Familial Chordoma Study

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Characteristics of Chordoma

- Comprises 1-4% of all primary bone tumors
- Incidence rate: less than 1 in 1 million people/year
- Male predominance: almost 2 to 1
- Mean age at diagnosis ~ 58 years (range, birth to over 90 years)
- Rare in people under 40 and in African-Americans
Chordoma: Notochordal Origin

- Notochord is an embryonic midline structure
  - induces the formation of the neural tube and axial skeleton
  - disappears by early childhood except for the
    - intervertebral disks (IVDs) and
    - remnants outside the IVDs in more than 20% of adults

- Chordoma occurs throughout axial skeleton:
  - skull base, vertebrae, sacrum/coccyx
Chordoma: Treatment

- Primary therapy is surgery
- Adjuvant radiotherapy may improve outcome
- Complications associated with tumor regrowing or spreading beyond its original location
- Metastases more common in patients with tumors involving the lower vertebrae/sacrum
- Need more effective treatments for aggressive tumors that return or spread
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- Goal: to identify genes that cause chordoma
- Hypothesis: Change in specific gene(s) one of the first steps in starting most chordomas
- In most people with chordoma, the specific gene change present ONLY in chordoma cells
- People with chordoma who have a changed gene only in chordoma cells:
  - Have “sporadic” chordoma
  - Have no other family members with chordoma
  - Will not pass the changed gene on to children
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- Our research focus: families with chordoma in 2 or more blood relatives
- In these families, people with chordoma have a change in a specific chordoma gene in ALL of the cells of their body:
  - Have “familial” chordoma
  - Can pass the changed gene causing chordoma to their children
  - Are more likely to develop more than 1 chordoma

- Chordoma in a member of a chordoma family is a marker for the presence of a changed chordoma gene
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- By studying chordoma families we hope to identify one or more chordoma genes.
- By identifying genes that cause chordoma, we can identify the cellular pathway(s) in which these genes act.
- These pathways may contain gene targets that can be the focus for development of new molecular treatments for chordoma.
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- Clinical component:
  - Includes patients, their parent(s), sibs and children
  - Personal and family medical history
  - MR imaging from skull base to tail bone
  - Blood for lymphocyte DNA
  - Medical records and pathology reports
  - Slides or blocks from chordoma
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- **Clinical component**
  - MR imaging from skull base to tail bone
  - Blood from all family members

- **Laboratory component**
  - Determine which DNA markers from each of 22 chromosomes are present in each family member

- **Combine clinical and lab results**
  - Look at DNA from family members with chordoma to find any region on one chromosome for which they all have the same markers
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- If all individuals with chordoma have the same DNA markers on one of the chromosomes, the region with those markers should contain the *chordoma* gene.

- Sequence all genes in the region with the shared markers in family members with and without chordoma.

- The *chordoma* gene should:
  - Have the same “altered” DNA sequence in all family members with chordoma, BUT
  - Be normal in unaffected relatives.
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- Initial results suggested that the chordoma gene in Families 1, 2 and 3 was on chromosome 7q BUT
- No abnormal DNA sequences found in 41 studied genes on chromosome 7q in these families
- MR images of a child in Family 1 suggested she has chordoma, BUT
  - She did not have the same 7q DNA markers as her father with chordoma
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- Is the chordoma gene on some other chromosome???
- Have been studying genes in several regions of interest.
- No results that I can report as yet.
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We are still committed to this effort, BUT to help identify chordoma genes:

Need to find and clinically evaluate more chordoma families.