

# The Genetic Evaluation

Of Developmental Delay,  
Autism,  
and Other Common Pediatric Complaints

# Scott McLean, MD

- Clinical Geneticist
  - Baylor College of Medicine
  - The Children's Hospital of San Antonio
- Member of a Scientific Advisory Board
  - FDNA – facial recognition tools to assist genetic medicine



# Objectives

- Explain the clinical tools and methods used by the clinical genetics team
- Recognize scenarios for which a genetics evaluation might have significant benefits

# What is in the Genetics Team's toolbox?



Р  
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# The Clinical Genetics consultation: a therapeutic performance, in 5 Acts



# Cast

Clinical Geneticists  
Genetic Counselors  
Trainees  
Genomic Associates  
Dieticians  
Social Workers  
Clinic Coordinators  
Genetic Nurses  
Genetic Nurse Practitioners

Genetic Physician Assistants  
Administrators  
Laboratorians  
Newborn Screening Program  
Primary Care Providers  
Medical Specialists  
Surgical Specialists  
Support Groups  
Medical Directors

Starring ..... The Patient!



And his or her family!



# The Theater -



# The Stage -

- The bedside ...
- Outpatient Clinic
  - At the Big Medical Center
  - Community Hospitals
  - Satellite Clinics
  - Private Practice
- Inpatient – on the ward, or the ICU
- Telemedicine



# Act 1. Scene 1.

- Who refers patients and why
- What patients expect
- Who comes to the appointment
- What are the ground rules



# What is the **contract** between the patient and the clinical provider?

- “How can I help you?”
- Clarifying the problem and the ideal solution
- Setting expectations for success
- Defining roles – consultation, management, follow-up
- Explaining the work ahead
  - Investigation
  - Education
  - Management and treatment
- Agreeing to proceed



# Act 1. Scene 2: The History

- Prenatal
- Delivery
- Neonatal
- Infancy
- Developmental
- Growth
- Systems



# Act 1. Scene 3. The family history

- Three generations
- Accurate biological relationships
- Thorough!!
- Critical facts checked
- Requires analysis
- GCs are the best



# Pedigree

- Origin: 1375–1425; late ME *pedegru* < AF, equiv. to MF *pie de grue* lit., foot of crane, a fanciful way of describing the appearance of the lines of a genealogical chart



# What do we ask about?

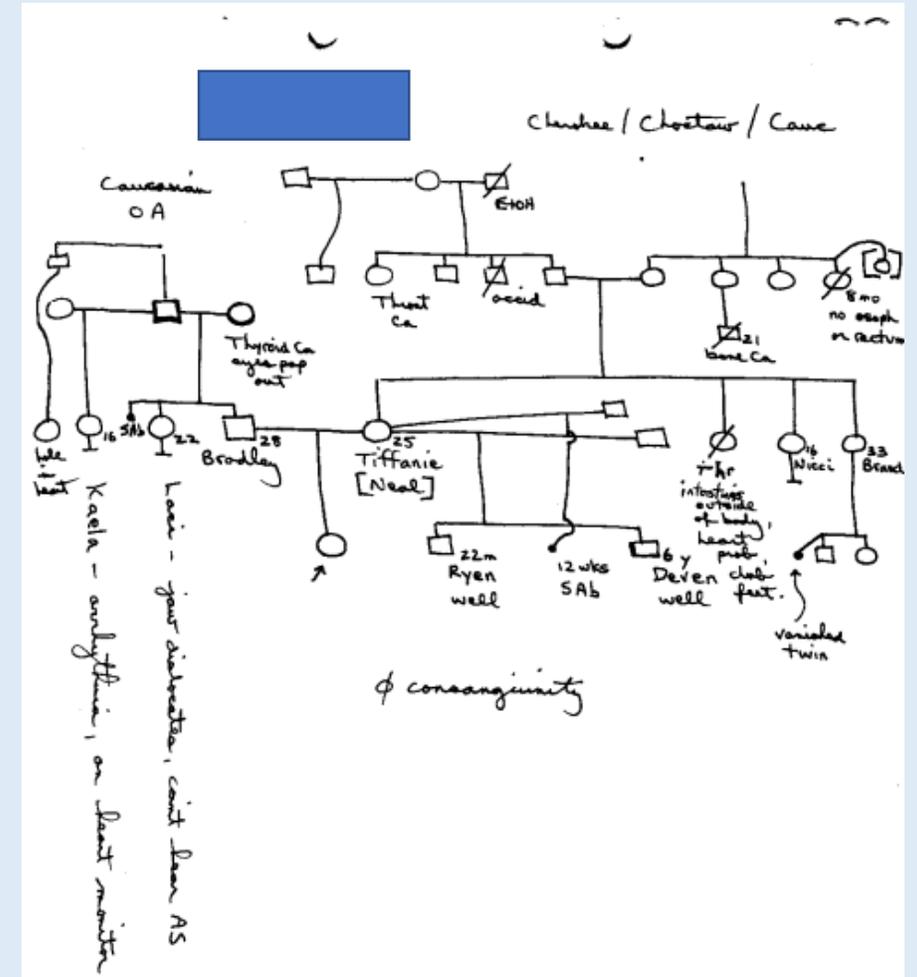
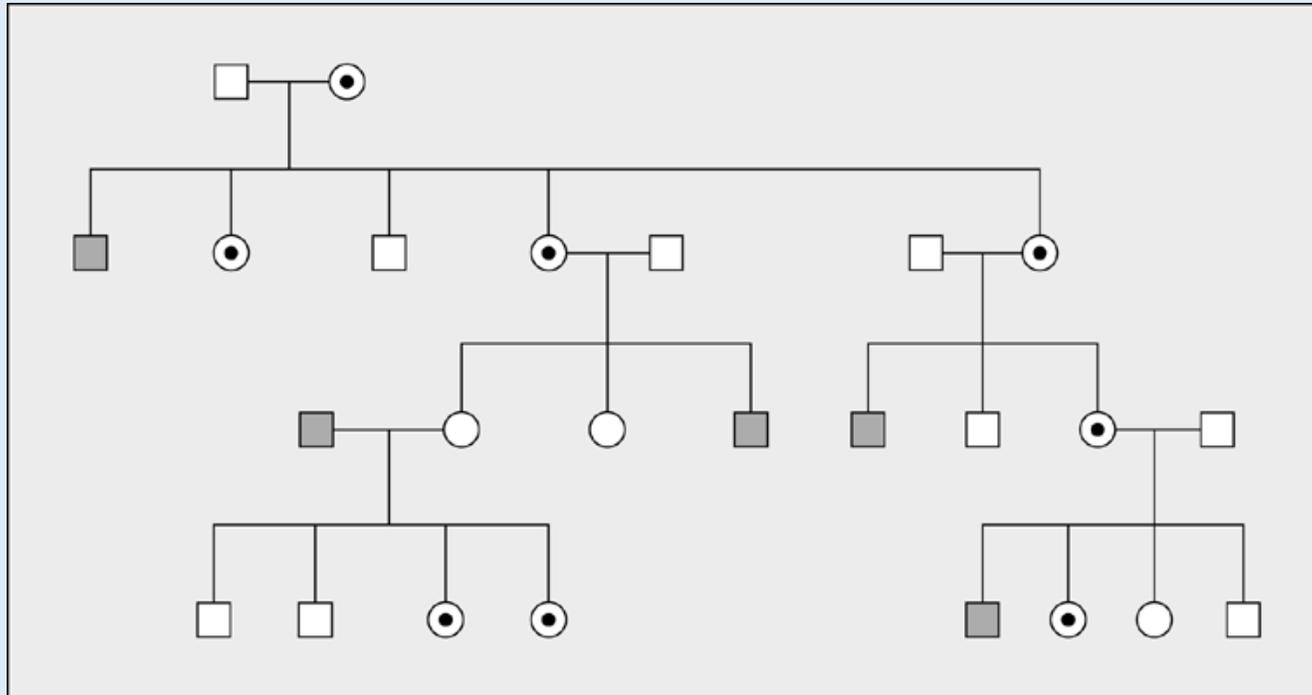
- Focused, e.g. on ID or ASD
- General
  - Developmental issues
  - Deafness
  - Blindness
  - Birth Defects
  - Growth problems
  - Heart, lung, brain, gastrointestinal, or kidney problems
  - Infertility or more than 2 pregnancy losses
  - Ethnicity



# Common Pedigree Symbols

	Male	Female	Gender not specified	Comments
1. Individual	 b. 1925	 30y	 4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
				With $\geq 2$ conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.
3. Multiple individuals, number known				Number of siblings written inside symbol. (Affected individuals should not be grouped).
4. Multiple individuals, number unknown or unstated				"n" used in place of "?".
5. Deceased individual	 d. 35	 d. 4 mo	 d. 60's	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/testing.
7. Proband				An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	 SB 28 wk	 SB 30 wk	 SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	 LMP: 7/1/2007 47,XY,+21	 20 wk 46,XX		Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.
Pregnancies not carried to term		Affected	Unaffected	
10. Spontaneous abortion (SAB)		 17 wks female cystic hygroma	 < 10 wks	If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)		 18 wks 47,XY,+18		Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)			 ECT	Write ECT below symbol.

# Pedigrees:



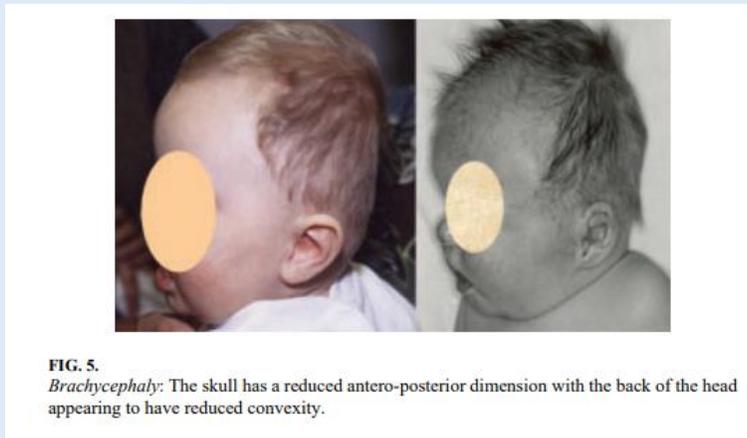
# Act 2. Scene 1. Physical Examination

- Measurements to understand growth
- Comprehensive – top to bottom
- Morphology & Dysmorphology
- Examination of siblings and parents
- Comparisons to standards
- Photographic documentation



# Human Phenotype Ontology

- It used to be that geneticists were more likely to share a toothbrush than nomenclature.
- Standardization of terminology for phenotypic features - 2009



**FIG. 5.**  
*Brachycephaly:* The skull has a reduced antero-posterior dimension with the back of the head appearing to have reduced convexity.

## Elements of Morphology: Standard Terminology for the Head and Face

Judith E. Allanson<sup>1,\*</sup>, Christopher Cunniff<sup>2</sup>, H. Eugene Hoyme<sup>3</sup>, Julie McGaughan<sup>4</sup>, Max Muenke<sup>5</sup>, and Giovanni Neri<sup>6</sup>

<sup>1</sup>Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Canada <sup>2</sup>Section of Medical and Molecular Genetics, Department of Pediatrics, University of Arizona, Tucson, Arizona <sup>3</sup>Department of Pediatrics, University of South Dakota, Sioux Falls, South Dakota <sup>4</sup>Royal Children's Hospital, Genetic Health Queensland, Brisbane, Australia <sup>5</sup>National Human Genome Research Institute, Medical Genetics Branch, National Institutes of Health, Bethesda, Maryland <sup>6</sup>Istituto di Genetica Medica, Universita Cattolica, Roma, Italy

### Abstract

An international group of clinicians working in the field of dysmorphology has initiated the standardization of terms used to describe human morphology. The goals are to standardize these terms and reach consensus regarding their definitions. In this way, we will increase the utility of descriptions of the human phenotype and facilitate reliable comparisons of findings among patients. Discussions with other workers in dysmorphology and related fields, such as developmental biology and molecular genetics, will become more precise. Here we introduce the anatomy of the craniofacies and define and illustrate the terms that describe the major characteristics of the cranium and face.

# Act 2. Scene 2. Review records



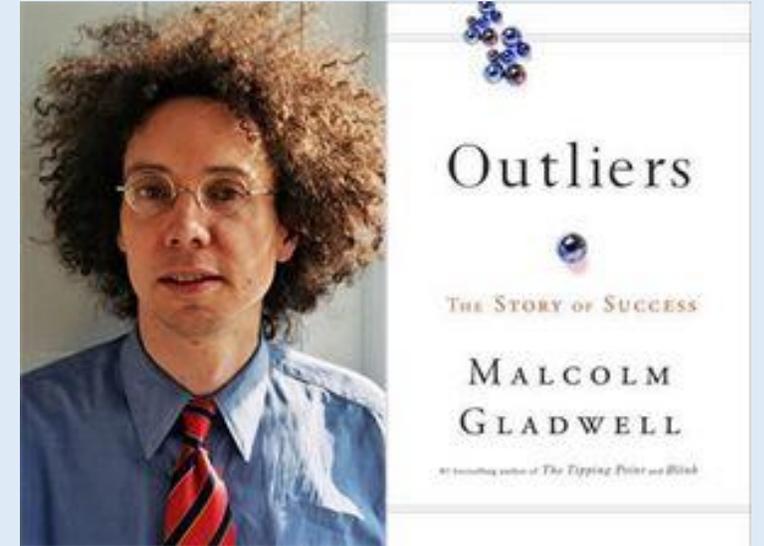
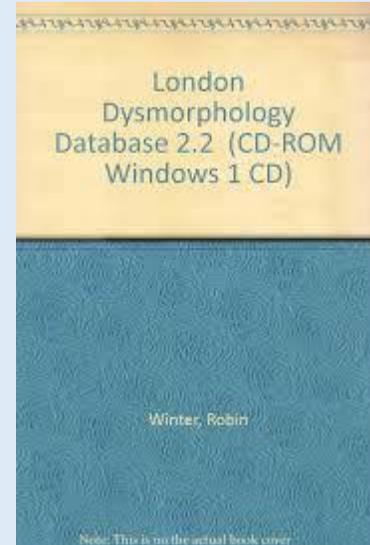
## *Act 3. Analysis.*

- Magic!
- Gestalt!
- Logic!
- Hard work!
- Buy a vowel!
- Call a lifeline!



# Diagnostic Strategies

- Experience
- Artificial Intelligence
  - London Dysmorphology Database
  - POSSUM
  - OMIM
  - SimulConsult
  - Face2Gene



# Act 3. Scene 1. The Diagnosis!



- Determine the clinical diagnosis (and decide the **certainty** of that dx)
  - Recognize a specific etiologic diagnosis with absolute certainty
  - Use published (consensus) diagnostic criteria
  - Assign to a general diagnostic category
  - Consider several possibilities (The differential diagnosis)
  - Become utterly confused
- Consider confirmatory or corroborating evaluations
  - Consultations
  - Radiographs
  - Laboratory tests



# Analytic strategies

Scotland Yard

Dr. Watson

Sherlock Holmes



"You know my method. It is founded upon the observation of trifles. Singularity is almost invariably a clue."

"The more outré and grotesque an incident is the more carefully it deserves to be examined."

"How often have I said that when you have excluded the impossible whatever remains, however improbable, must be the truth."

"I make a point of never having any prejudices, and of following docilely where fact may lead me."

"It is a capital mistake to theorize in advance of the facts. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts."

# Act 3. Scene 2. The Fishing Expedition

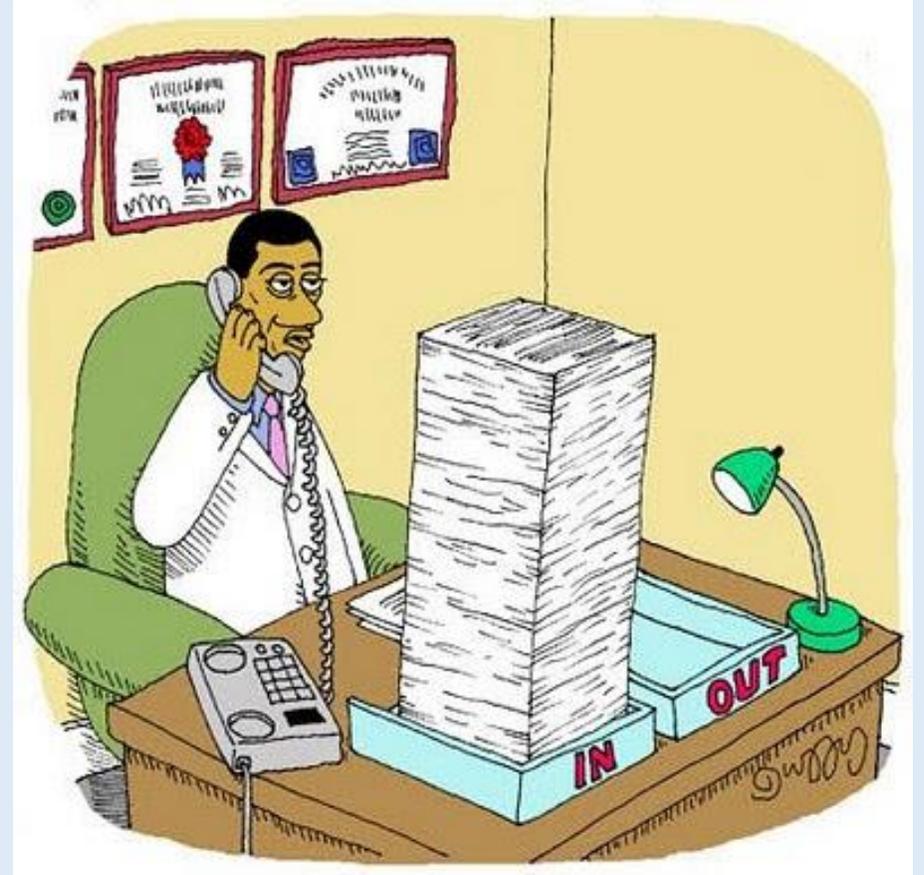


- Karyotype
- Chromosome microarray
- Metabolic testing
- One gene at a time
- Several genes at a time
- Lots of genes at a time
- Exome
- Genome
- Research testing – RNA, UDN, academic labs



# Act 3. Scene 3. Funding the Fishing Expedition

- Preauthorization
  - Medically necessary?
  - Experimental?
  - Investigational?
  - A covered benefit?



# Act 3. Scene 4. Informed Consent.

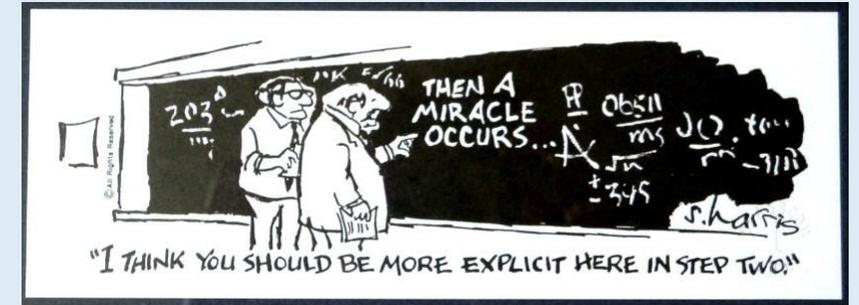
- Pre-test education
  - The technology
  - Possible outcomes
  - Pros
    - Understanding
    - Prognosis
    - Recurrence risk
  - Cons
    - Non-paternity
    - Consanguinity
- Clarify that genetic testing is a choice
  - Perfectly acceptable to choose yes or no



# Act 4. Scene 1.

## The genetics laboratory *performs a miracle*

- Receives the specimen, the paperwork
  - And (ideally) some **clinical information**



- And sends you the results



# Act 4. Scene 2.



- What do the results mean??!!
  - It's a lab report, but **the ordering clinician** is responsible for the final decision about meaning, value, and significance
- You strategize with your team and the lab about ...
  - Disclosure of the results
    - Telephone vs face-to-face
    - Educational materials
  - Additional testing
  - Recommendations for management



# Act 4. Scene 2 {offstage right}

- Additional testing?
  - Variants of uncertain significance
  - Deletion/duplication studies
  - Sequencing
  - Metabolomics
  - Enzyme activity
  - Skin or muscle biopsy
  - More aggressive testing

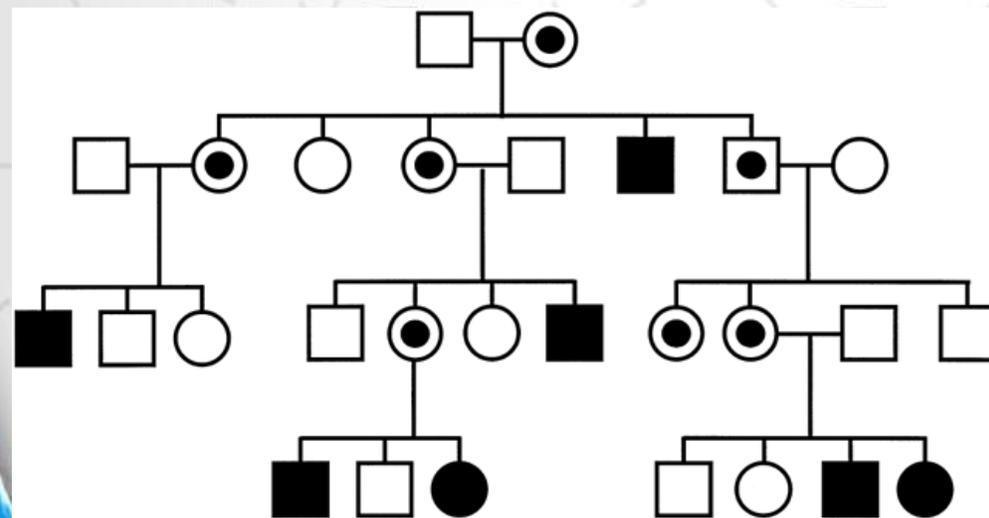


# Act 5. Scene 1. The follow up visit

- Disclosure of results, or a review of the telephone disclosure
- Explanations
- Pop quiz
- Discussion of prognosis
- Implications for management
- Recurrence risk
- Action Plan
- Assign homework
  - Information
  - Support groups
  - Consults
  - Familial testing



# Developmental delay – Intellectual disability



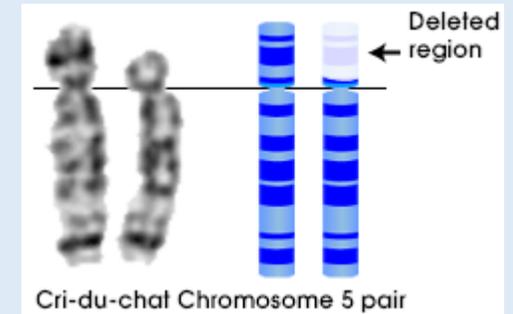
# Autism



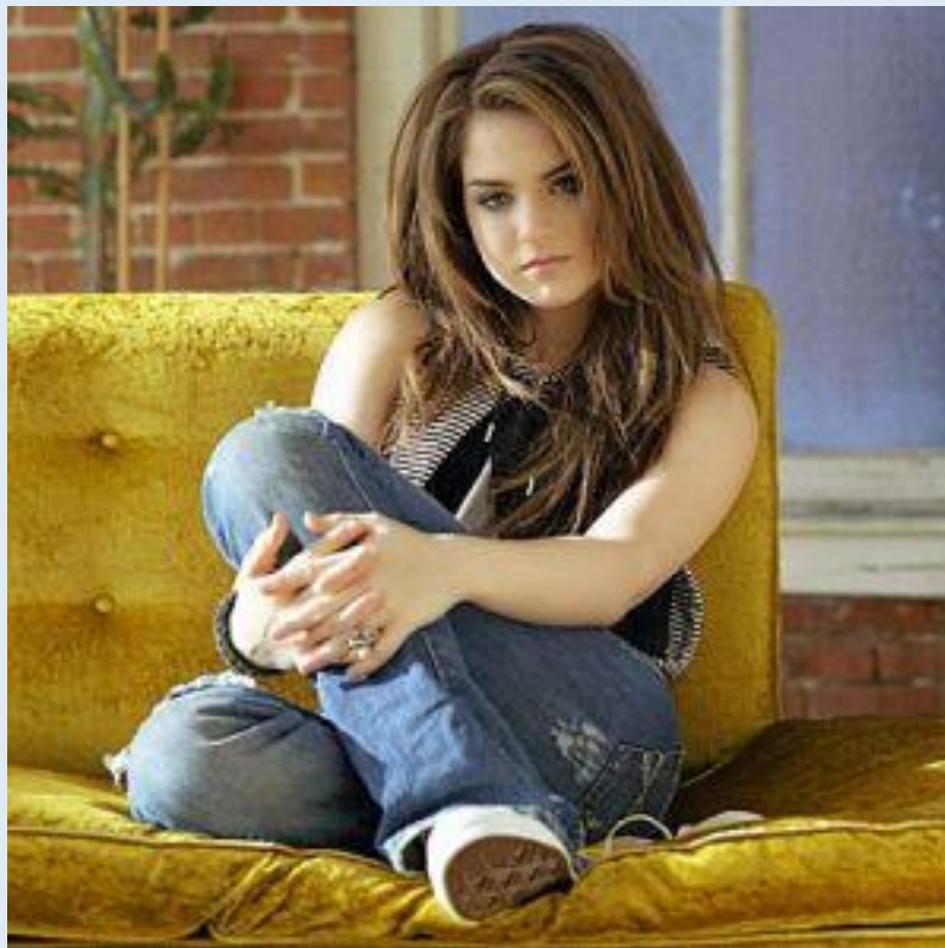
# Multiple congenital anomalies



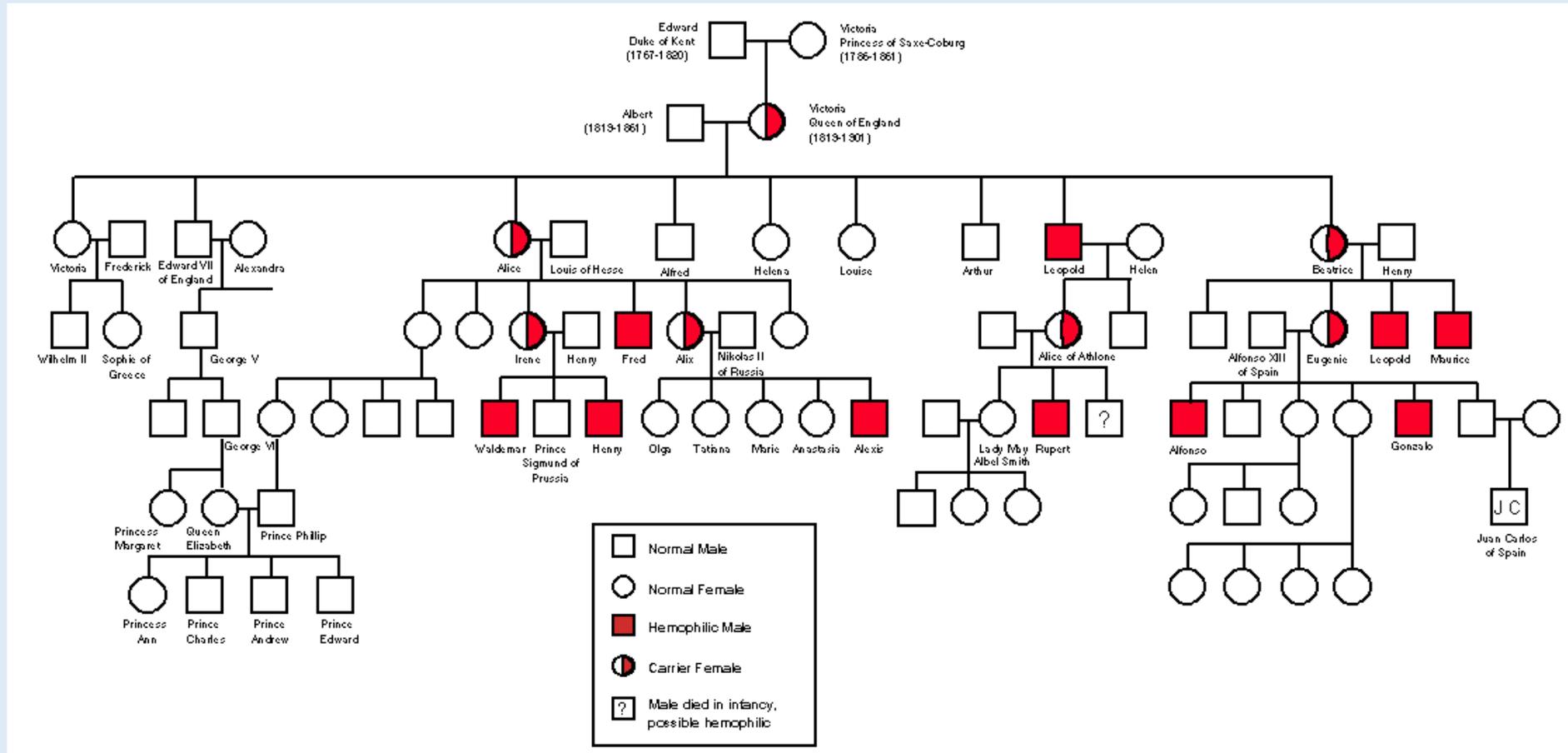
# Dysmorphic facial features



Short stature



# Family history of genetic disease



# Hypermobility



# Hypotonia



A theater stage with red curtains. The word "Fin" is written in a white, elegant script font in the center of the stage. The foreground shows rows of dark theater seats.

*Fin*

# Epilogue

If we shadows have offended,  
Think but this, and all is mended,  
That you have but slumber'd here  
While these visions did appear.  
And this weak and idle theme,  
No more yielding but a dream ...

