Update on genetics research

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US Public Health Service, DHHS

Who are we?

- National Institute on Deafness and Other Communication Disorders
- National Institutes of Health
- U.S. Public Health Services
- U.S. Department of Health and Human Services

- Your tax dollars at work

Fact #1- Not all stuttering is genetic

- Of the people who come to stuttering therapy, about half report a family history and half have no family history
- So, perhaps half of stuttering is due to genetic factors
- The other half is due to unknown causes
  - Low birth weight, perinatal hypoxia

Fact #2 - Genes do not entirely control stuttering in anyone

- Severity varies from day to day, and in children, from month to month
- Stuttering therapy can largely eliminate stuttering
  - Their genes have not changed

The power of genetics

- If a disorder is genetic in origin, we can find the gene that causes the disorder
- Once we have the gene, we can see what the gene codes for, and what the gene product does, both normally and in individuals who stutter
- Can lead us to the cells and molecules involved in the disorder

Genetics is great, but…

- How do we know stuttering has anything to do with genetics?
- Nature vs. nurture

Evidence for genetic factors in stuttering

- Twin studies
  - Identical twins always more alike regarding stuttering than fraternal twins
- Adoption studies
  - Adopted children raised by stuttering parents do not stutter any more than children in the general population
- Family clusters of stuttering
  - Several large families have been described that have many, often distantly related members who stutter
- Segregation analysis
  - Stuttering does not generally occur in families like a simple inherited trait

NIH genetics research

- Genetic linkage studies
- Performed in families
- Applicable to any inherited disorder
- Identify the location of the gene or genes that cause the disorder

Focus

- Persistent stuttering
- Family history of stuttering

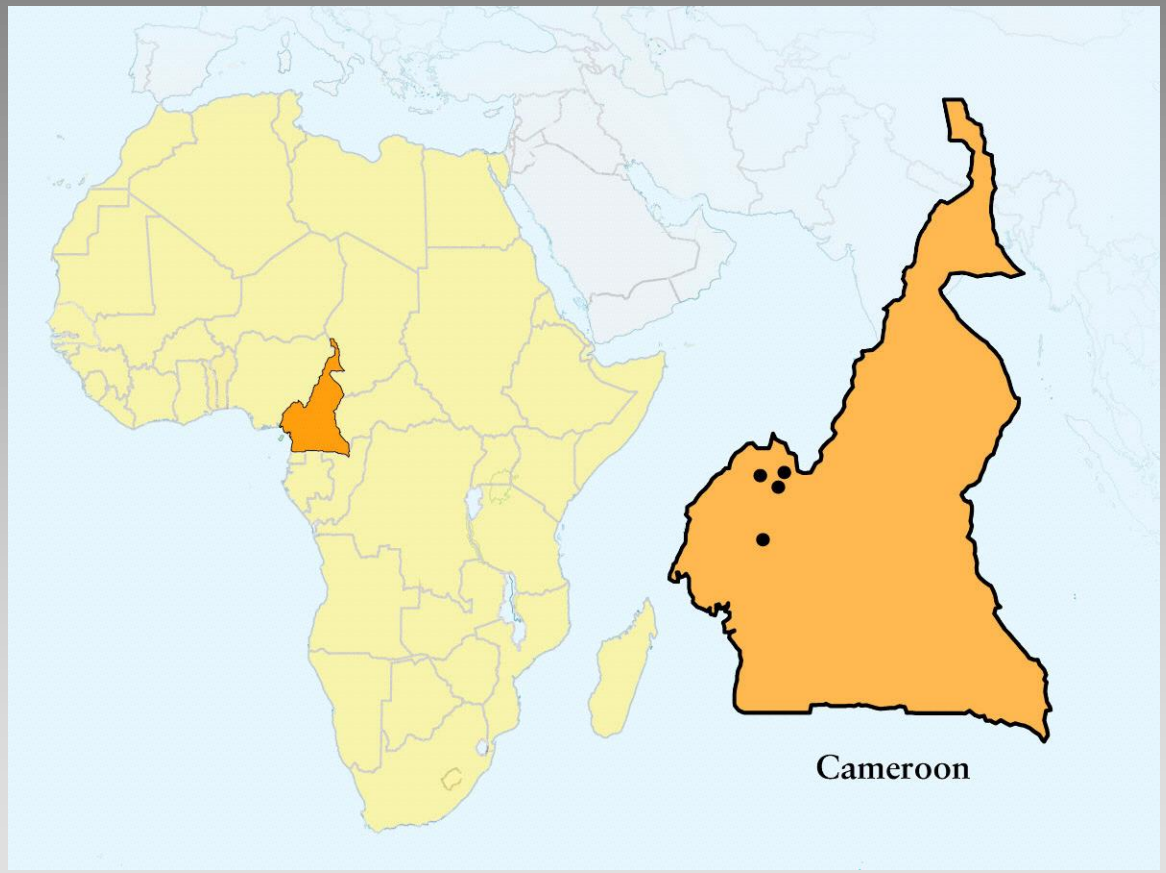
NIH linkage studies

- North American families
  - Not very enlightening
- West African families
- Pakistani families

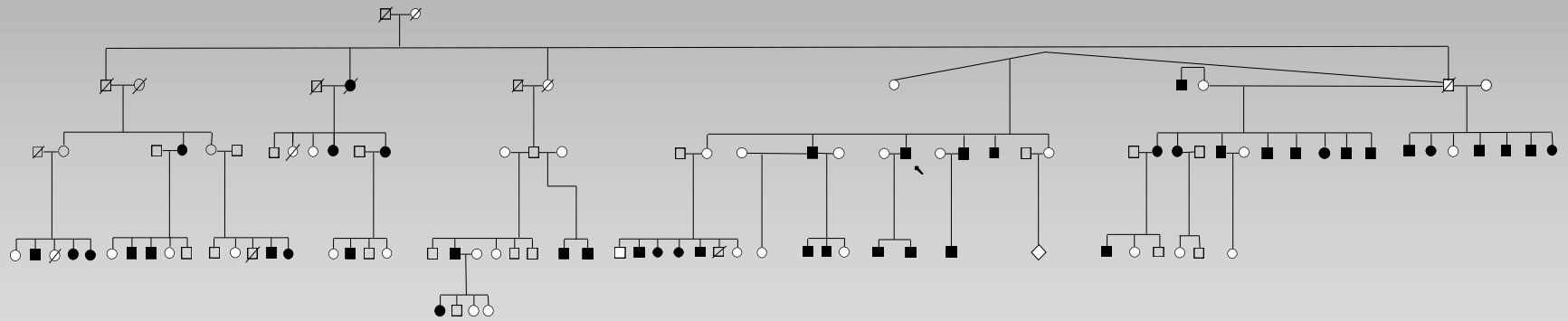
Cameroon, West Africa

- Initial contact came through the online symposium sponsored by Stuttering Home Page
- Query from individual in Cameroon
- Initial information difficult to interpret
  - Subsequent exam at the N.I.H. Clinical Center showed no medical abnormalities except stuttering

Linkage studies – Cameroon



Cameroon Family 1



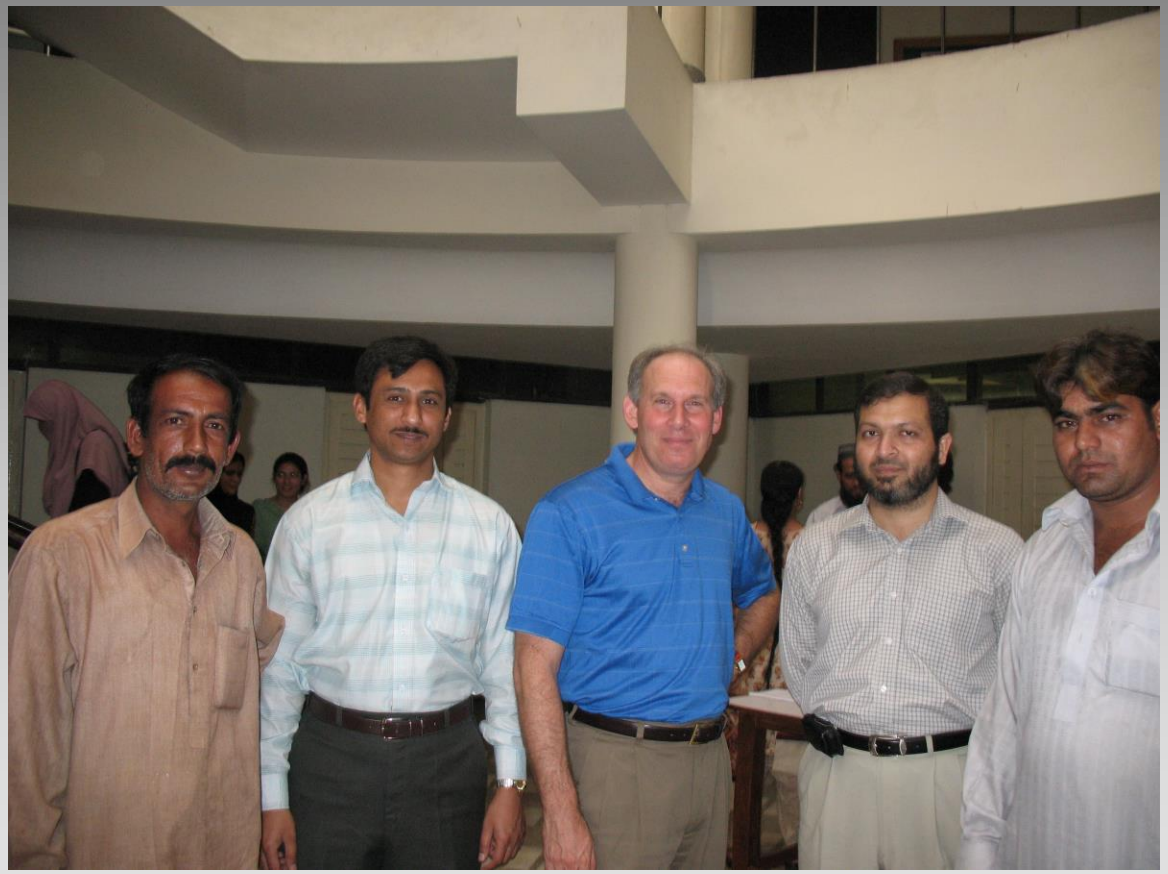
Cameroon linkage
The long march

- Did one survey and found a signal on chromosome 1
  - Did not replicate
- Did two additional surveys, using two different methods
  - Took ~ 2 years of work
- Found clear signal on chromosome 15

Cameroon linkage

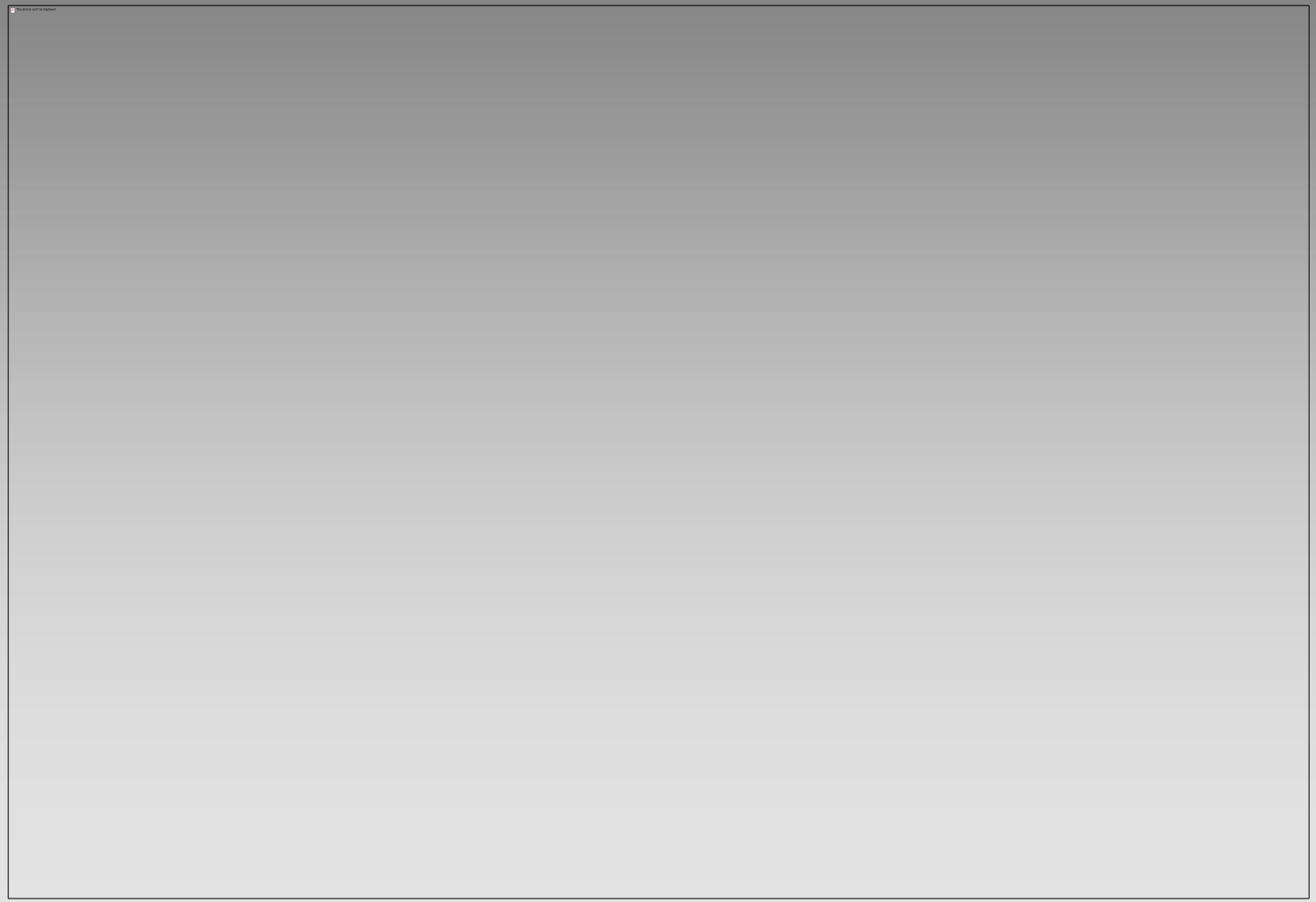
- Linkage on chromosome 15 still has puzzling aspects
- There's likely to be more than one variant gene at this location at work in this family
- Don't yet know what this gene is

Linkage studies - Pakistan



Pakistani stuttering families

PKST 072



Pakistan project

- Enrolled and analyzed 44 families
- Found strong evidence for linkage on chromosome 12
- This region contains 87 genes
- Analyzed these genes in:
  - Family PKST 72
  - Other Pakistani stuttering families
  - 96 unrelated Pakistanis who stutterer
  - 96 unrelated normally fluent Pakistanis

New Results

- In review at a major scientific journal
  - Nothing is true until the reviewers and editors at the journal say it's true
- All information strictly embargoed prior to publication

Results of gene analysis

- Found mutation that went along with stuttering in family PKST 72
- Same mutation in the same gene is present in affected members (but not in normal members) of 3 other Pakistani stuttering families
- Same mutation in the same gene is observed in several unrelated Pakistani individuals who stutter
- Same mutation was observed in a single affected individual of Indian descent in the U.S.
- This mutation was not observed in normally fluent individuals

Chromosome 12 gene analysis

- Examined the entire gene in:
  - 96 unrelated Pakistani affected individuals
  - 270 unrelated North American affected individuals
  - 96 unrelated normally fluent Pakistanis
  - 265 unrelated normally fluent North Americans
  - All have a family history of stuttering
- Found several other mutations in this gene that occur in individuals who stutter but do not occur in normally fluent individuals

Looking beyond chromosome 12

- The chromosome 12 gene is part of a well-known process within the body
  - A metabolic pathway
- Other parts of this process are carried out by the products of other well-known genes

Examining other genes

- Found a number of mutations in each of two other genes
- These mutations were found in multiple individuals who stutter
- These mutations were not found in normally fluent individuals

How common?

- Together, the mutations we've found in these three genes appear to account for 5-10% of familial stuttering
- This amounts to 50,000 to 100,000 individuals in the U.S.
- Mutations in these genes probably account for many more individuals who stutter worldwide

What's next?

- These genes provide an exciting possibility for therapy in this group of individuals
  - Replace what's missing
  - Personalized medicine
- Making a new drug takes many years and many hundreds of millions of dollars
  - Can't expect a cure next week

What about the other 90%?

- Studies have shown that genetics works
- Enrolled a new group of Pakistani stuttering families, each of which is large enough to be useful for a linkage study on its own
- Chromosome 12 has already been ruled out in these families
  - Likely to find other places containing stuttering genes
- Chromosome 15 will hopefully identify another new gene

Current conclusions

- Studies have shown that genetics works
- There's good hope for finding other genes that cause stuttering, leading to additional insights
- At least some stuttering is clearly in the realm of clinical medicine

Acknowledgments

- NIDCD
  - Changsoo Kang
  - M. Hashim Raza
  - Naveeda Riaz
  - Eduardo Sainz
  - Joe Kleinman
- NISC/NHGRI
  - Alice Young
  - Jim Mullikan
- NCBI
  - Alejandro Schaffer
- Hollins Communications Research Institute
  - Jennifer Mundorff
- University of Chicago
  - Stacy Steinberg
  - Anna Pluzhnikov
  - Nancy Cox
- CEMB/University of the Punjab
  - Jamil Ahmad
  - Shahid Khan
  - S. Riazuddin
- Stuttering Foundation of America
- British Stammering Association
- National Stuttering Association
- Speak Clear Association of Cameroon
  - Joseph Lukong

- Stuttering research subjects worldwide

How do we make progress?

- You can help!
- Enrolling research subjects here today, immediately following this workshop
- Compensation provided

What's needed?

- Family history of stuttering
- Provide a small blood sample, taken from your arm
- Understand and agree to the risks involved
- Provide a Social Security number to receive your compensation
  - $25