

Finding a New Gene

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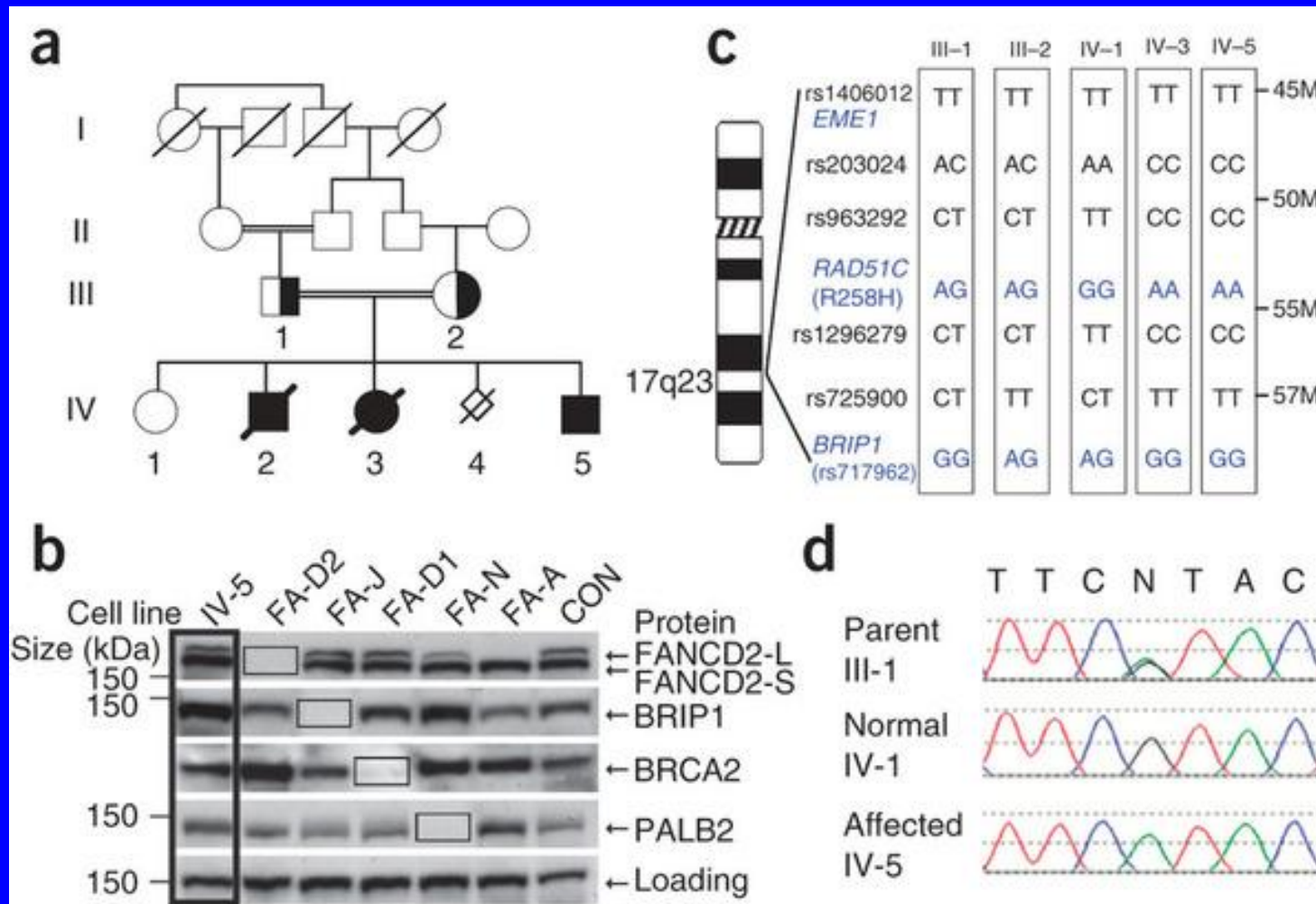
Bethesda, MD

FA Camp 2010

Definition of an FA Gene

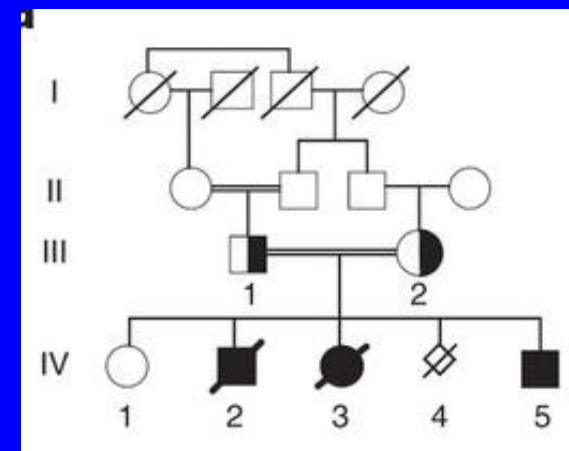
- Identified as fitting into the FA DNA repair pathway
- Found in at least 2 unrelated patients

Finding a New Gene



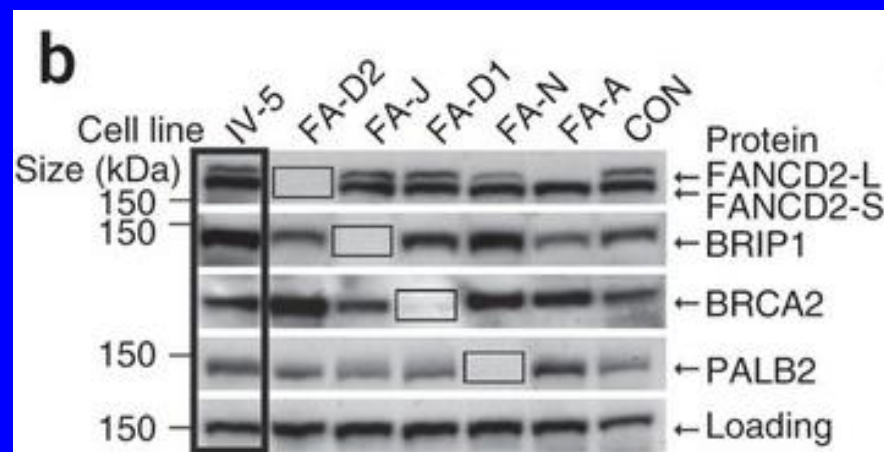
New Gene, 2010

- Pakistani family with 3 affected children
 - Parents first cousins
 - Female died 2 mo, abnormal thumbs, congenital heart, imperforate anus, hydronephrosis
 - Male died 2d, intestinal, anal. Respiratory abnormalities
 - Unknown, miscarriage at 11 weeks
 - Male, 10 yo, hypoplastic radii, proximal thumbs, cystic kidneys, duodenal web, rectal atresia, undescended testes, small genitalia
 - 1 unaffected female



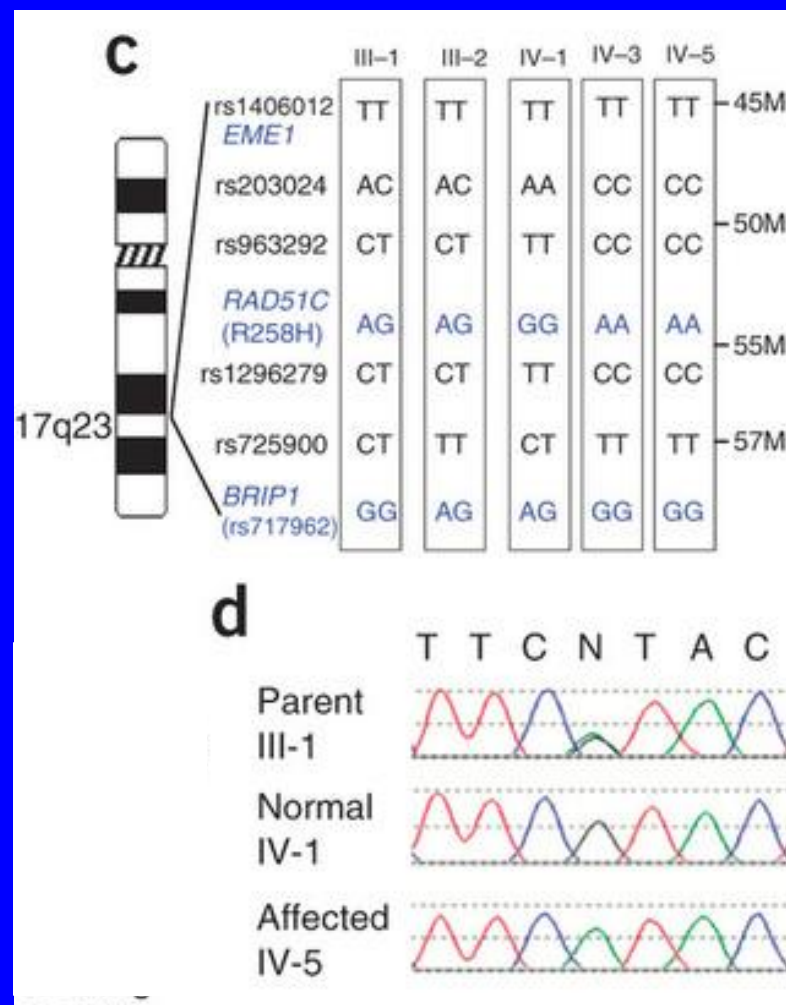
Identification of New Gene

- Increased chromosome breakage with DEB or MMC
- No complementation with known FA genes
- Western blot of D2, present and ubiquitinated
- *BRIP1*, *BRCA2*, *PALB2* sequences normal
- SNP array, Affymetrix 10K
 - 7 regions of shared homozygosity (>3Mb)
- 14.6 Mb, 17q21-q24
- Candidate genes
 - *EME1*, *BRIP1* (both normal),
 - *RAD51C*

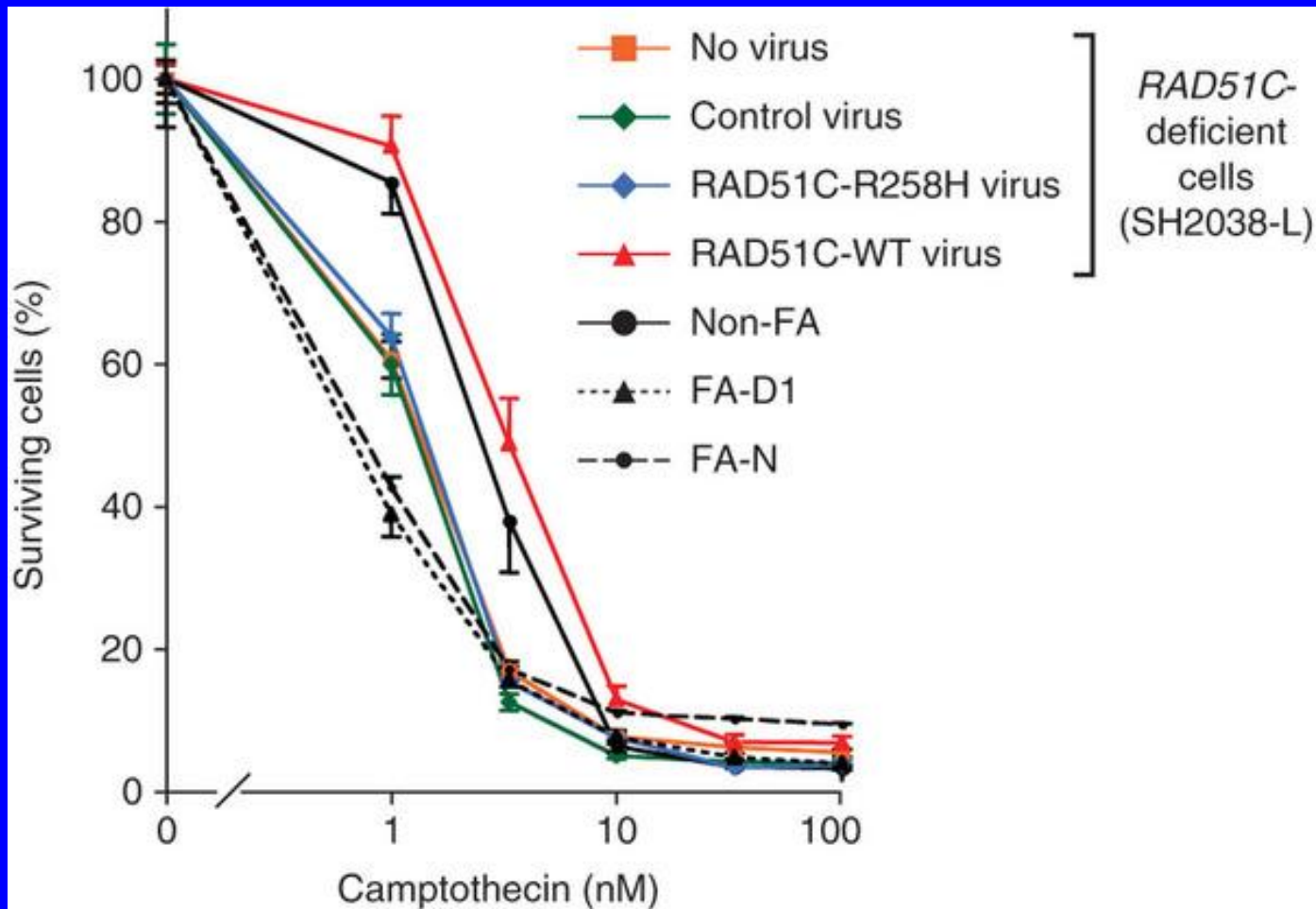


New Gene, *RAD51C*

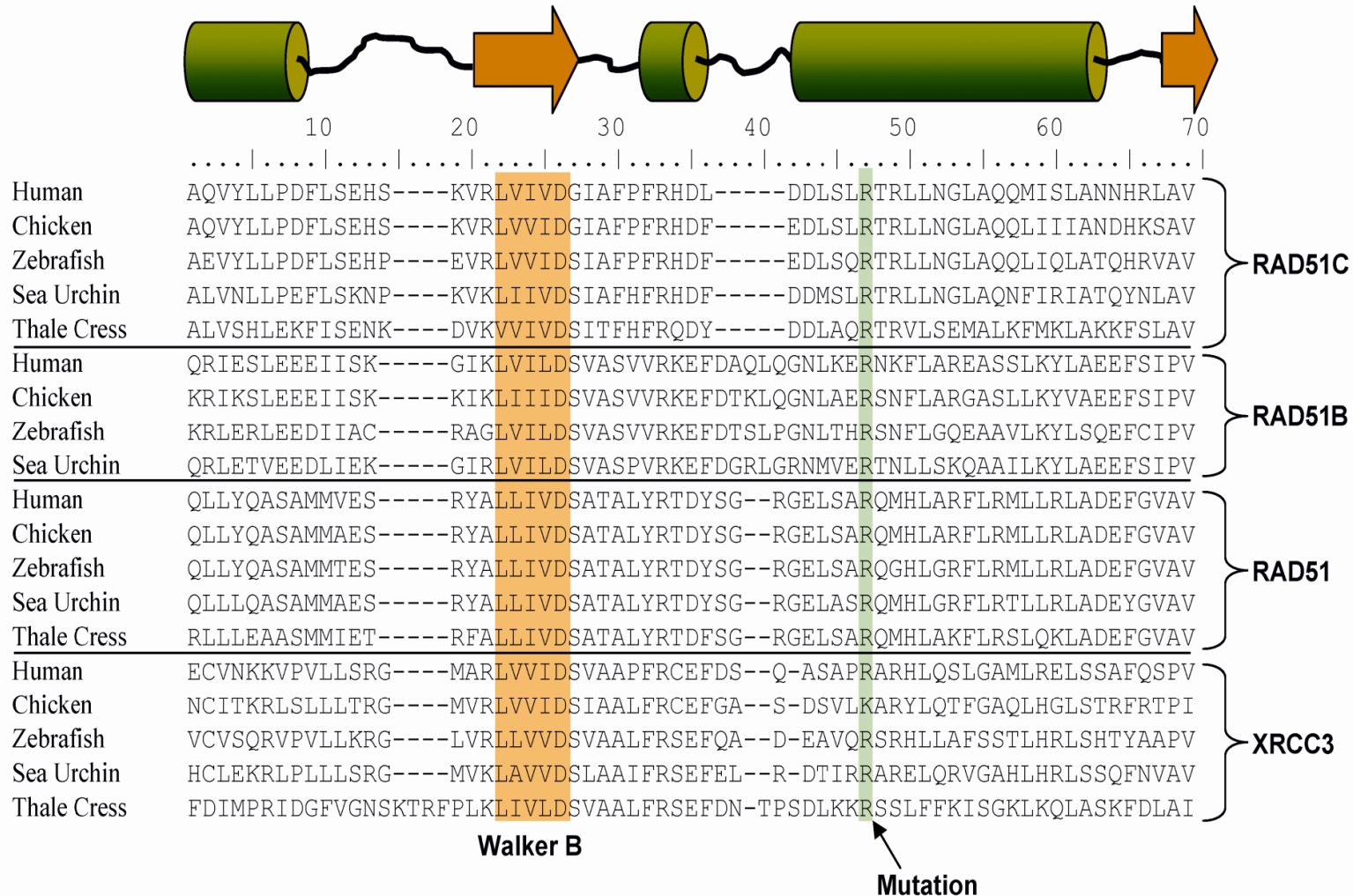
- Sequenced *RAD51C*
- Exon 5 G773A, R258H
- Parents carriers, normal sib wild type, affected sibs homozygous
- Not found in 47 Pakistani controls
- Not found in 21 other FA unknown
- Hypomorphic, because knock-out in mice is embryonic lethal
- “Less cancer-susceptible than FA-D1 (*BRCA2*) and FA-N (*BRIP1*)”



RAD51C Complementation



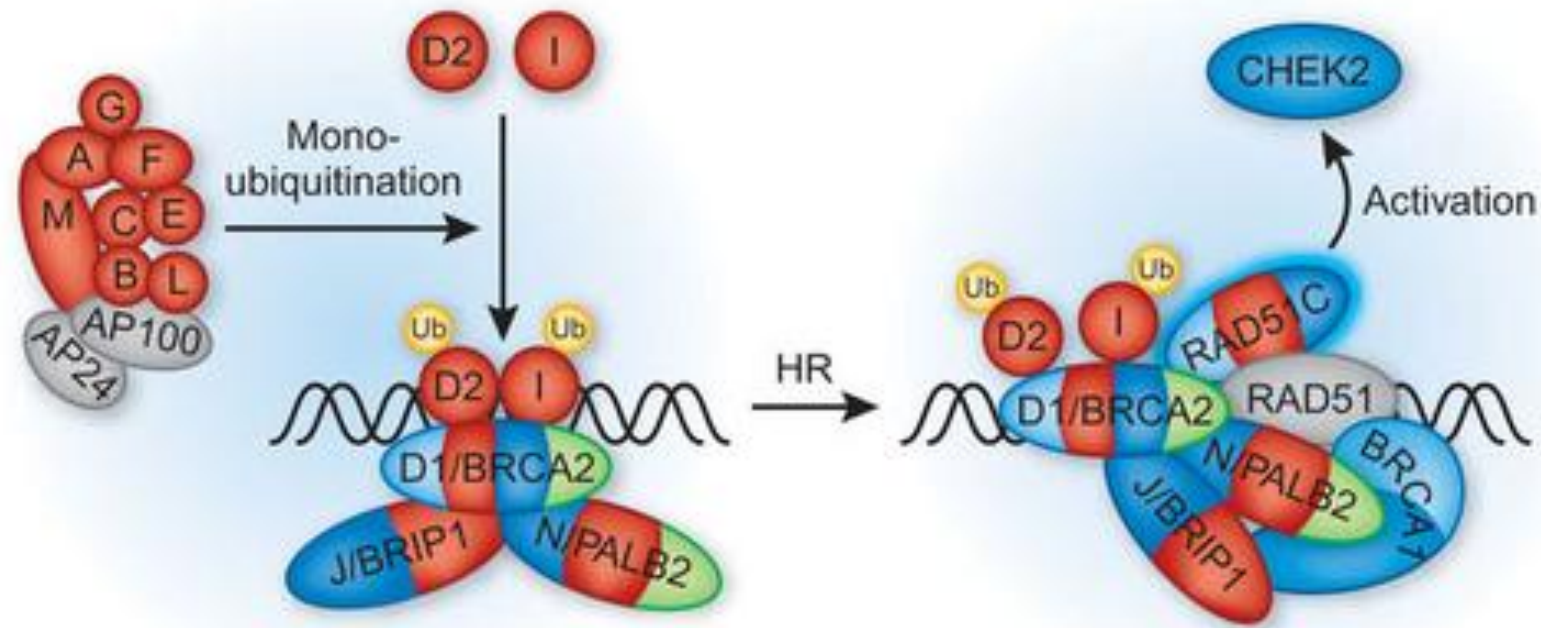
Evolutionary Conservation of R258 in the RAD51 Protein Family



Role of RAD51C

- RAD51-mediated DNA recombination
- Persists at sites of DNA damage
- Activation of CHK2 and cell cycle arrest in response to DNA damage
- Associated with breast and ovarian cancer
- 480 German families with breast and ovarian cancer
 - 6 mutations
- 620 breast cancer only; 2912 healthy controls
 - No mutations

FA/BRCA Pathway with RAD51C



— Fanconi anemia

— Solid childhood tumors
(Wilms, medulloblastoma, neuroblastoma)

— Ovarian cancer

— Breast cancer

FA or FA-like?

- That is the question.