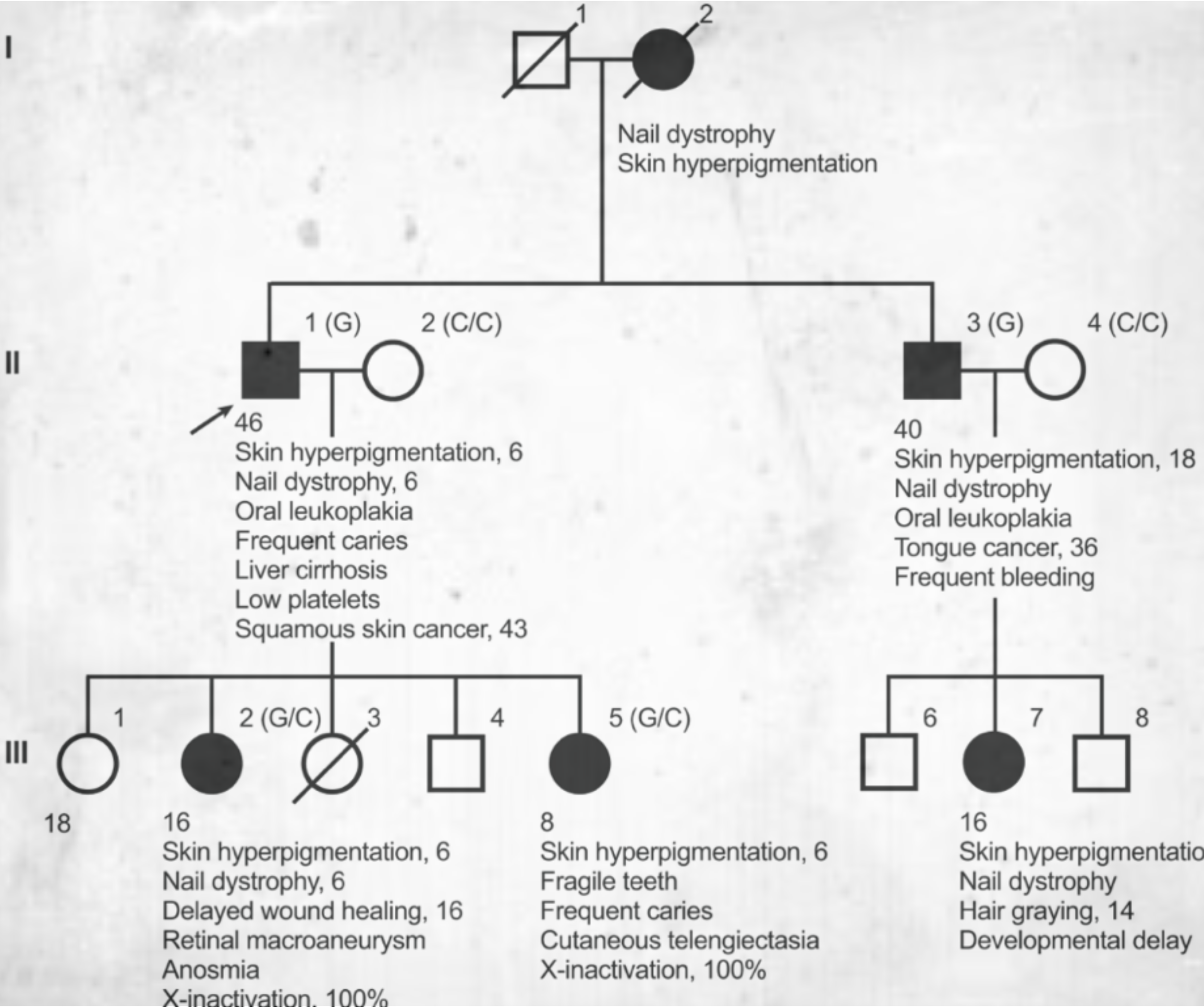
DKC1 is on the X chromosome, she's a woman

Hum Mutat. 2013 November ; 34(11)

Telomere phenotypes in females with heterozygous mutations in the dyskeratosis congenita 1 *(DKC1)* gene

Jonathan K. Alder[1], Erin M. Parry[1], Srinivasan Yegnasubramanian[1], Christa L. Wagner[1],

The X-inactivation skewing theory


I
1
2
Nail dystrophy
Skin hyperpigmentation
II
1 (G)
2 (C/C)
3 (G)
4 (C/C)
46
Skin hyperpigmentation, 6
Nail dystrophy, 6
Oral leukoplakia
Frequent caries
Liver cirrhosis
Low platelets
Squamous skin cancer, 43
40
Skin hyperpigmentation, 18
Nail dystrophy
Oral leukoplakia
Tongue cancer, 36
Frequent bleeding
III
1
2 (G/C)
3
4
5 (G/C)
6
7
8
18
16
Skin hyperpigmentation, 6
Nail dystrophy, 6
Delayed wound healing, 16
Retinal macroaneurysm
Anosmia
X-inactivation, 100%
8
Skin hyperpigmentation, 6
Fragile teeth
Frequent caries
Cutaneous telengiectasia
X-inactivation, 100%
16
Skin hyperpigmentation, 7
Nail dystrophy
Hair graying, 14
Developmental delay

THE CLINICAL PICTURE WORSENS

- Warts and bacterial infections
- Diffuse granulomatosis
- Hepato-Splenomegaly and icteric cholestasis
- Diffuse T clone
- Pulmonary insuffiency
- Tubular acidosis with chronic kidney failure ...

CONCLUSION

- New X-linked Genetic disease ?
- DKC1 mutation… but
  - Neither Dyskeratosis Congenita
  - Nor Hoyeraal Hreidarsson
- Familial segregation & functional tests … have to be done

TAKE HOME MESSAGES

- Women may have some features of X-linked diseases
- Telomeropathies are
  - Are responsible for many pulmonary fibrosis
    - Prevent DNA from reparation —> genomic instability
- DICV causes
  - Auto-immune diseases
  - Lymphoproliferation and cancers
  - Infections

Genetics is neither black nor white
It's just complicated
but it's fun

Thank you

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HOYERAAL HREIDARSSON

- Bone marrow failure
- Intrauterine growth retardation
- Microcephaly
- Immunodeficiency
- Cerebellar atrophy

DYSKERATOSIS CONGENITA

- skin hyper pigmentation
- nail dystrophy
- oral leukoplasia
- aplastic anemia
- +/- lung disease, cirrhosis, other bone marrow discrasias