Genetics and the Growing Spine

2nd International Congress on EOS

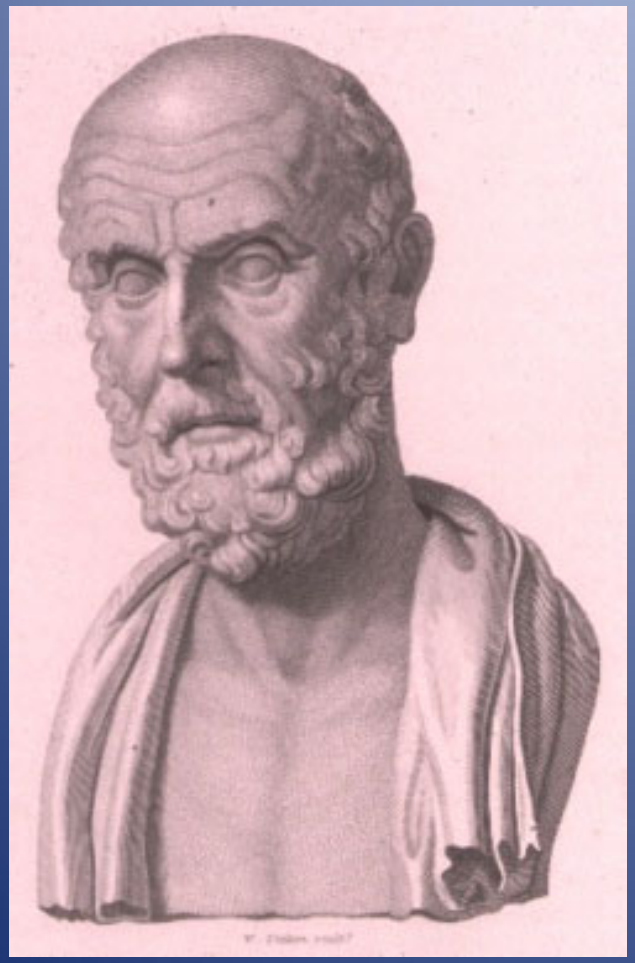
Montreal, Canada

James W. Ogilvie, MD

Shriners Hospital for Children

Salt Lake City, Utah

Hippocrates 420 B.C.



- “There are many varieties of curvatures of the spine even in persons who are in good health…and the spine is liable to be bent from old age and from pain.”

Scoliosis Diagnosis

A. Observational (phenotype) - Ancient

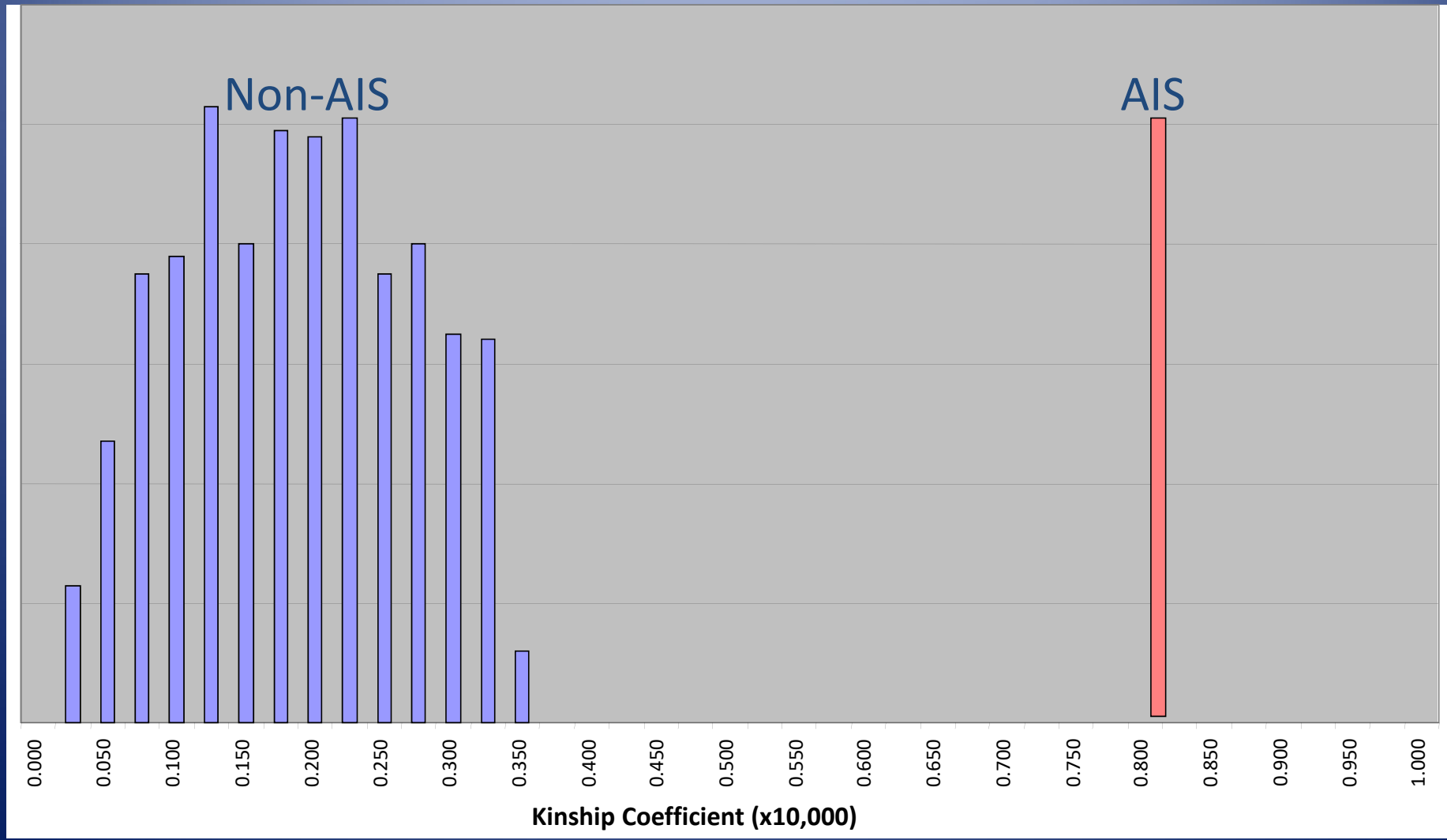
A. + B. Röentgen - 1896

A. + B. + C. Genotype - Present

Genotype Information

- Provide genotype homogeneity for disease groups.
- Differentiate Idiopathic EOS from AIS.
- Surrogate outcome for specific genotype.
  -Evidence-based treatment decisions
  -Genotype homogeneity in study cohorts

Adolescent Idiopathic Scoliosis



Idiopathic Scoliosis

Prof. J.I.P James

- Age:

  0-3 years – infantile
  4-9 years – juvenile
  } ~10%

  10 years to skeletal maturity - adolescent

Adolescent Idiopathic Scoliosis

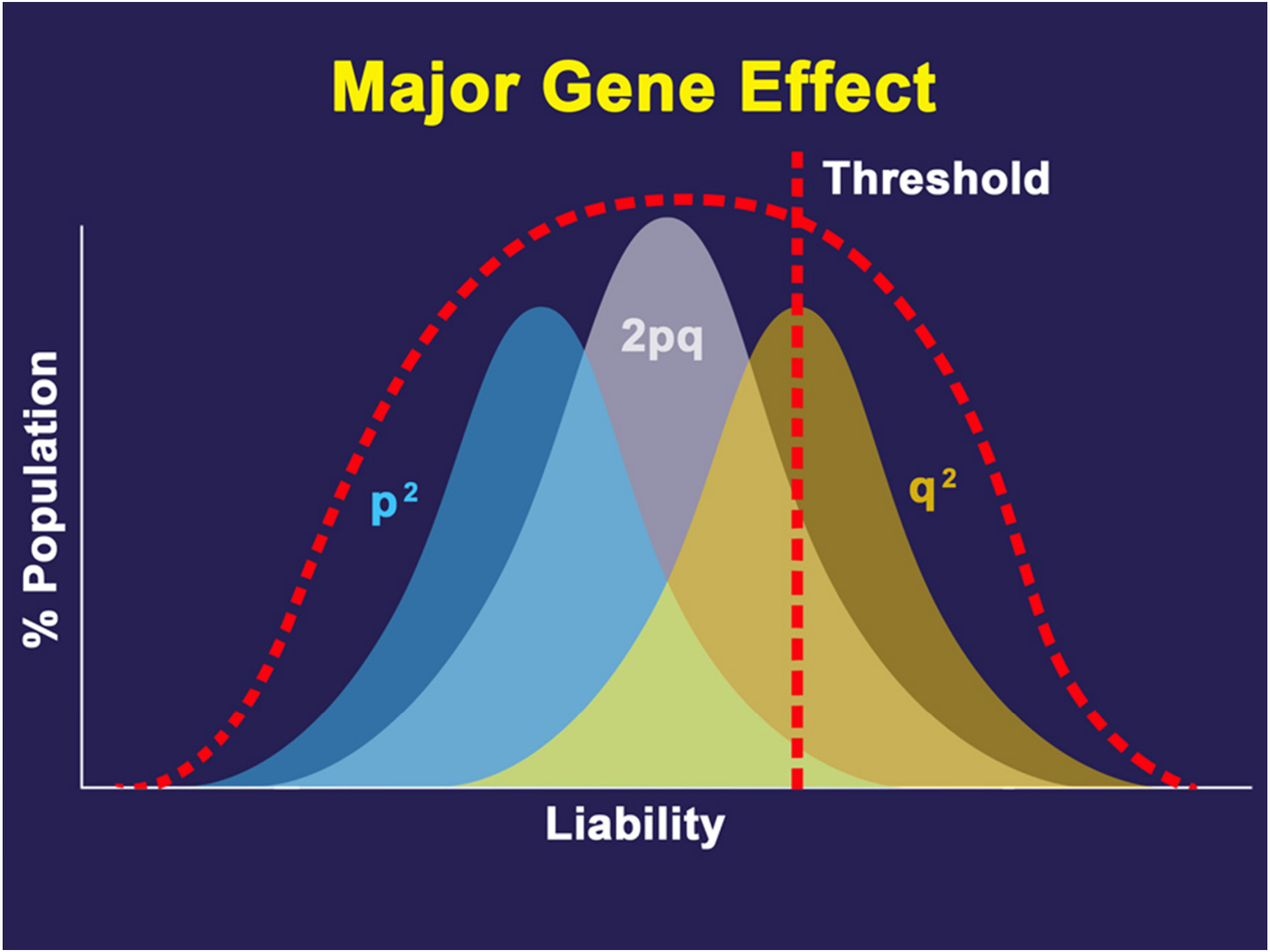
- Polygenic disorder
- Epigenetic/environmental influences have not been identified, probably <3% determinative.
- Autosomal dominant, not X-linked
- Not estrogen receptor related

Adolescent Idiopathic Scoliosis

- **Caucasian/Latino cohort:** 276 genetic markers associated with AIS. 53 genetic markers significant for predicting curve progression.
- **Asian Cohort:** Different allele frequency than Caucasian or African
- **African Cohort:** African-African different than African-American.

Idiopathic EOS

- Idiopathic by exclusion
- X-rays → CT scans → MRI, genetic testing
  Higher incidence of abnormal MRI in younger age group.
- Smaller, more focused study cohort


Major Gene Effect
Threshold
2pq
p 2
q 2
% Population
Liability

Idiopathic EOS

Traditional-

- Infantile IS: Up to age 3 years.
- Juvenile IS: Age 3 to 10

Genetically-

- Cut point at age 9 years, >9000 samples.
- IEOS has a different marker set than AIS.
- IEOS 210 samples.

Syndromic EOS

- Marfan Syndrome: FBN1 gene encodes for extracellular matrix glycoprotein fibrillin-1

  FBNI gene determines height in general population. Mutations associated with skeletal abnormalities.

✓ 30 reported mutations of FBN1 may explain spectrum of "Marfanoid" phenotypes. Spectrum of connective tissue disorders, Ehlers-Danlos, OI, Stickler, et al.

- Rett Syndrome: X-linked dominant neurodevelopmental disorder caused by mutations in MeCP2. MeCP2 deficiency results activation of ID(1-4) genes and causes postnatal neuronal maturation arrest. ~60% have scoliosis.

Syndromic EOS

- Neurofibromatosis NF1

✓ Neurofibromin, encoded by NF1 (17q11), down-regulates key molecules for many cellular functions including oncogenesis.

✓ AIS markers may be useful for incidence studies and differentiating dystrophic from AIS-like curves.

Syndromic vs. Idiopathic Scoliosis

- Is Idiopathic (adolescent and EOS) a syndrome?
- Spine deformity common molecular cascade?
- Spine deformity pathways similar in different syndromes?

Somatic vs. genetic scoliosis

Maximum somatic influence

Maximum genetic influence

CP, spinal cord injury, congenital, et al.

Idiopathic

AIS Molecular Pathways

Biological Process

A. Transporters & carriers (including calcium channels)
synaptic transmission, calmodulin-melatonin,
iron transport

B. RNA splicing and other processes
general

C. Transcription factors, co activators and regulators:
axon development, proliferation/apoptosis

D. Receptor-mediated signaling transduction
cytokines, hormone, stress signaling

AIS Molecular Pathways

Biological Process

A. Transporters & carriers (including calcium channels)
synaptic transmission, calmodulin-melatonin,
iron transport

B. RNA splicing and other processes
general

C. Transcription factors, co activators and regulators:
axon development, proliferation/apoptosis

D. Receptor-mediated signaling transduction
cytokines, hormone, stress signaling

Transcription Factors

- **ID2--- basic helix-loop-helix (bHLH) family**
- **ISL1--- LIM/homeodomain family**
- **CUTL2--- cut-like homeodomain family**
- **FOXB1---winged helix family**

NEUROGENESIS

Important regulator of CNS development and maintenance, especially caudal midbrain and hypothalamus.

Genotype Determination in EOS

- Focus on IEOS: Genotype homogeneity for clinical research.
- Surrogate Outcome: Evidence-based management decisions, novel interventions.
- Basic science: Molecular pathways of disease pathogenesis.


Thank You