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Factors Contributing to Longevity in Adults with FA

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Fanconi Anemia Research Fund's
22nd Annual Family Meeting

June 28 – July 2, 2013
Camp Sunshine, Casco, Maine

How old do men become?

Maximum lifespan:
The oldest human

Jeanne Calment
(died at 122)

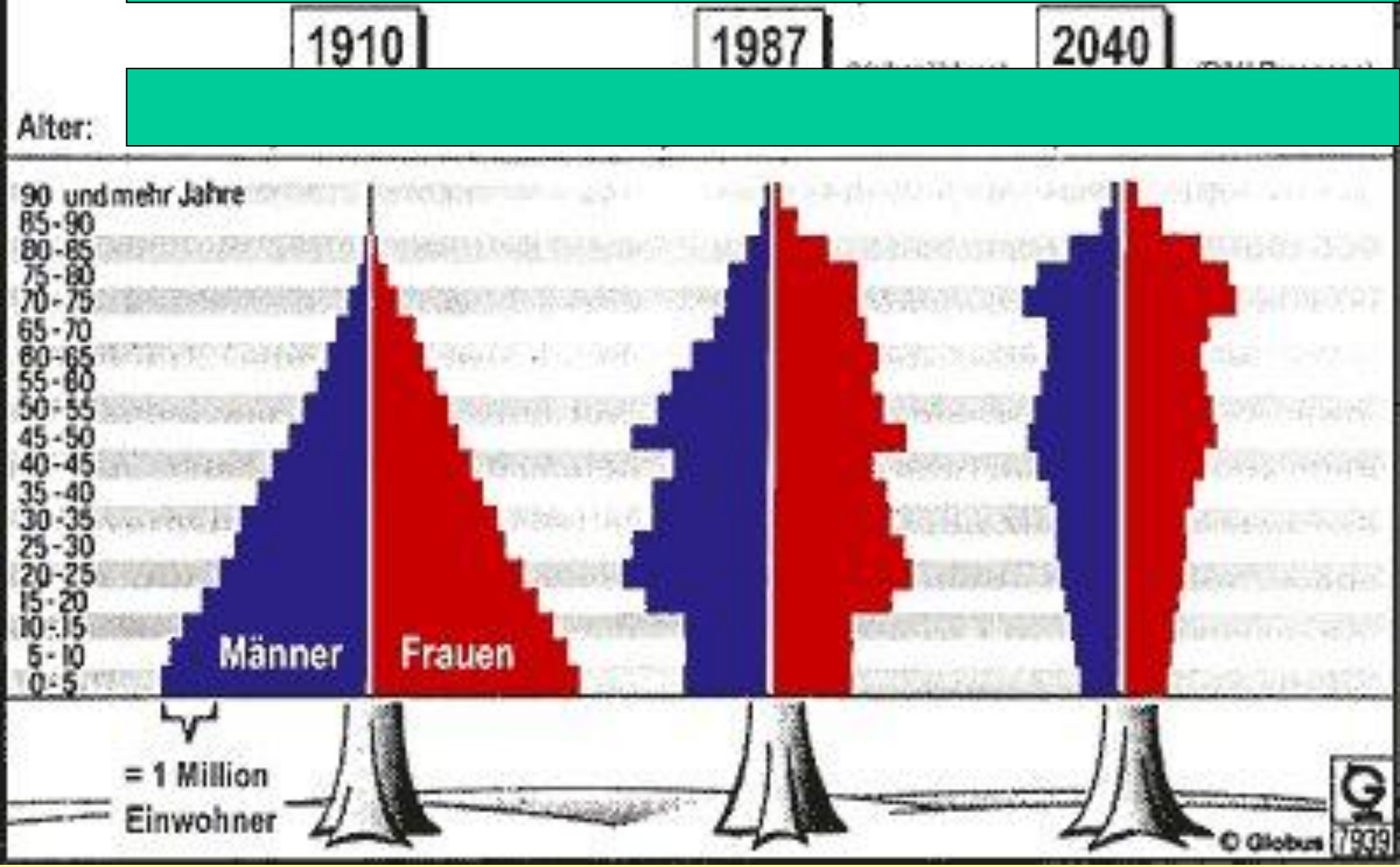
Three Fs:

Female,
French,
Frugal (1 kid)

Early demise of husband,
Early to bed,
Glass of Port per day,
Crossword puzzle per day

Average lifespan:

Age structure in Germany

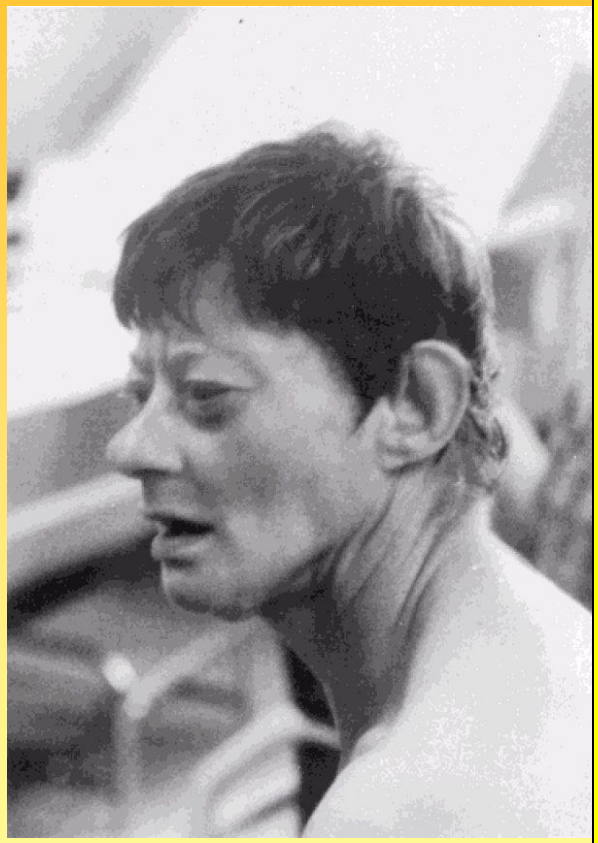


How old do individuals with FA become?

In memoriam

Paula Guidara Ceresa	56 y
Richard Briga	53 y
Glenn Russo	51 y
Jerry Gorga	49 y
Forrest Engel	49 y
Evelyn (`Lynn`) Welfare Mendenhall	49 y

The oldest FA person and her brother



Dysmorphology not typical for FA

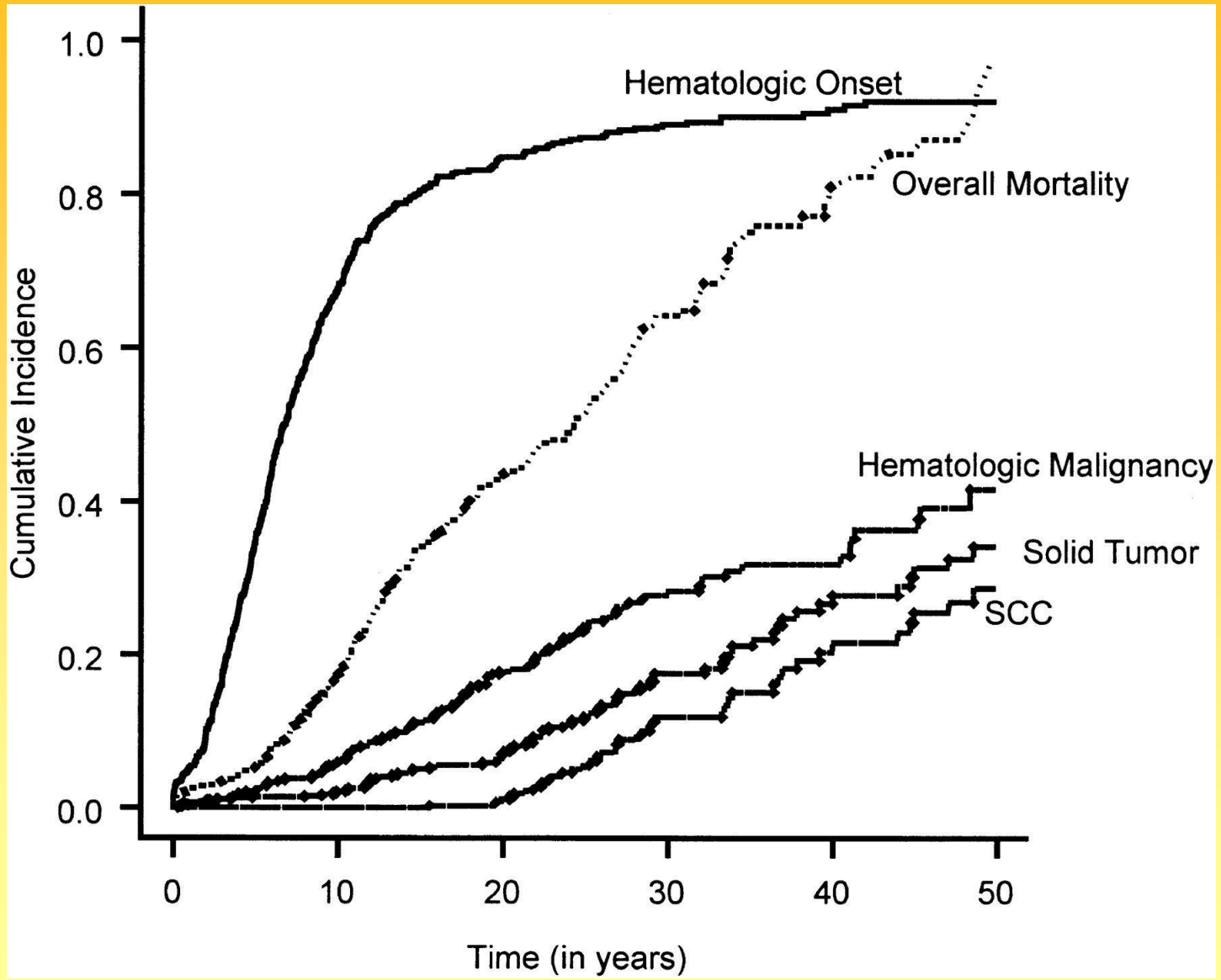
Unknown Syndrome?

died at 67, with no sign of malignancies

Kwee et al, 1997

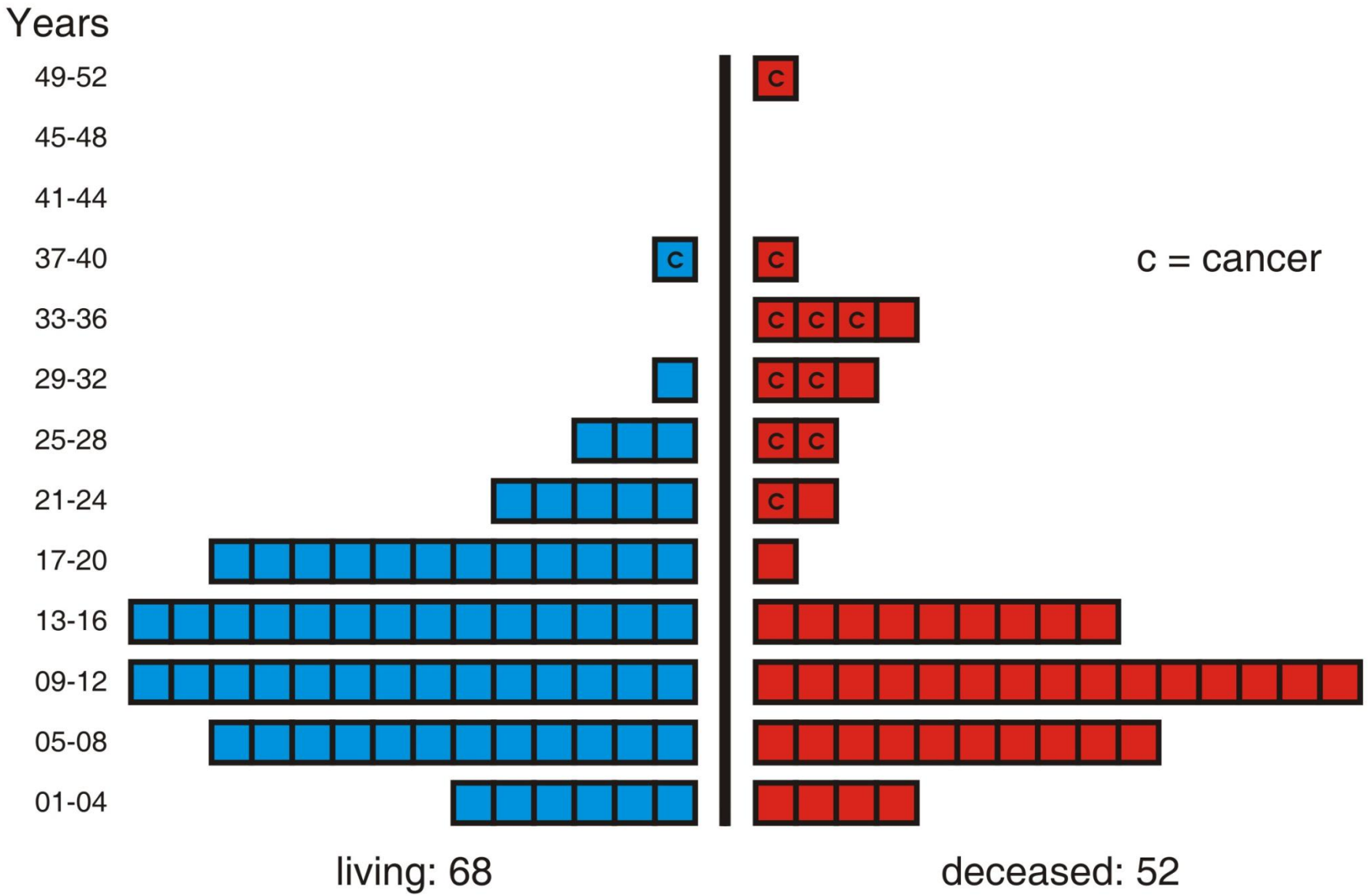
Why does a greater proportion of FA patients become less old than controls without FA?

Risc curves in FA patients



Kutler et al, 2003

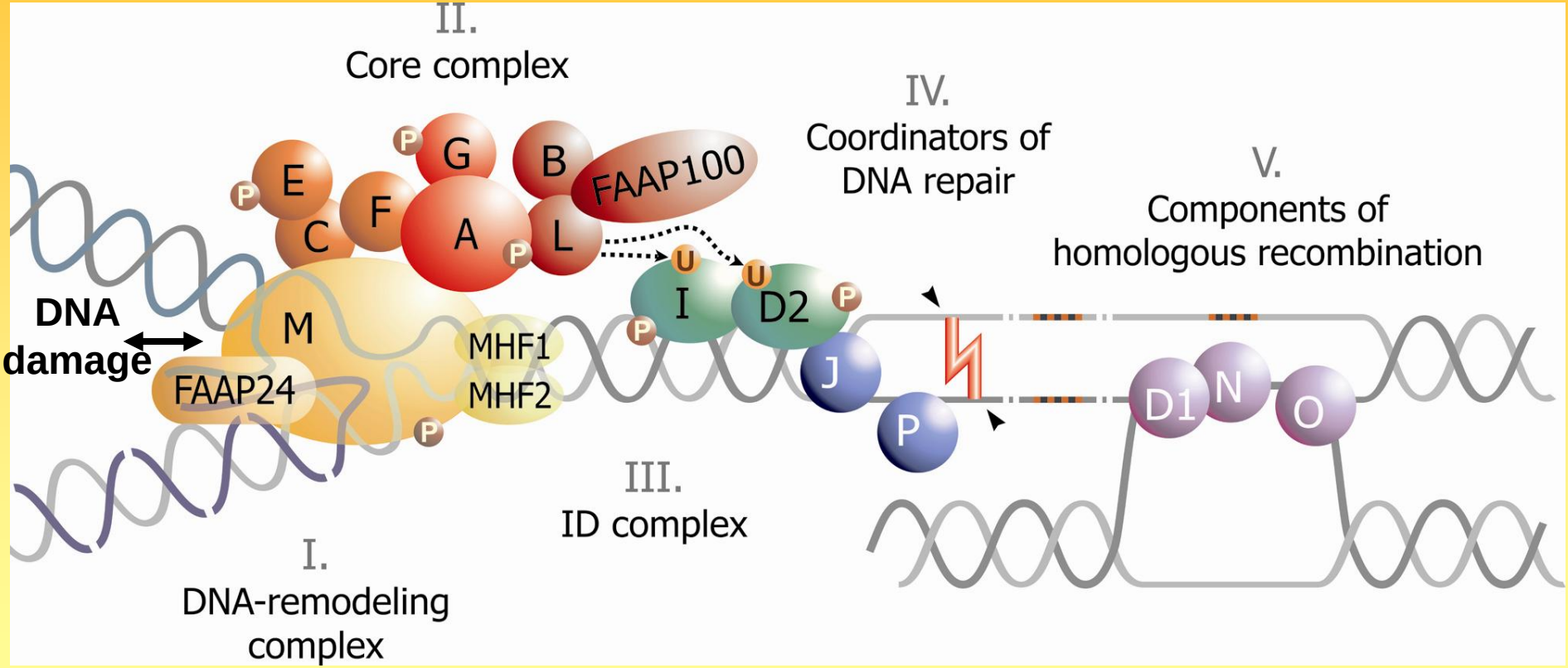
Age distribution of German FA patients (2004)



Courtesy of Ralf Dietrich

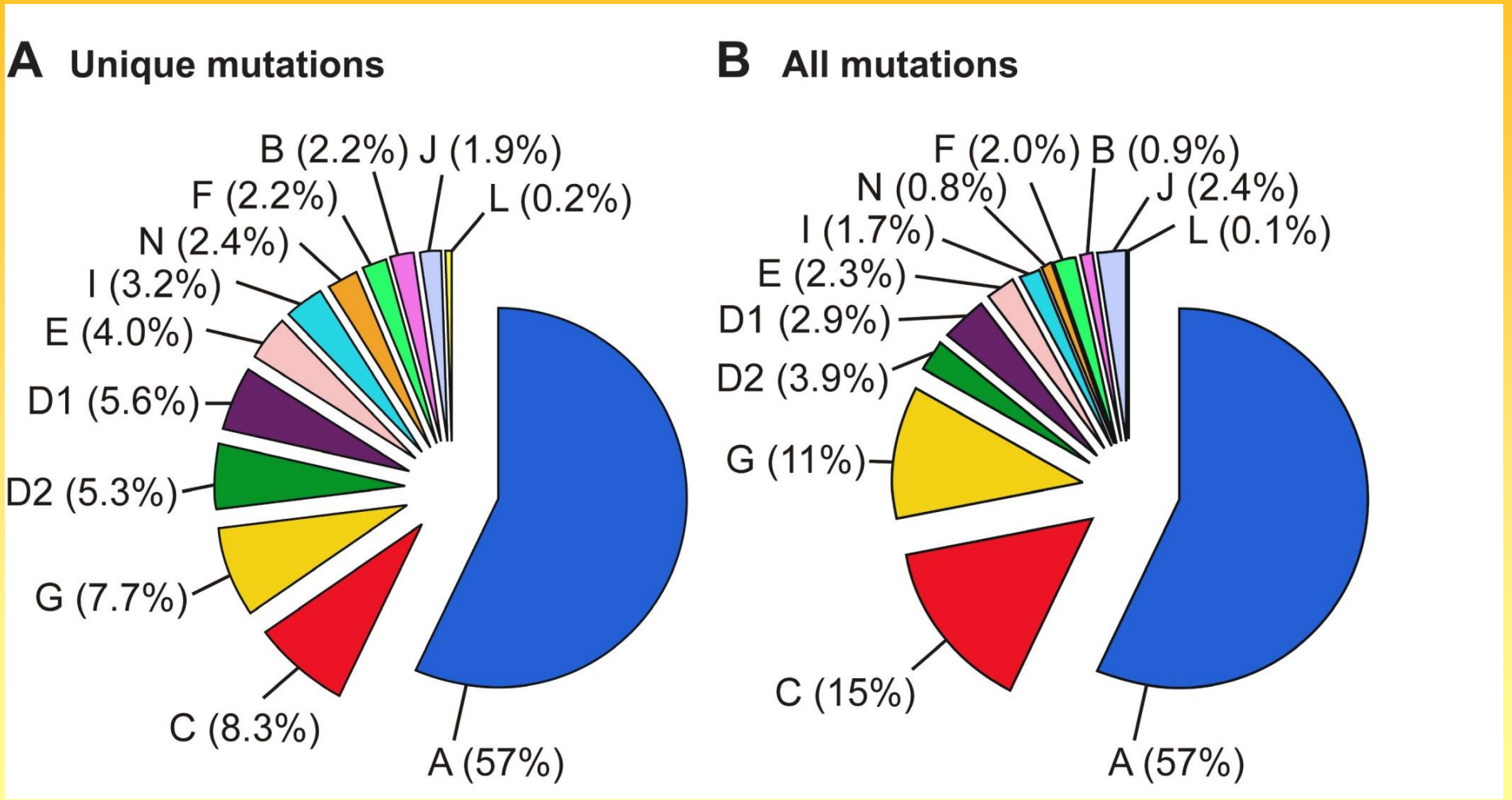
Fundamentals to understand the present study

The FA pathway



Schindler, Endt and Neveling, 2011

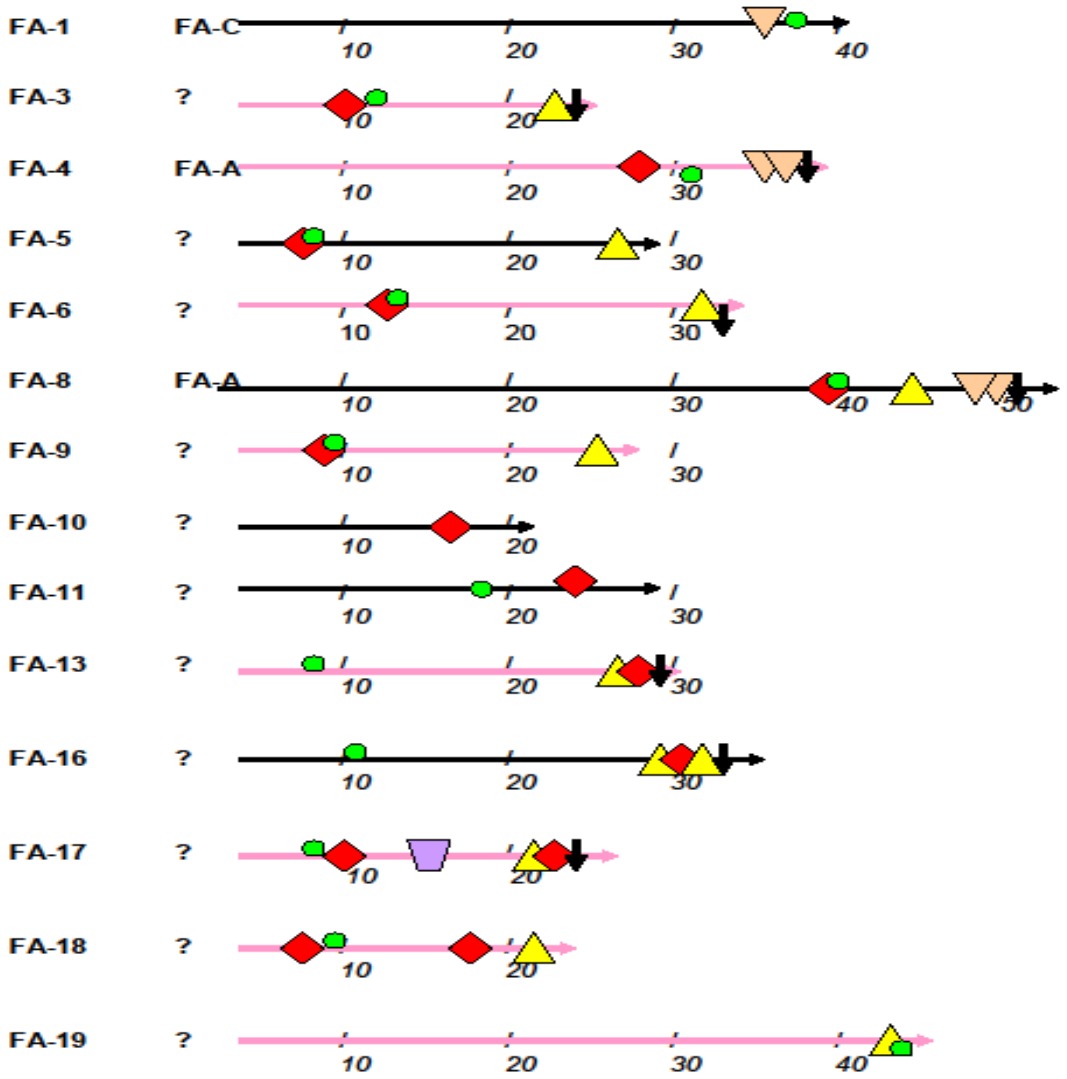
Distribution of mutations in the FA genes

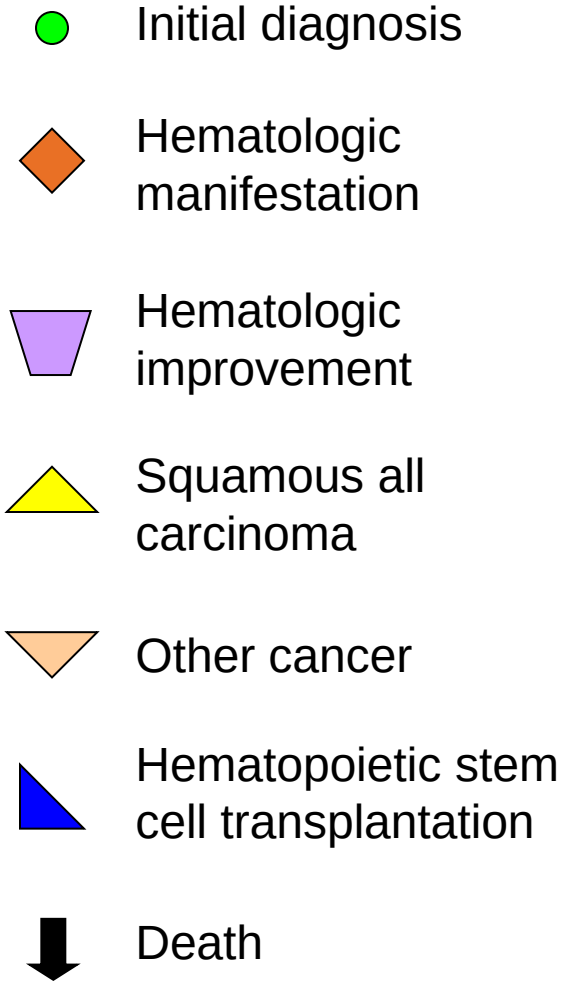


Source: Fanconi Anemia Mutation Database (Rockefeller/Leiden),1,968 mutations (Dec 15, 2008)

Neveling et al, 2009

Longterm-surviving FA patients (≥20 y) - Way of analysis





Local observations (*n* = 92) and review of the literature (*n* = 42).
Not all data were available for all patients.

Hohnbaum, 2009

Study design

Data source: Evaluation of out-patient histories and of published cases

Study type: Retrospective cohort study with open time frame

Way of analysis: Intra- and inter-cohort comparisons (other cohorts: all FA patients, general population)

Problems:
- Limited number of patients in old FA cohort
- Potential ascertainment biases
- Acquisition interval reaching far back in the past
- Factors (therapies) changed during the period surveyed
- General problems common to cohort studies

OUTLINE

Longevity factors connected to the genetic basis of FA

Longevity factors indirectly influencing the clinical course of FA

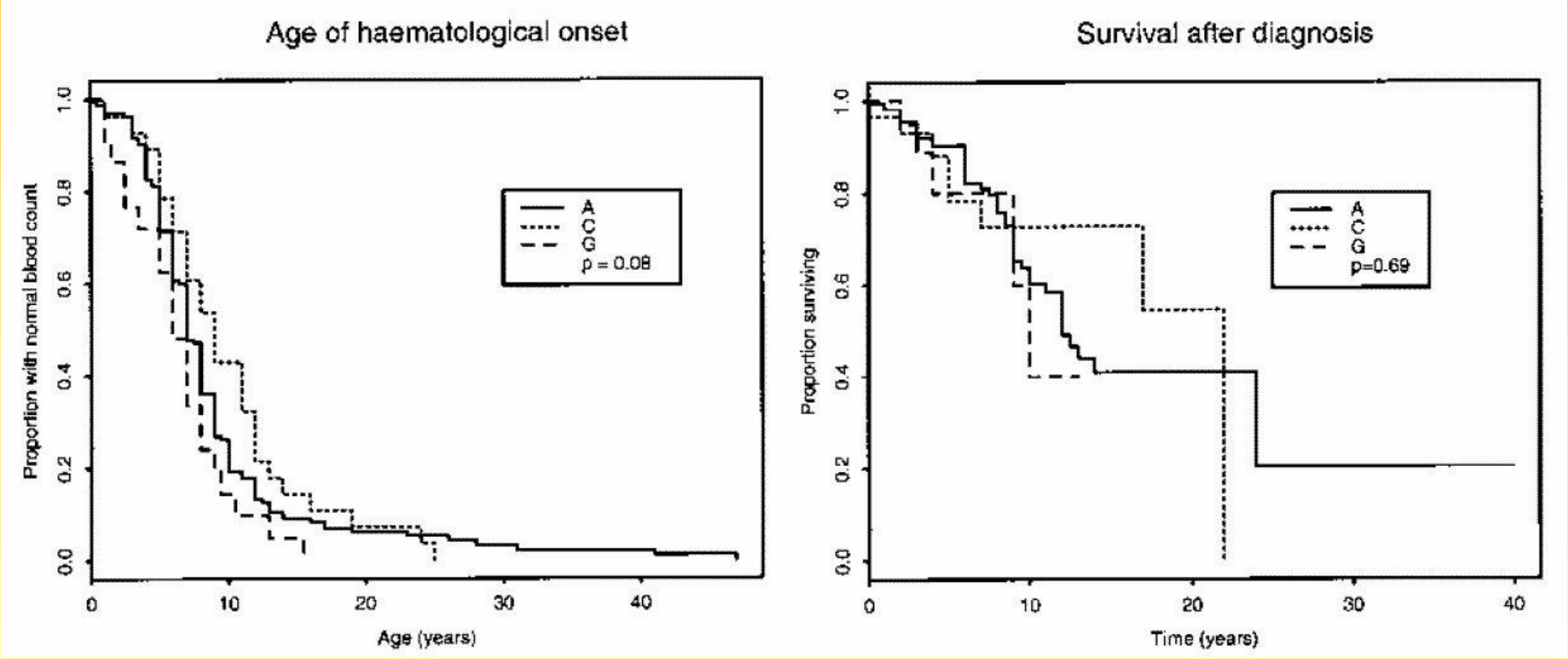
Longevity factors relating to medical intervention and prevention in FA

(Potential) longevity factors related to experimental therapies in FA

Longevity factors connected to the genetic basis of FA

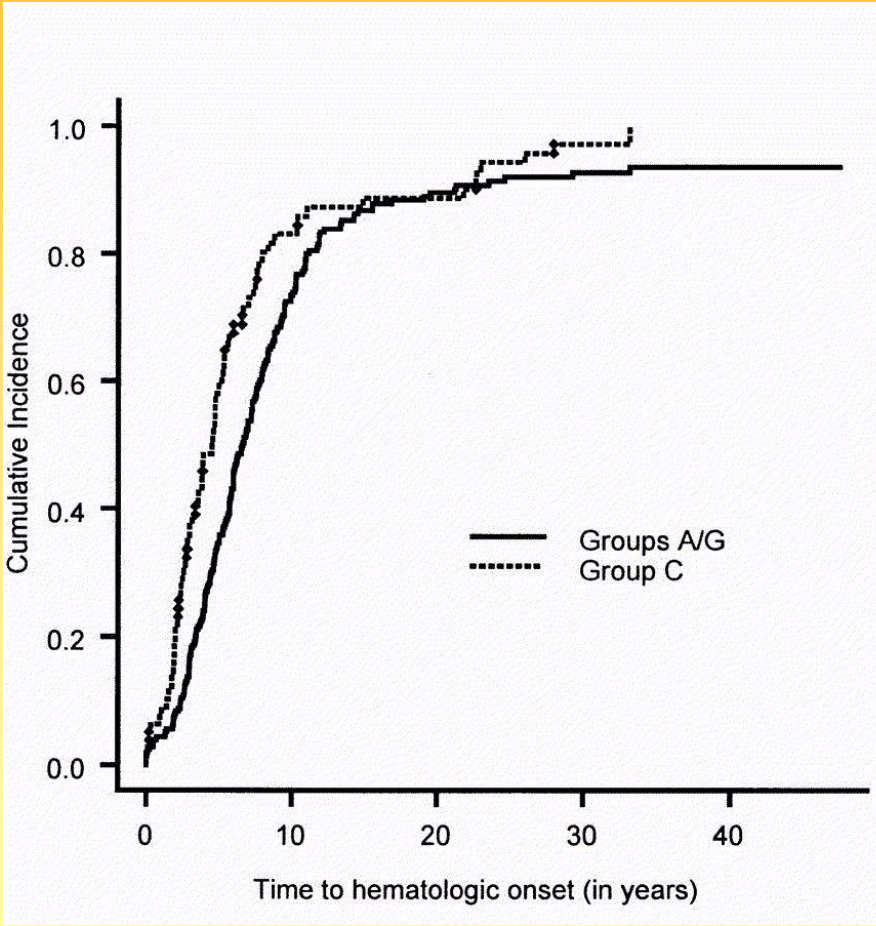
- **Complementation group**
- Type of mutation
- Revertant mosaicism

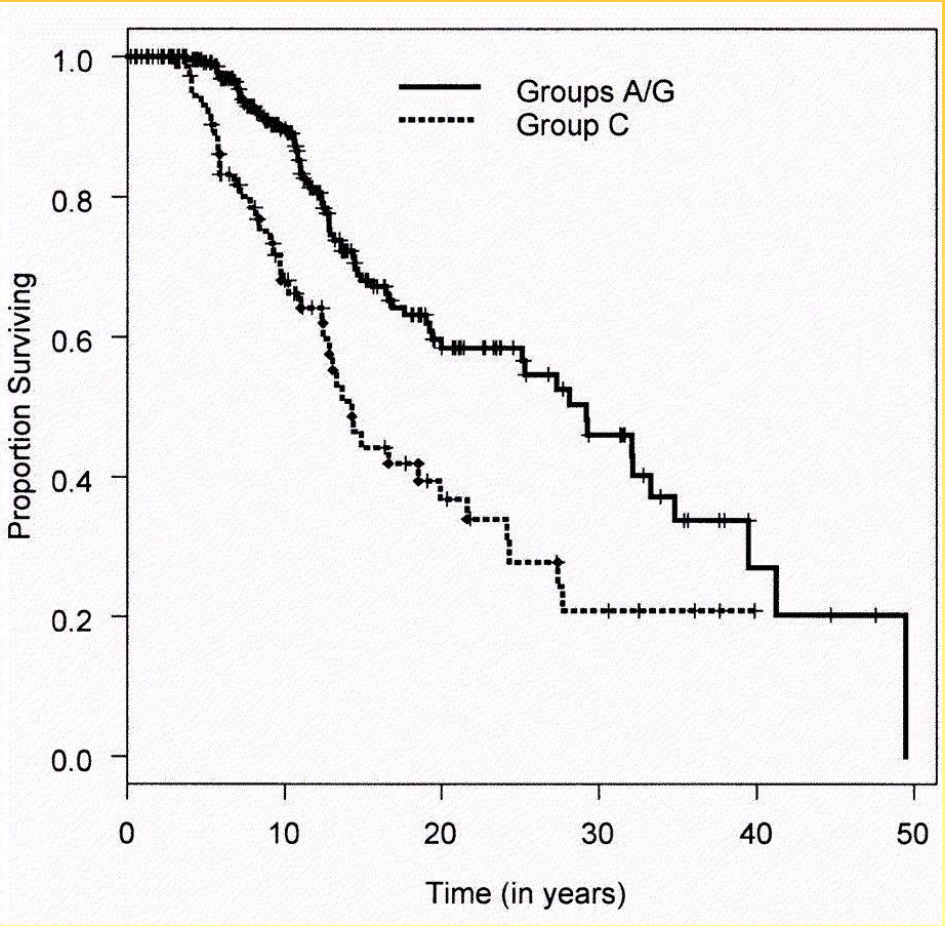
Complementation group FA-C was suggested statistically to take a milder course compared to A and G A European study



Faivre et al, 2000

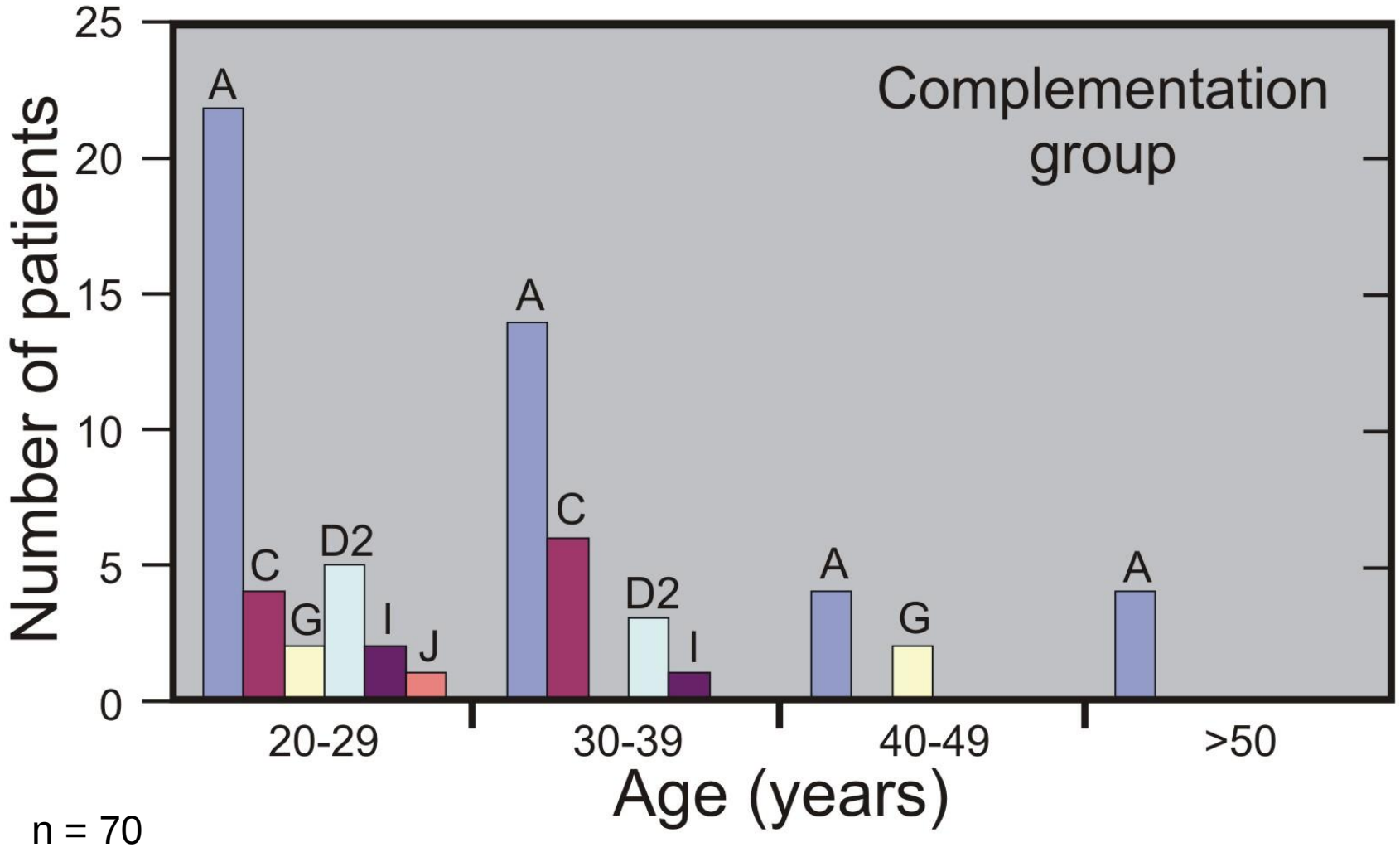
FA patients of group C appeared statistically more severely affected than those of group A or G
An American study





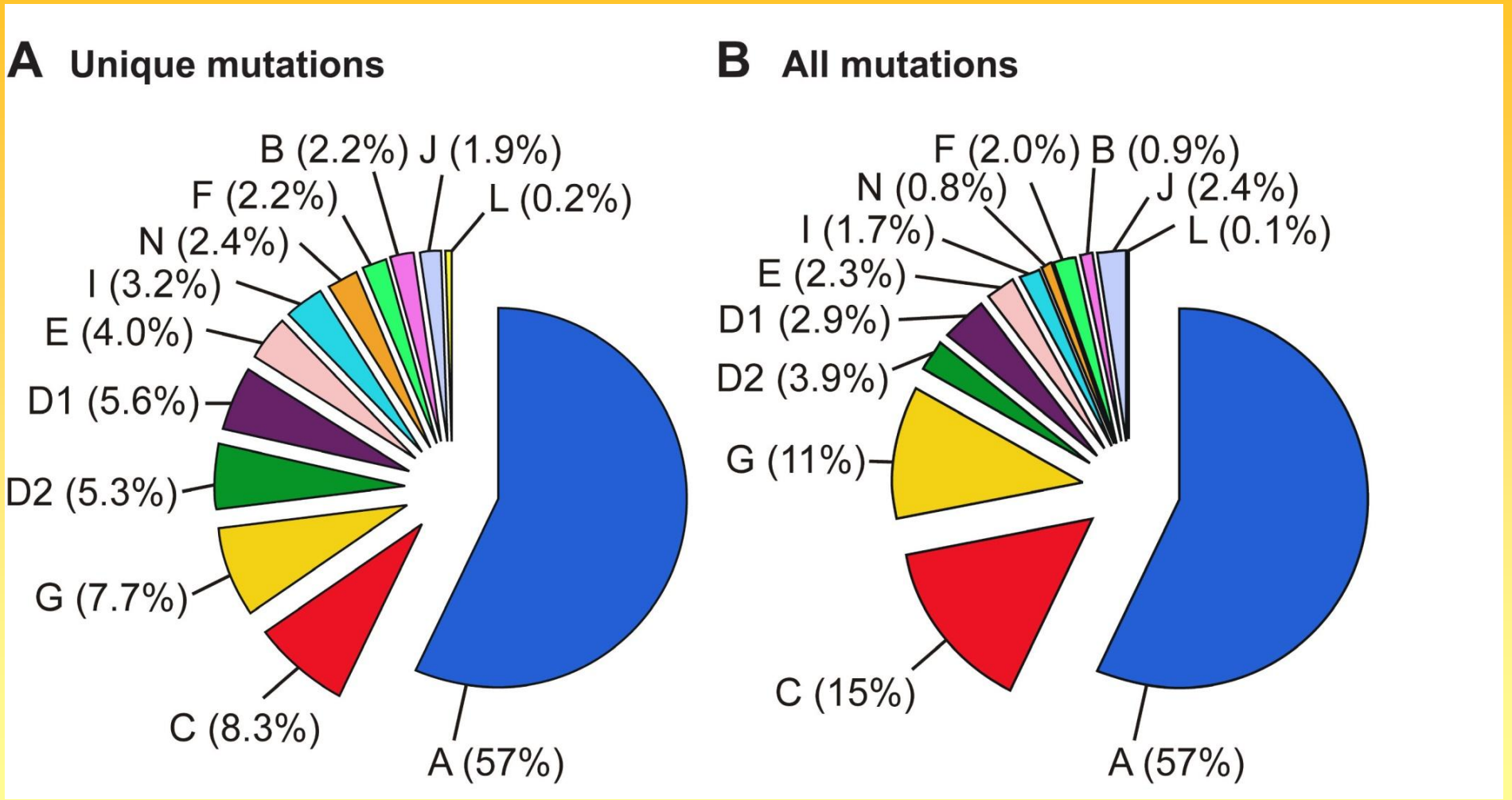
Kutler et al, 2003

Among FA patients 20 y and older, the proportion of subtype A increases with age



Neveling et al, 2009

Distribution of mutations in the FA genes



Source: Fanconi Anemia Mutation Database (Rockefeller/Leiden),1,968 mutations (Dec 15, 2008)

Neveling et al, 2009

Conclusion 1

The role for complementation group

•Complementation groups corresponding to defects in genes encoding members of the FA core complex statistically define average severity of disease parameters with the manifestations varying individually.

•Complementation group A represents myriad private mutations in the *FANCA* gene with some probability for them to be mild (but there are others, too).

•Presumably for that reason, in addition to complementation group A being most common, FA-A patients are most frequent among long-lived (individually and statistically).

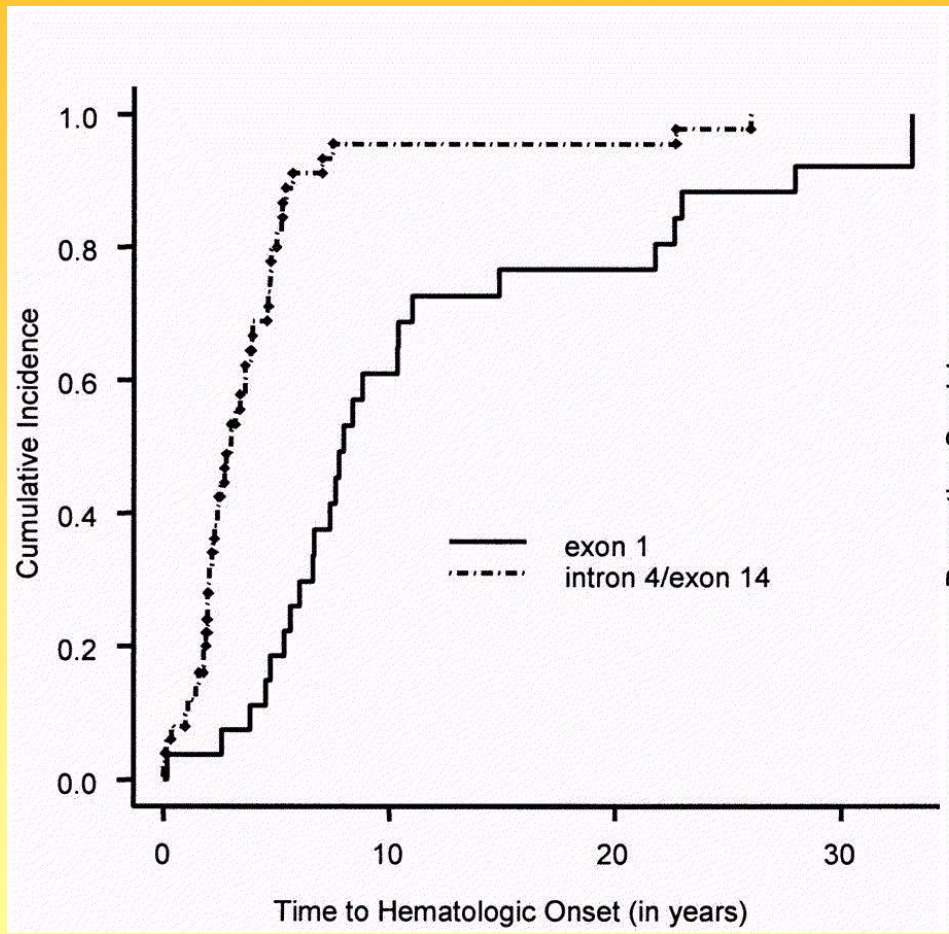
Longevity factors connected to the genetic basis of FA

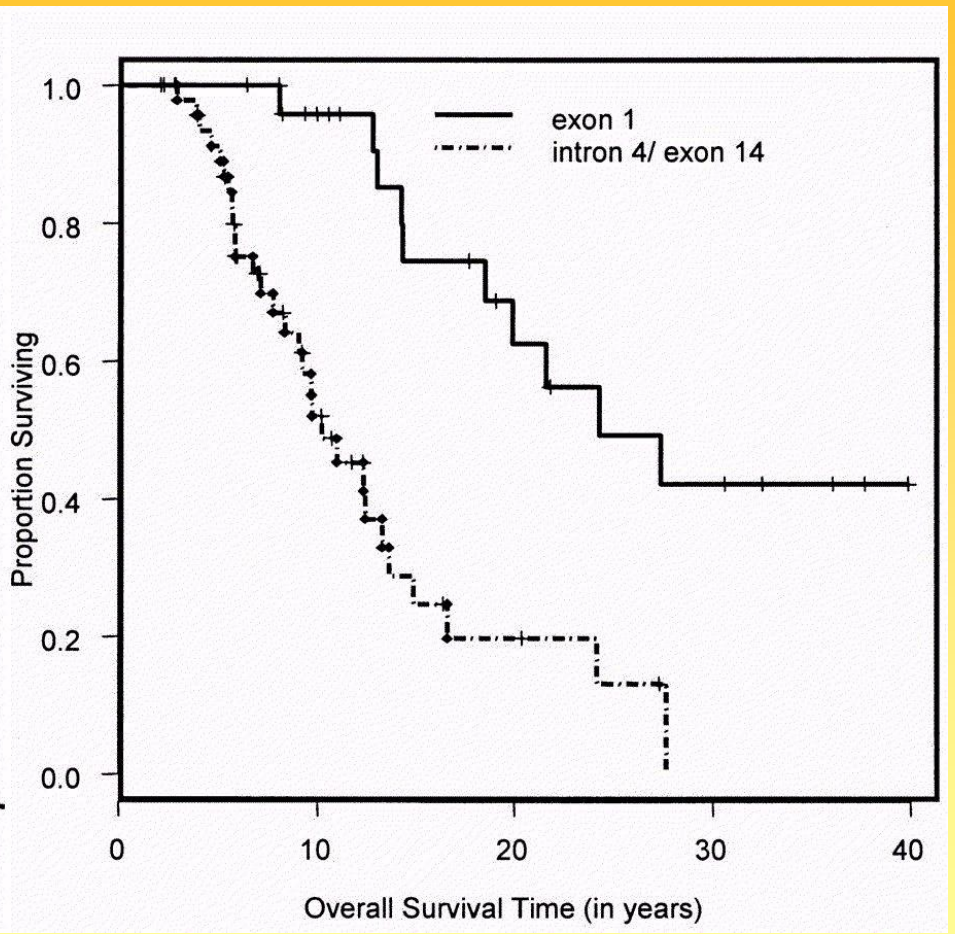
- Complementation group
- **Type of mutation**

`null` mutations (no functional protein)
`hypomorphic` mutations (residual protein)
`mild` mutations (mild clinical course)

- Revertant mosaicism

Influence of type of mutation (1) – *FANCC*

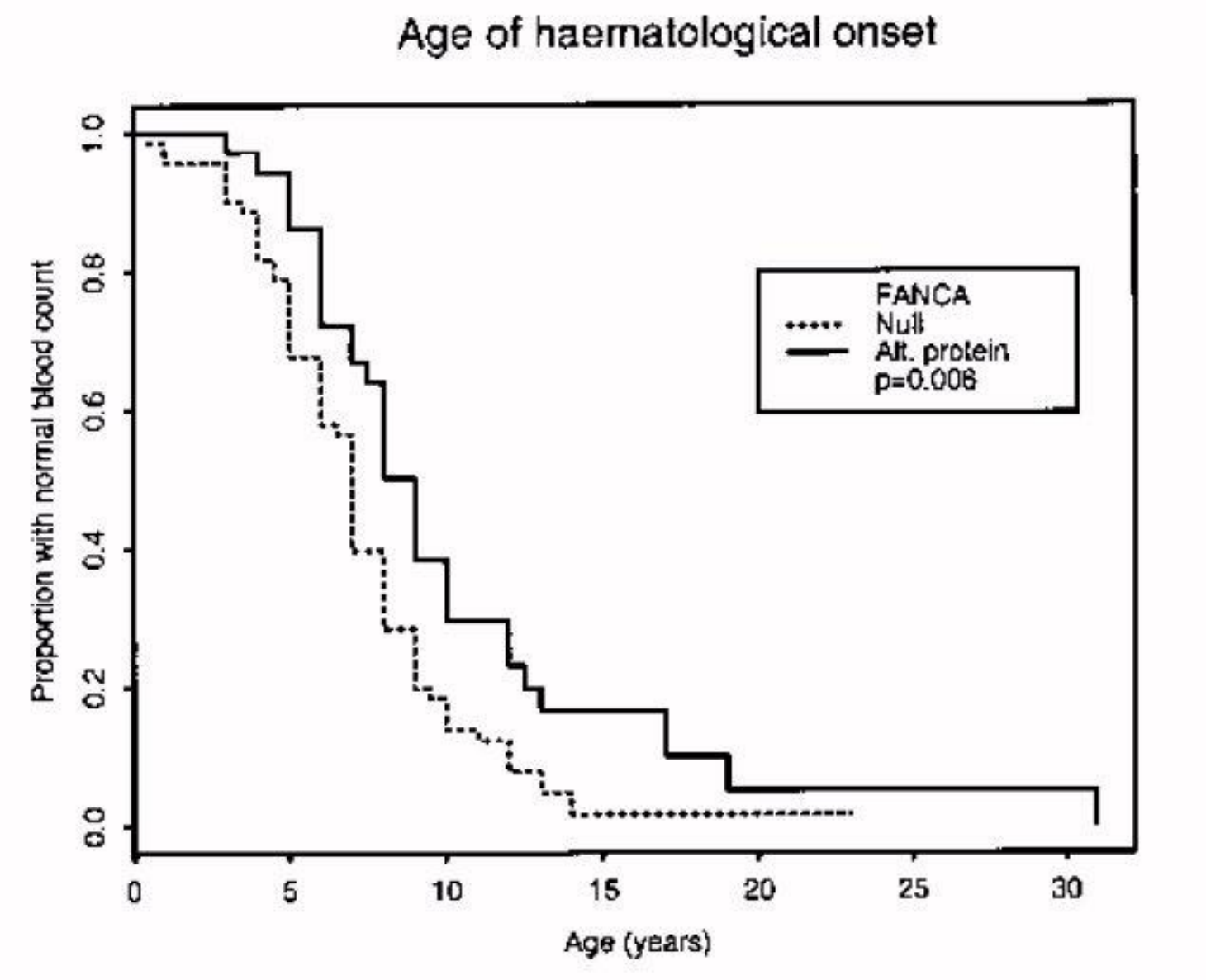




c.67delG (exon 1) vs. c.456+4A>T (intron 4)

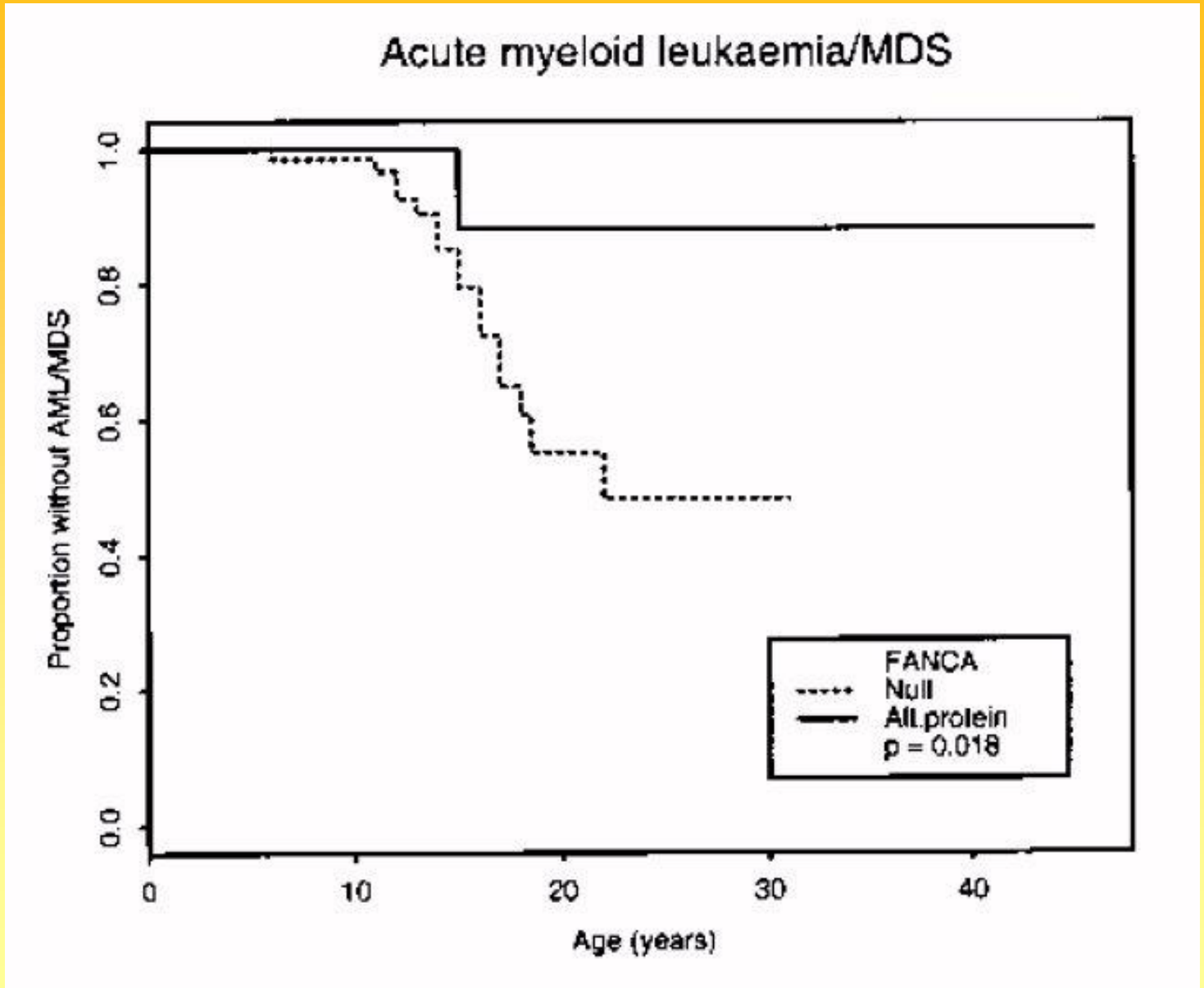
Kutler et al, 2003

Influence of type of mutation (2) – *FANCA*



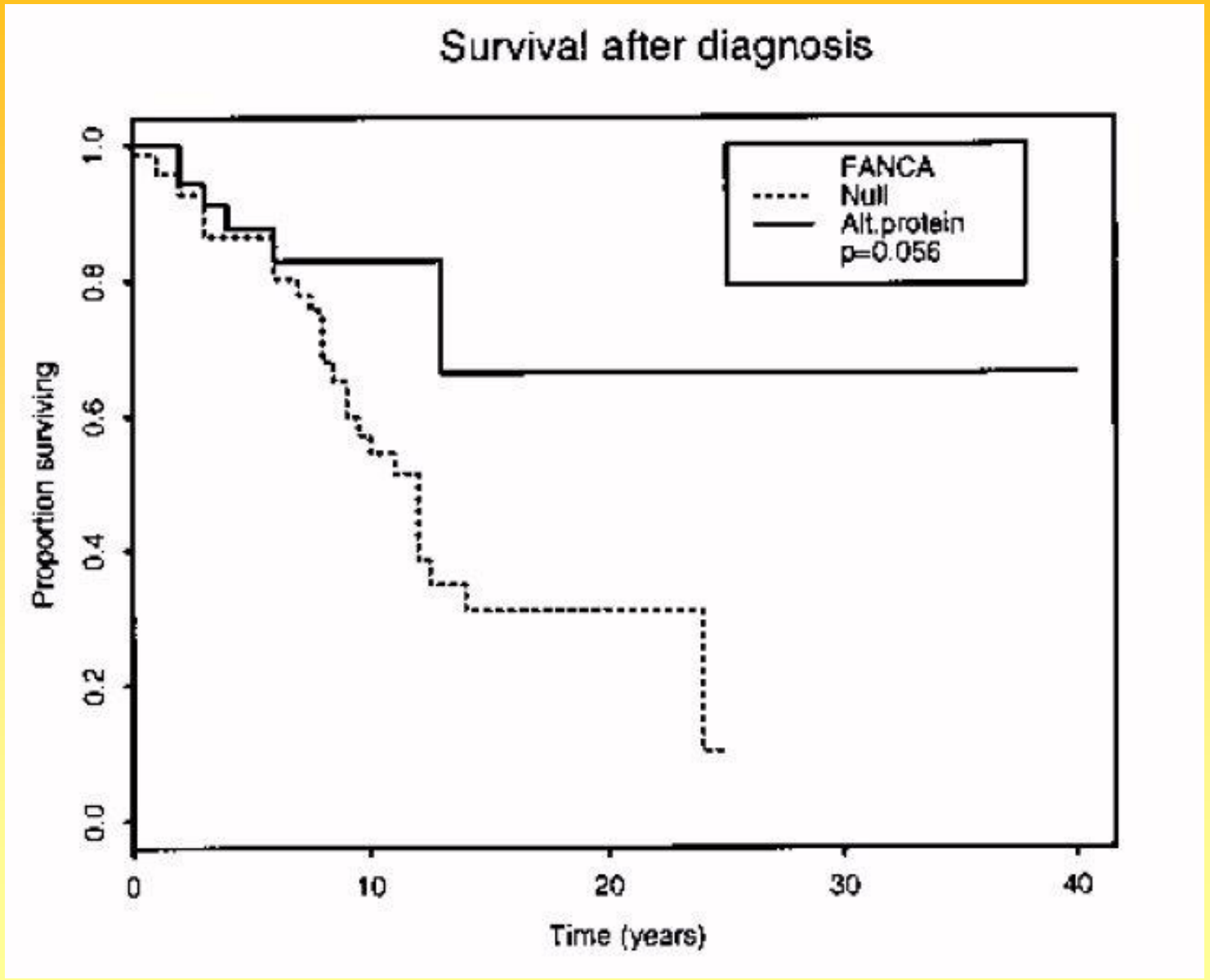
Faivre et al, 2000

Influence of type of mutation (3) – *FANCA*



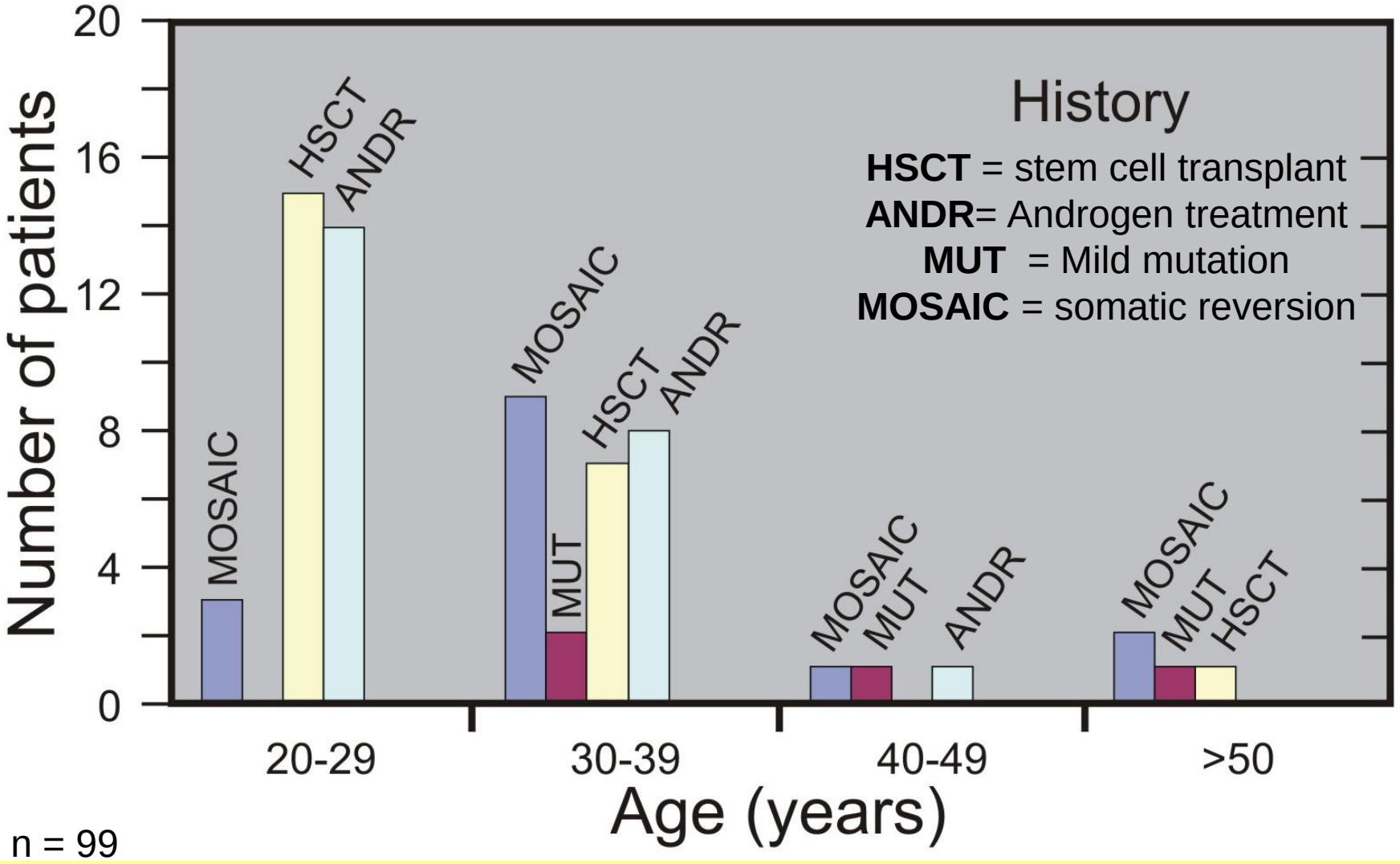
Faivre et al, 2000

Influence of type of mutation (4) – *FANCA*



Faivre et al, 2000

Among FA patients 20 y and older, the proportion of those with mild mutations increases with age



n = 99

Neveling et al, 2009

Conclusion 2

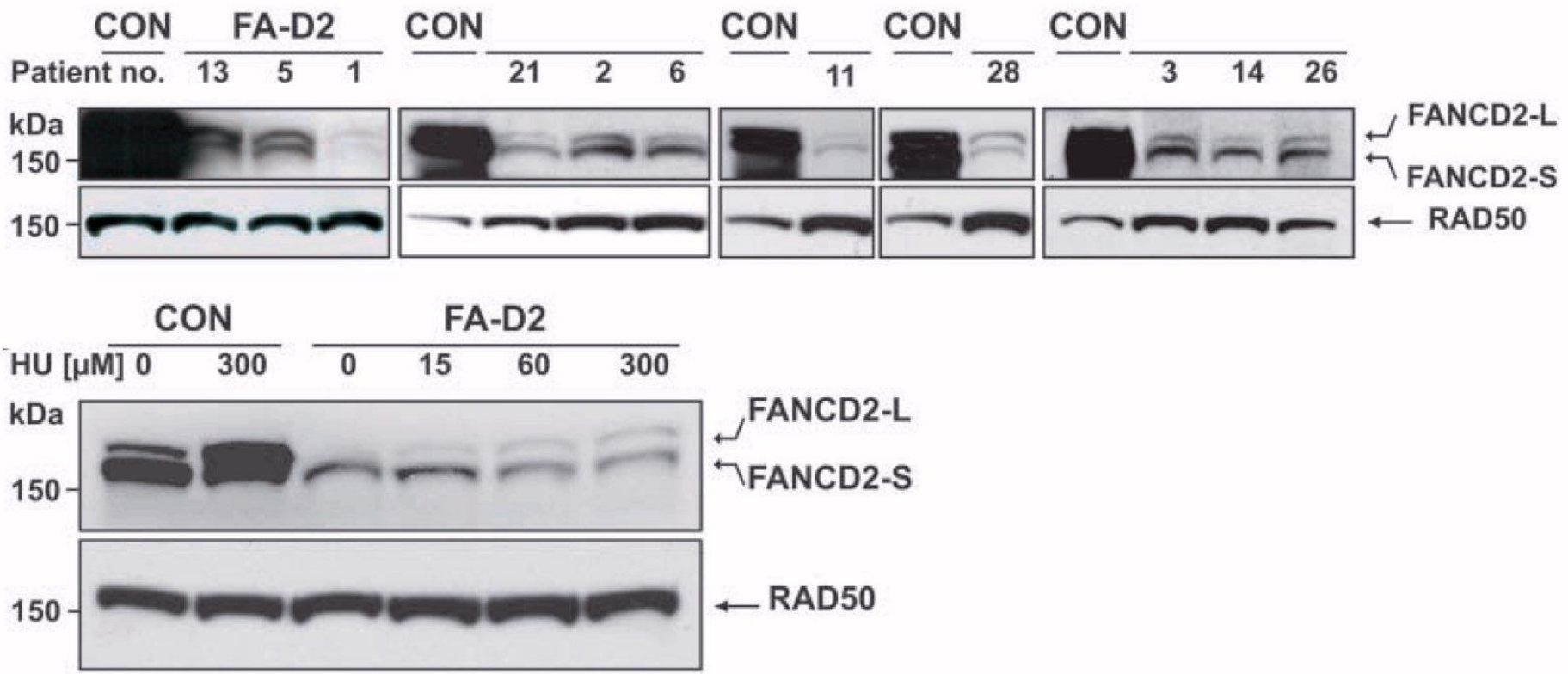
The concept of mutation type

•There are FA gene mutations whose nature permits the maintenance of residual protein (`hypomorphic` mutations).

•They constitute often, but not always, missense mutations. Vice versa, missense mutations are often, but not always, `hypomorphic` mutations.

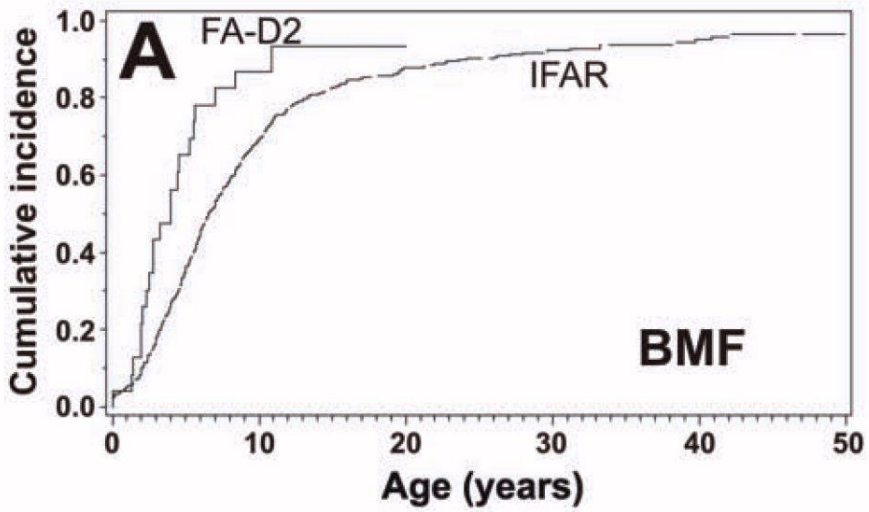
•It can make a difference if patients got a mutation without the capability to retain residual protein (`null` mutations) or if they got a `hypomorphic` mutation. The latter may be associated with milder disease manifestations (`mild`mutation).

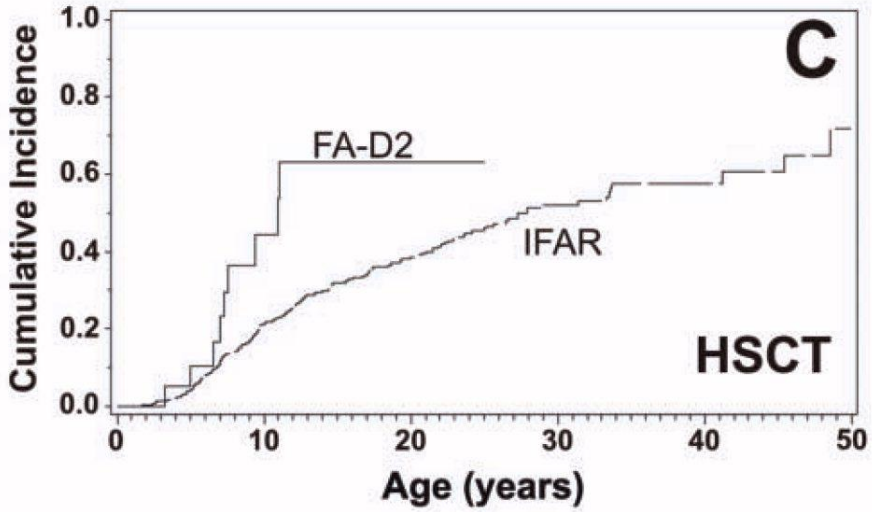
All combinations of biallelic mutations in *FANCD2* are hypomorphic (preserve residual functional protein)

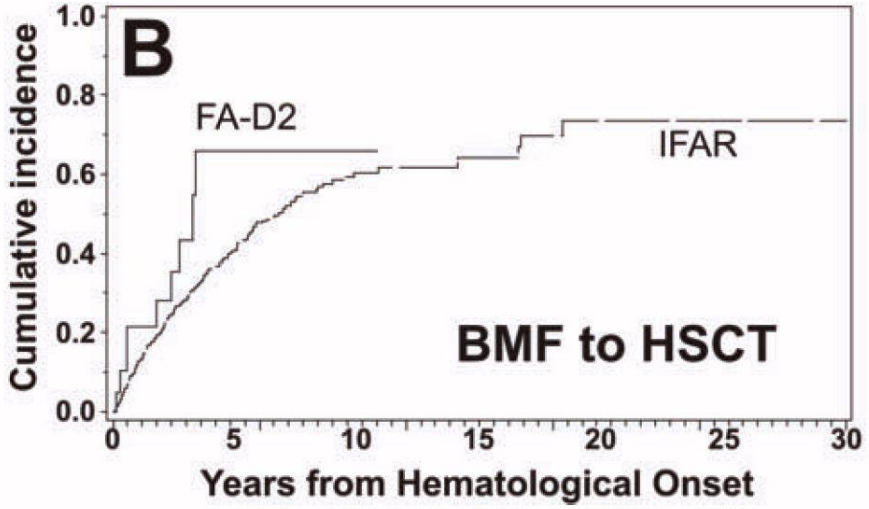


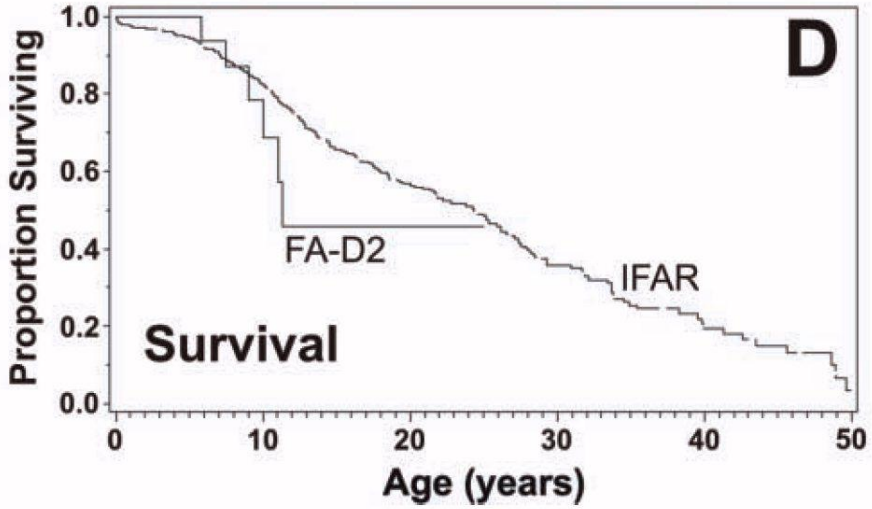
Kalb et al, 2008

`Hypomorphic` combinations of mutations in *FANCD2* do not result statistically in a milder disease course



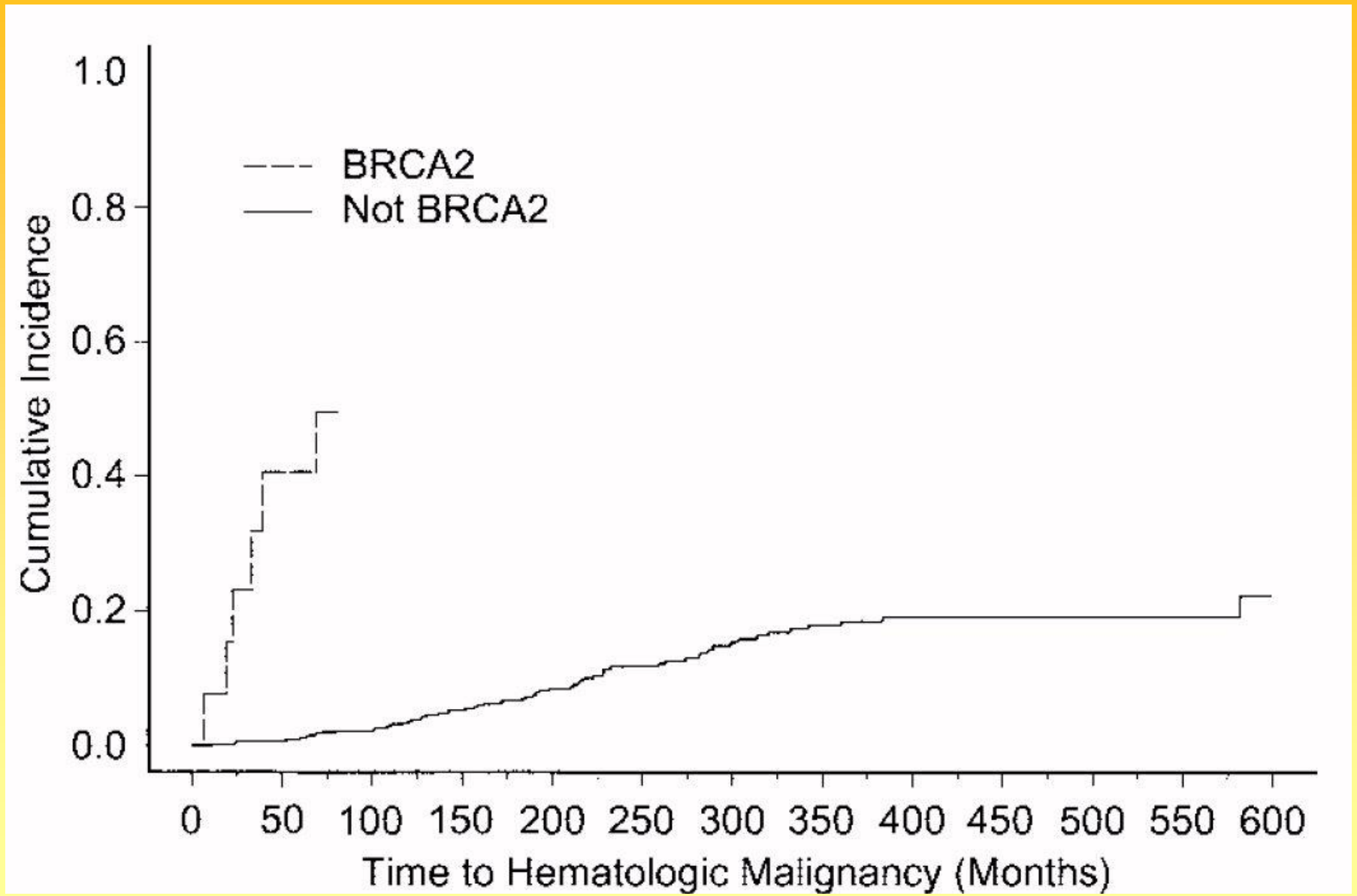






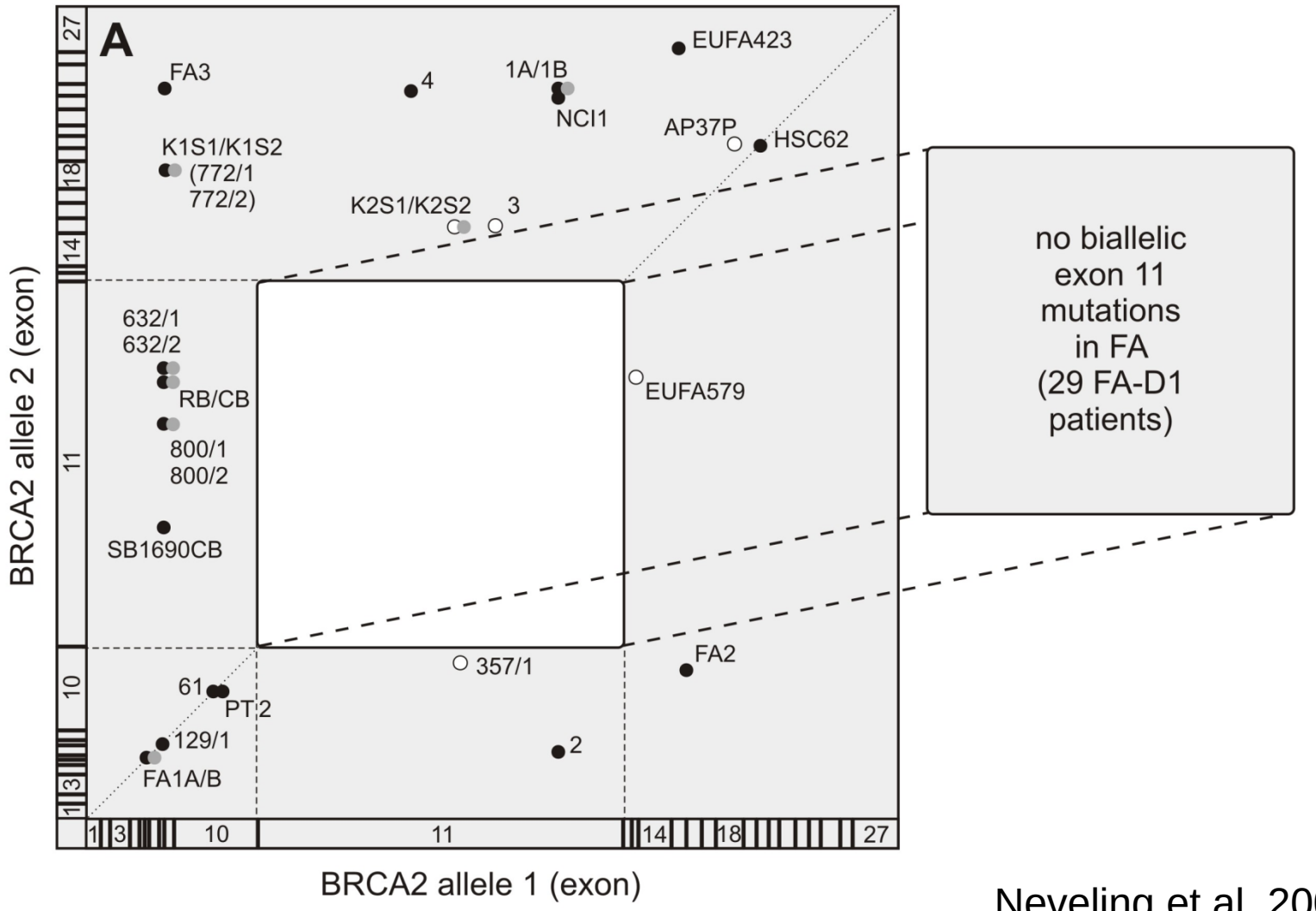
Kalb et al, 2008

Early-onset AML in FA patients with biallelic *BRCA2* mutations



Wagner et al, 2004

Distribution of biallelic *BRCA2* mutations in FA patients of subgroup D1



Neveling et al, 2009

Conclusion 3

Mutation status of particular FA genes

•Complementation groups D2 and I reflect defects in the genes encoding members of the ID complex (FANCD2 and FANCI) and tend to have are a more accelerated disease course, although they are caused by `hypomorphic` combinations of mutations (statistical difference).

•Complementation groups D1 and N are early prone to a set of specific malignancies (`embryonal` tumors). These subtypes may represent a subclass of FA patients with severe course and short life span, although only mild biallelic mutations in *BRCA2/FANCD1* or *PALB2/FANCN* appear to be compatible with life (individual and statistical difference).