

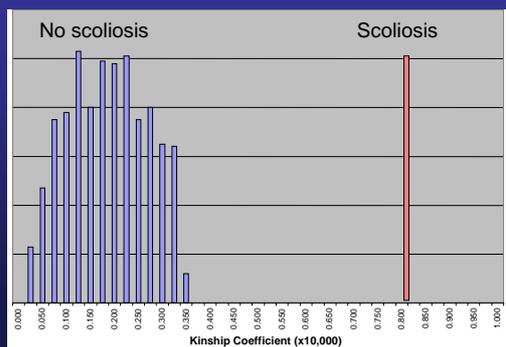
Adolescent Idiopathic Scoliosis: Genetic Testing and Treatment Implications

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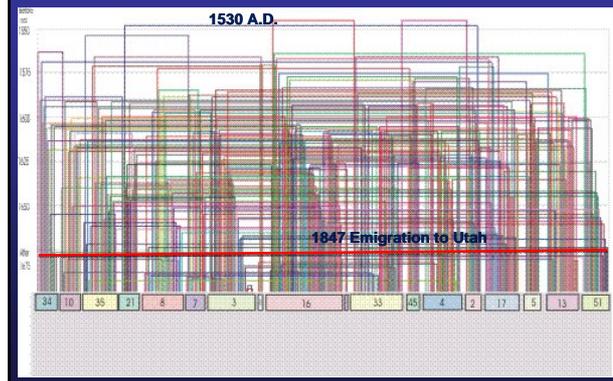
AIS is a Genetic Disorder

- Wynne-Davies 1968
 - Cowell 80% familial 1972
 - Riseborough, Wynne Davies 1973
 - Blank, Raggio, et al 1999
 - Ogilvie, Ward, et al 2006
- 97% of scoliosis patients are related to other scoliosis families.

Relatedness in AIS



Complex, Polygenic Trait



Founders' Effect



-14 families found to have a common ancestor in England circa 1560

-17 families have a common ancestor in England circa 1530

Candidate gene vs. genome wide

- A. Candidate gene approach: Identification of a **single gene** that may be related to a disease process.
- B. Case controlled genome wide association studies: Examination of the **entire human genome** to statistically establish disease-genotype associations.

Random (candidate gene) VS. specific drilling (genome-wide)



Genome-wide Association Study



- 5 years
- Thousands of samples
- Tens of millions of dollars
- Billions of genotypes
- Trillions of calculations



Adolescent Idiopathic Scoliosis

- Autosomal polygenic disorder.
- Recessive, dominant, co-dominant, possibly some have X-linked effects.
- Not estrogen receptor related.
- Epigenetic/environmental influences have not been identified, but are small.
- Genotypes of AIS are different from idiopathic early onset scoliosis; e.g. juvenile and infantile idiopathic scoliosis.

Adolescent Idiopathic Scoliosis

- 276 Single Nucleotide Polymorphism (SNP) markers associated with AIS.
- Step-wise backward logistic regression analysis.
- 53 markers with prognostic significance for curve progression.

Role of Genetic Testing

- Genotype acts as surrogate outcome.
- High predictive value allows personalized evidence-based medical treatments.
- Provide a basis for prospective clinical trials on standard and novel interventions.

Which hand was your patient dealt?





-What would you have told parents at age 8?
-Sibling had surgery for AIS.



-What would you have told parents at age 8?
-Sibling had surgery for AIS.
-Still 10° at age 15
-Risk score: 3

What do you tell the parents of an 11 year old girl with an idiopathic 9° curve?



- Risser 0
- Tanner 1
- No family history of scoliosis
- A family in their church recently lost a child due to AIS (complications of A/P fusion and instrumentation)

Progression	Brace Start	Correction	Brace End	Post-Op
12 yrs. - 26° Risser 0	12 yrs. - 30° Risser 0	13 yrs. - 31° Risser 0	14 yrs. - 44° Risser 3	14 yrs. Risser 4

High Risk for Progression:
Risk Score:194

Progression	Brace Start	Correction	Brace End	Post-Op
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Predictive/Prognostic Test

Clinical information:

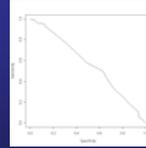
- Chronologic age
- Gender
- Menarche
- Cobb angle
- Risser sign, triradiate cartilage, bone age
- Family History

Brace Efficacy

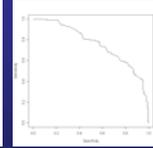
- 32% of Risser 0, 1 with 20-29° will not progress without treatment.
 - >20% will fail brace treatment and have surgery.
- Lonstein and Carlson
JBJS, 1984.
- Lonstein and Winter
JBJS, 1994.

Less than 50% likelihood that brace will benefit.

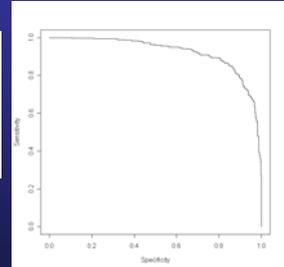
AIS Progression: Sensitivity vs. Specificity



Early clinical data



Late Clinical data



Genotype criteria only

Receiver Operating Characteristic (ROC) Curves

Predictive Test: Impact

- AIS predictive test could eliminate inefficiencies in the mild scoliosis group at great individual and aggregate savings.
- Pre-symptomatic identification of patients at highest risk offers possibilities for novel treatments.

Non-progressive Curves

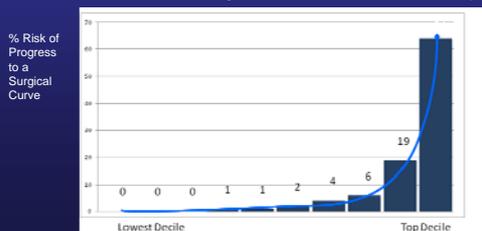
- With 53 genetic markers, there is 95% accuracy in predicting progression to <math><25^\circ</math>.
- With 53 genetic markers **plus** chronological age and Cobb angle at presentation, there is >99% accuracy.

What does it tell us?

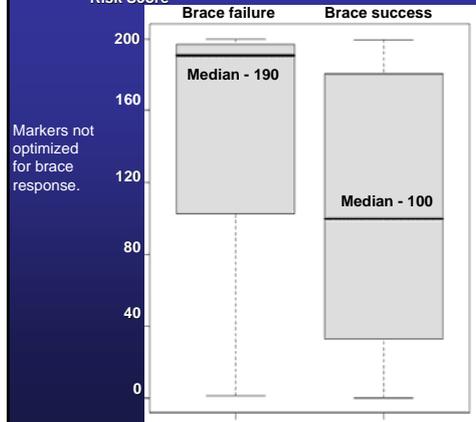
With increasing risk score:

- Increased risk of progression to a moderate curve
- Exponential increase in the rate of surgical curves
- Bracing may be less effective

Evidence-based management decisions, enhance compliance



Risk Score



Markers not optimized for brace response.

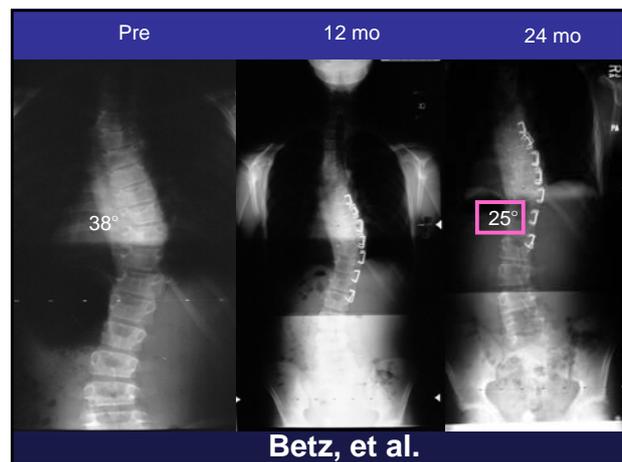
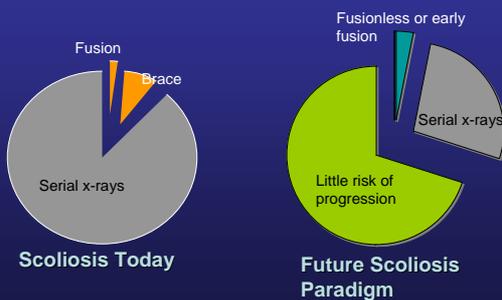
DNA-based Test

- 60+ DNA markers for all ethnicities.
- Present 53 DNA markers taken alone are superior to all current clinical predictors.
- Assists in stratifying patient risk of curve progression.
- Supports decision making on appropriate management.

Genetic Profile

- **Low Risk 1-40:**
>99% likelihood of no significant progression.
- **Intermediate Risk 41-180:**
Follow current regime of monitoring.
- **High Risk >180:**
95% risk of curve progression to surgical range even if braced.
Risk score ≥ 195 , no brace successes

Paradigm Shift



Molecular Pathways

Biological Process	SNPs involved	Percentage of hits
Transporters & carriers (including calcium channels) synaptic transmission, calmodulin-melatonin, iron transport	19	9%
RNA splicing and other processes general	21	10%
Transcription factors, co activators and regulators: neuro development, proliferation/apoptosis	22	11%
Receptor-mediated signaling transduction cytokines, hormone, stress signaling	32	16%

Changes in Care Delivery

- 70-80% patients: fewer visits, fewer x-rays and less cost.
- Evidence-based decisions on bracing.
- Evidence-based understanding of prognosis may allow intervention with innovative fusionless treatments.
- Earlier intervention in those with high risk genetic profile.

Thank you

