Genetics in Neonatology: What You Should Know in 2022

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Following this session, the participant should be able to:

- ***Describe the types of DNA testing***
- ***Recommend appropriate DNA testing for their patients and families***
- ***Demonstrate in their practice why pediatric knowledge is crucial for DNA testing***

What value genetics?

Old man--cough and fever, progresses to severe respiratory distress with fatigue.
Could have gone on to ARDS, renal failure, myocardial infarction, stroke but vaccines, boost, and Paxlovid.

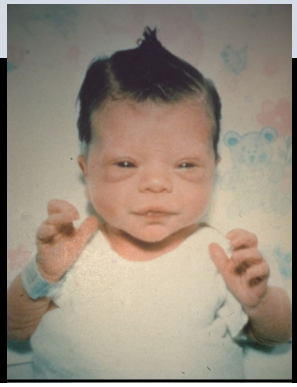
1.5 months later has persisting cough, difficulty with word recall and concentration (brain fog), sleep difficulties for 1 month.

Molecular technology provided RNA vaccines; ?little value genetics in ID.

Need for clinical geneticists?

1. A child born at 28 weeks has ongoing retinal, pulmonary, developmental problems

2. A newborn declines after feeding with lethargy, anion gap



3. Unusual facies, heart defect, hypercalcemia

1. Prematurity

Immature CNS and muscles: global hypotonia, poor oromotor function

CNS bleeds: Cerebral palsy, seizures, hydrocephalus

Poor nutrition, enterocolitis: Malabsorption, fragile bones, combined oromotor/absorptive defects

Retinopathy, CNS problems: Visuospatial, coordination problems

Parental support: Strain on resources

Genetic contribution ill-defined:
Neonatal, Developmental, Ophthy, Neuro care
>>>> Geneticist

But don't dismiss genetics: If cannot cure, can always heal

2. Newborn Screening ACT Sheet

Elevated C3 Acylcarnitine; **Propionic Acidemia and Methylmalonic Acidemia**

TEXAS Department of State Health Services

Medical Emergency: Take the Following IMMEDIATE Actions

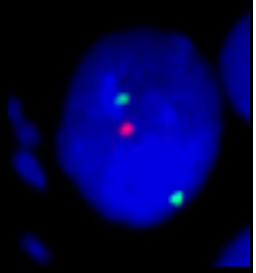
- **Contact family, repeat screen if second not done.**
- **Evaluate the newborn; check urine for ketones.**
- **Initiate confirmatory/diagnostic testing –now often DNA.**
- **Plasma amino acids, plasma acylcarnitine profile, and urine organic acids.**
- **Consult with metabolic specialist. (See attached list.)**
- **Educate family, report to newborn screening program.**

Neonatologist, pediatrician to tertiary metabolic specialist >> Clinical geneticist

?Expanded screen to genomic screen

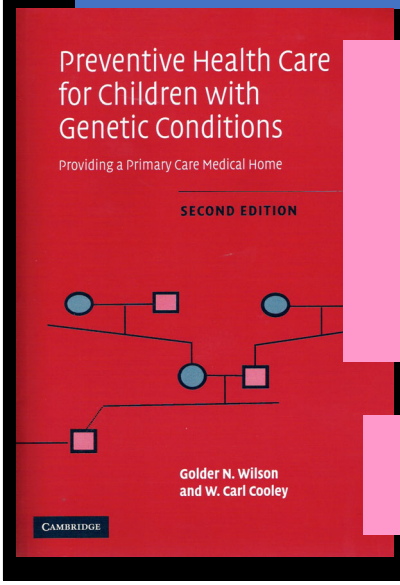
3. Unusual facies, pattern of defects, minor anomalies

Williams syndrome
Elfin appearance
~~FISH to show 7q11.23~~
Microarray analysis



Pediatrician to laboratory geneticist
> Clinical geneticist

Preventive Health Care
Providing a Medical Home



DNA for genetic influence
Clinicians for holistic care
Databases for rare diseases
www.omim.org

Primary attention, referral
Subspecialty return

DNA strands--Velcro strips with stick, cut, replace, extend

- GATTACATACGTATGTAATC
- CTAATGTATGCATACGTTAG----------(+ dup or – del)----
- Primer

G

T One letter at time = DNA sequencing

A One, panel or all genes (genomics)

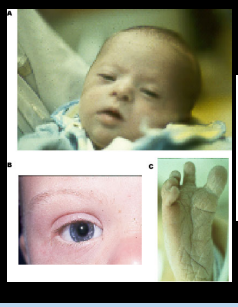
Labelled DNA or probe

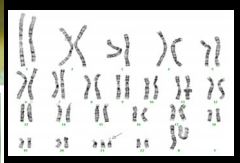
Cycle, amplify = PCR

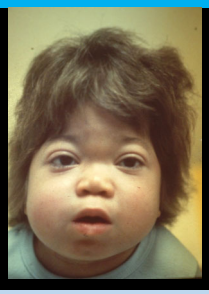
Match yellow and white DNA strands (strips), cross-cut, replace defective nucleotides

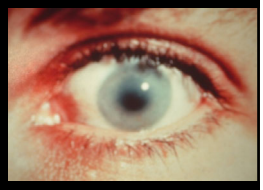
Clustered Regularly Interspersed Palindromic Repeats (CRISPR)

Genome book errors









Hunter Sx GATTACA

Extra/missing chromosome material (DNA) = extra/missing pages Binding error detected by bookstore

Whole chromosome study (karyotype)/microarray analysis

Single or several DNA nucleotide letter change = typo

Text error detected by copy editor

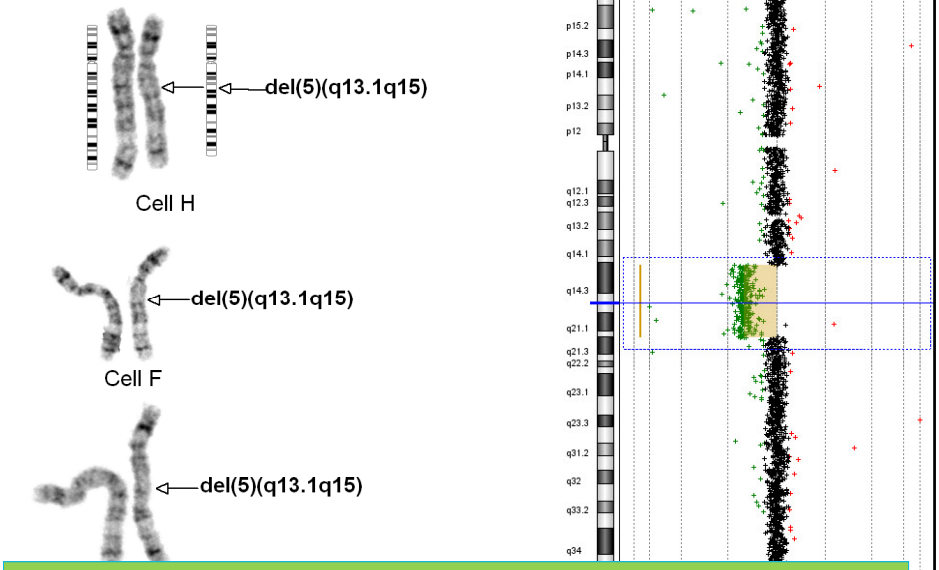
DNA sequencing = single gene, panel, whole exome, whole genome sequencing

Case 6: Normal newborn with epilepsy and later LD

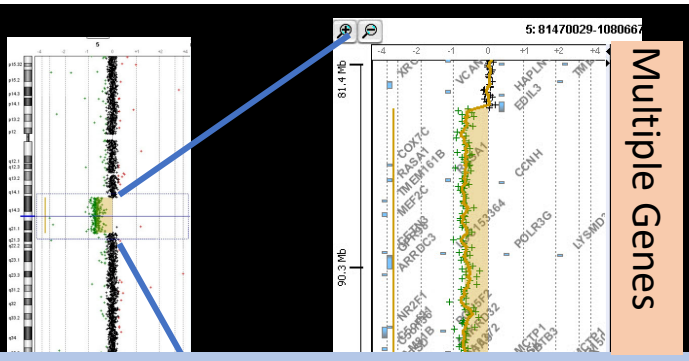
Baby girl born to 28-year-old parents with no prenatal concerns. She had some trouble breastfeeding in the nursery but mother was able to pump until 2 months of age.

- Normal motor milestones with mild speech delay that responded to therapy
- Epilepsy-early febrile seizures, later anticonvulsants, seizure free by teen years
- Difficulties with reading and math but no sensory or social difficulties. Later balance of mainstream and resource classes, graduated high school but living with parents.

Hypotonia
Feeding Issues
Dysmorphology
Delay
Microarray first



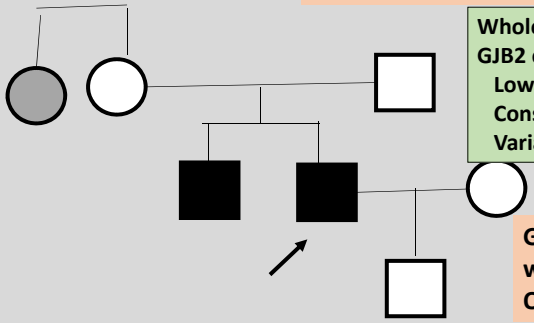
arr cgh del5q13.1q15 (83,592,798-104,671,993)x1 21.08 Mb



Fundamental problems for microarray and DNA tests in general:

1. **Multiple genes in deletion/duplication interval--no comprehensive theory for how imbalance causes syndromes**
2. **Difficult interpretation—basis is prevalence in normals versus affected patients but most "variant of uncertain significance"**
3. **Clinical patterns are extremely variable, complicating anticipatory guidance**
4. **Ethics—Economic and discrimination issues (high costs, poor insurance/Mcaid-Mcare coverage)**

27-year-old man developed lower extremity aches and weakness during sports in high school, increased to weakness and poor balance in 20s so needed cane to walk. Had classic steppage gait and altered NCV with Dx Charcot-Marie-Tooth by neurology. Normal facial appearance and cognitive function on exam. Main concern was whether 1-year-old son would be affected

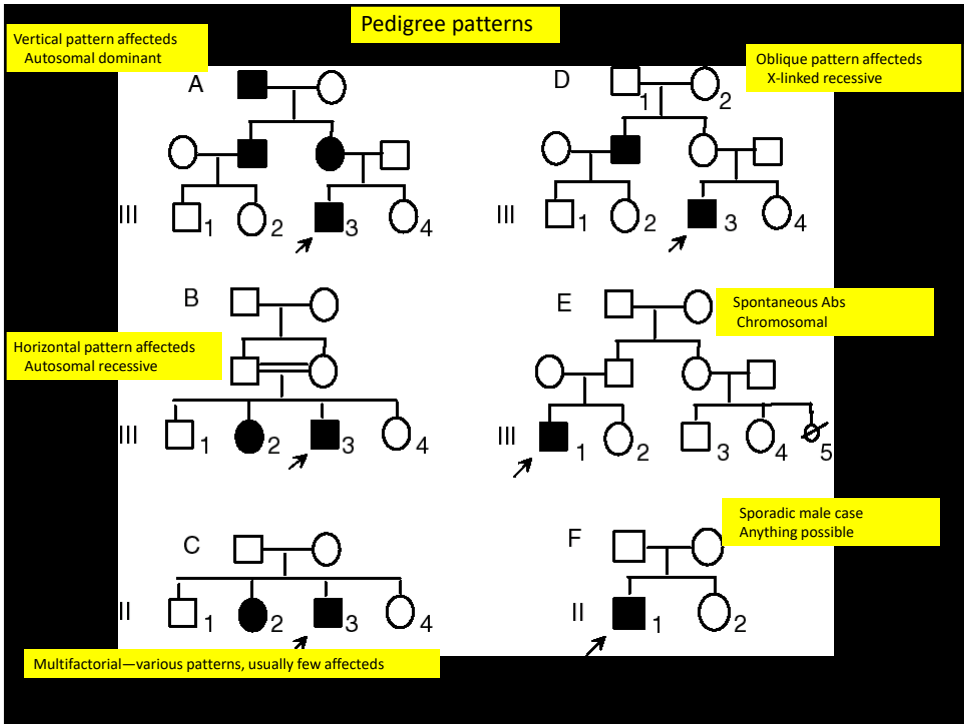


Microarray normal to exclude 17p PMP22 deletion

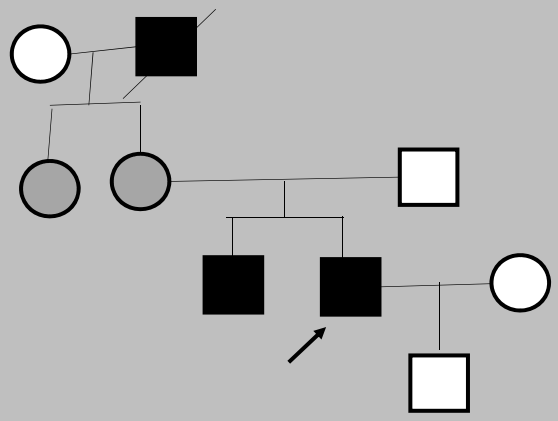
Whole exome sequencing
GJB2 c. 209A>G p.Lys70Arg or p.K70R
- Low population prevalence
- Conserved amino acid change
- Variant of uncertain significance

Gap junction beta-1 gene, associated with X-linked form of CMT
OMIM #302800 www.omim.org

Concerned about son



With this information, talked more to mother and found that his decreased maternal grandfather had many signs of CMT



X-linked dominant, variable expression, son cannot be affected

Algorithm for DNA testing and patient-parental counsel

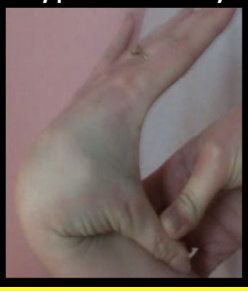
ORDERING

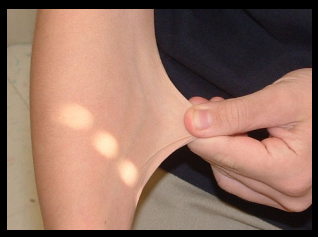
1. Microarray first for children with dysmorphology, delays—blood sample to Dr. Tonk
2. DNA sequencing (one gene, panel, WES, WGS) for disorders with Mendelian inheritance—buccal swabs common.
3. Genome sequencing evolving, simultaneous tests standard
4. Be aware of OOP costs of $2500-3500 for insured patients, Mcaid-Mcare rarely accepted.
5. System specialist (cardiologist, etc.) optimal to order, often have lab associations, can get costs

COUNSEL

1. Emphasize Ancestry, 23-Me good for relations, not disease
2. Look at variant prevalence--MTHFR 10-30% and bullroar
3. Accept variants VUS or path, state contribute to disease
4. Arrange parental studies for family, severity counsel

Hypermobility complex/Ehlers-Danlos syndrome

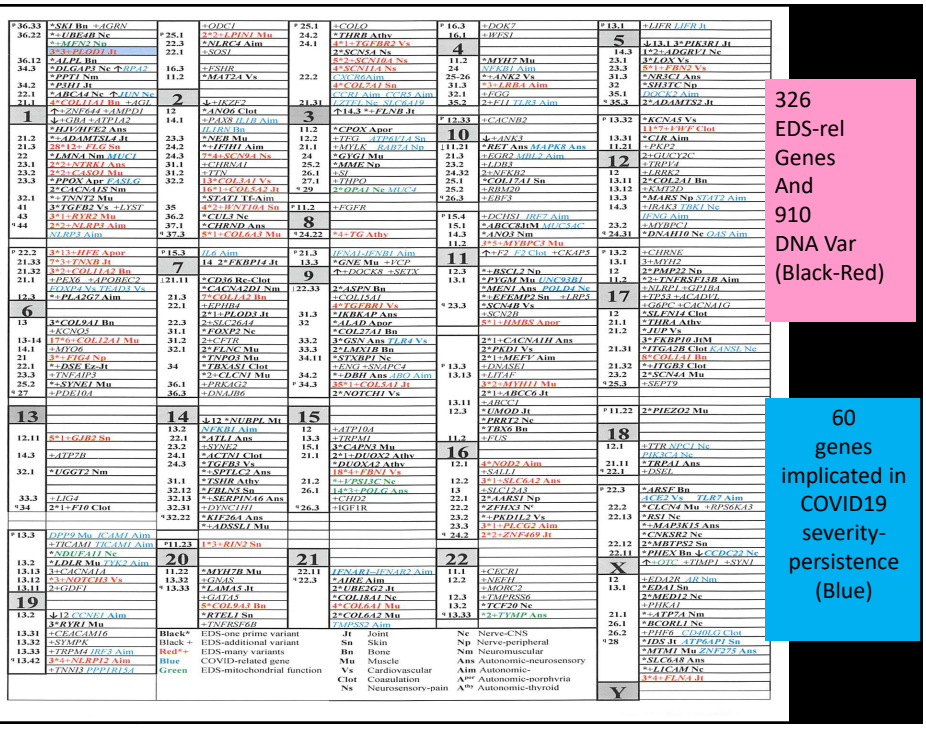




1899 patients with EDS, 905 with whole exome sequencing, 566 with potentially significant variants by clinical qualification

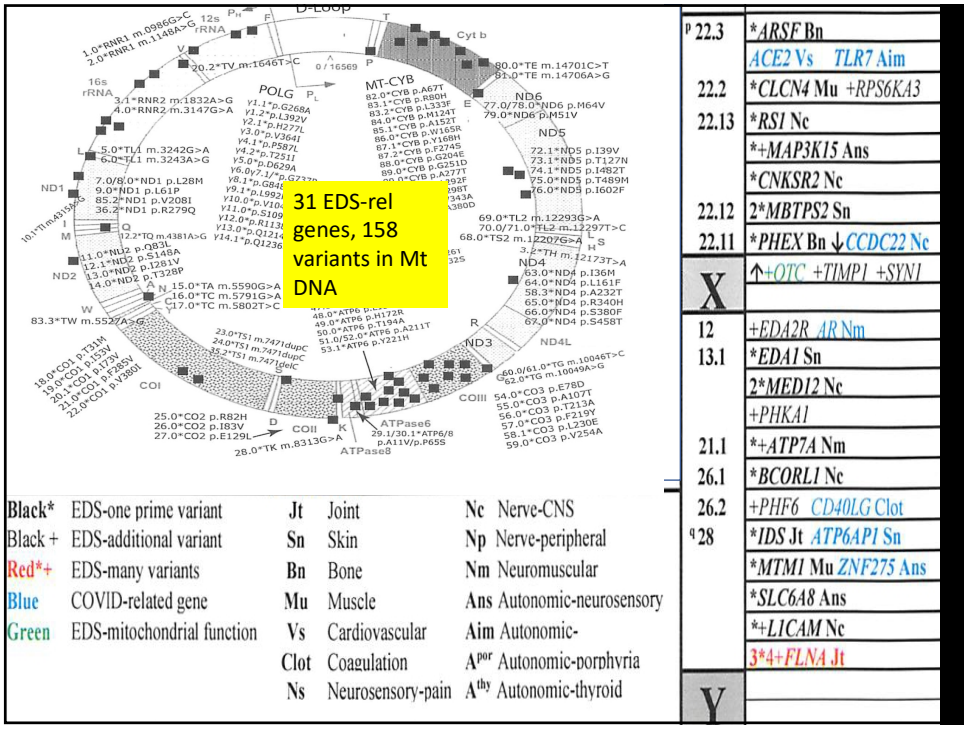
Must recognize autonomic imbalance as part of spectrum—POTS, IBS, increased mast cell/inflammation and altered immunity

Variant utility/contribution by clinical mechanisms: Tissue laxity + Dysautonomia (lower body blood pooling in flexible vessels decreases cerebral blood flow, with reactive adrenergic "fight-or flight" stimulation (POTS-brain fog, fatigue, tachycardia, anxiety: MCAS- asthma, rashes, hives, food-medicine intolerances), and cholinergic suppression (IBS-bowel irregularity, reflux, nausea)



326 EDS-rel Genes And 910 DNA Var (Black-Red)

60 genes implicated in COVID19 severity-persistence (Blue)



Comparison "long COVID19" or PACS and EDS dysautonomia symptoms

	Long COVID19 1.2:1 M:F		EDS 1.2:1 M:F		COVID genes	EDS genes
Finding	**Range %**	**Mean %**	**Mean %**	**Range %**	**SAME**	**SAME**
Brain fog-confusion	30--70	55	75	27--89	*F2*	*F2*
Chronic fatigue	30--60	52	79	38--91	*LIFR*	*LIFR*
Dyspnea-asthma	20--52	37	40	32--52	*NLRP3*	*NLRP3*
Anxiety	12--40	35	60	48--72	*TICAM1*	*TICAM1*
Sleep difficulty	20--35	33	56	45--68	SIMILAR	SIMILAR
Tachycardia	20--48	32	71	54--86	*DOCK2*	*DOCK8*
Difficulty walking	17--55	25	50	35--72	*FOXP4*	*FOXP2*
IBS symptoms	14--78	22	75	67--89	*IRF3/IRF7*	*IF1H1*
Muscle weakness	15--25	20	31	22--49	*MAPK8*	*MAP3K15*
Muscle aches	12--22	19	54	41--79	*NFKB1*	*NFKB1A/B2*
Arthralgia/arthritis	15--27	17	47	32--94	*PIK3CA*	*PIK3R1*
Syncope	0--14	13	39	24--52	*SLCA19*	*SLC6A2/8*
Dizziness-vertigo	10--50	10	85	39--89	*STAT1*	*STAT2*
Transient rashes	7--20	8	41	14--45	*TMPRSS2*	*TMPRSS6*
Headache	2--17	8	72	55--78	*ZNF 275*	*ZNF469/644*

Common conditions involve multigene networks, DNA changes (mutations) contributors rather than diagnoses.

Gene repair-replacement limited, engineered therapies (Gleevec etc.) powerful and proliferating

Cell-free DNA in maternal or cancer patient bloodstreams one of the ongoing insights from DNA technology

Era of pediatrician and pediatric specialist plus laboratory, not clinical genetics

Era of single gene disorders giving way to genomic technologies that show gene networks, the "rest of the story" that explains incomplete penetrance, variable expressivity and disease severity

NextGen genetics is of value, consider genetic influence even in environmental disorders with severe or unusual outcomes.

“The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music.”
Lewis Thomas MD

golder.wilson@ttuhsc.edu
Covenant-sponsored clinic second Monday-Tuesday
Scheduling ph 806-743-7334 fax -7332
Currently chromosomes-microarray through Dr. Tonk