Finding a New Gene

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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

Vaz et al, Nature Genetics 42:406, 2010
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

![Graph showing survival rates of cells under different conditions.]
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

[Diagram showing interactions and pathways involving proteins such as D2, I, Ub, AP100, AP24, D1/BRC2A2, J/BRIP1, N/PALB2, and RAD51C.]

Legend:
- Red: Fanconi anemia
- Green: Solid childhood tumors (Wilms, medulloblastoma, neuroblastoma)
- Blue: Ovarian cancer
- Blue: Breast cancer

Mono-ubiquitination and activation pathways are indicated in the diagram.
FA or FA-like?

- That is the question.