Next-Gen Informed Consent for Prenatal Testing: Case Presentations

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- No disclosures

cfDNA Cases

Case 1

38 year old G1 at 11 weeks

Medical history: anxiety disorder

Genetic/Family history: African American

Elects to have cfDNA testing for AMA

Case 1

cfDNA result: +22q11 deletion

Amniocentesis at 16 weeks: 46, XY; FISH negative for 22q11.2 deletion

Normal microarray: arr(1-22)x2,(XY)x1

Ultrasound: Appropriate fetal growth, no structural abnormalities identified, male external genitalia

Case 1

Additional genetic history

- "Learning disabilities"- patient graduated from community college and works as a sales clerk
- Brother died shortly after birth from a cardiac defect
- Father had a history of anxiety and depression; died suddenly at age 55 years-? etiology

What should you do next?

Case 1

22q11 deletion testing on patient: Positive

Implications:

- Future pregnancies
- Family members
- Patient's health

Case 2

- 42 yo G2P1 at 15 weeks
- cfDNA positive for T21
- Amniocentesis 46XY with normal appearing US
- Patient diagnosed with metastatic breast cancer
- Tumor studies pending

Case 3

- 36 year old G3P2 at 14 0/7 weeks gestation
- cfDNA for AMA
- Medical hx: non-significant
- Genetic hx: patient and her husband are of Irish descent, no hx of birth defects, DD/ID, stillbirth or genetic syndromes

Case 3

- cfDNA result: XO, negative screen for trisomy 21, 18, 13

- What do you do next?

Case 3

- Ultrasound: no abnormalities detected
- Amniocentesis: 46, XX
- Patient karyotype: 45X[3]/46XX[27]
  - Age-related loss or gain of an X chromosome in white blood cells occurs in normal females

Case 4

- 36 yo: cfDNA - XXX
  - amniocentesis: 46, XX
  - maternal karyotype 47, XXX

Case 5

- 35 yo G2P0010 at 13 weeks gestation
- Hx of prior pregnancy diagnosed with Down syndrome at 16 weeks gestation
  - Had amniocentesis after a positive sequential screen
  - Fetal karyotype 47, XY, +21
- NIPT: XYY, screen negative for trisomy 21, 18 and 13

Case 5

- Amniocentesis: 46, XYY
- Patient and her husband were initially very upset and considered pregnancy termination
- Elected to continue the pregnancy but the husband had some reservations

Detection of Sex Chromosome Abnormalities

SCA*	Detection Mazloom [1]		Detection Bianchi[2]		Detection Nicolaides[3]		Combined	
45X	25/30	(83%)	15/20	(75%)	43/49	(88%)	83/99	(88%)
47XXY	11/13	(85%)	2/3	(67%)	1/1	(100%)	14/17	(82%)
47XXX	5/6	(83%)	3/4	(75%)	5/6	(83%)	13/16	(81%)
47XYY	3/4	(75%)	3/3	(100%)	3/3	(100%)	9/10	(90%)

*Mosaics not included

[1]Mazloom et al. Prenat Diagn 2013;33:591-7
[2]Bianchi et al. Obstet Gynecol 2012;119:890-901
[3]Nicolaides et al. Fetal Diagn Ther Dec 2013

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The false-positive and false-negative rates for the detection of SCAs with cfDNA testing need to be more precisely defined.

Chromosomal Abnormalities in Newborns

Abnormality	Frequency at birth
Balanced translocation	1 in 500
Unbalanced translocation	1 in 2000
Pericentric inversion	1 in 100
Trisomy 21	1 in 700
Trisomy 18	1 in 6000
Trisomy 13	1 in 10000
47,XXY	**1 in 1000 males**
47,XYY	**1 in 1000 males**
47,XXX	**1 in 1000 females**
45,X	**1 in 5000 females**

Sex Chromosome Aneuploidy Phenotypes

- Prognosis for intellectual and psychological functioning is less certain vs concrete outcomes (infertility)
- Ascertainment bias
  - Earlier adult studies reporting a strong association with mental deficiency and psychological disturbance- case reports mental and penal institutions
- Majority of individuals with SCAs will go through life without knowing they have the condition-mostly within the “normal range” of development

SCA: Potential Benefit of Prenatal Diagnosis

Individuals prenatally diagnosed with SCAs may benefit from early screening and medical interventions

- 45X - RCT 149 girls[1]
  - Growth hormone Rx-adult height 5 cm greater vs placebo
  - Estrogen Rx-neurocognitive and behavioral benefits

- 47 XXY-Testosterone supplementation beginning at puberty
  - Normal male phenotype development
    - Increases penile size
    - Decreases gynecomastia and abdominal obesity
  - Improves cognition and social integration

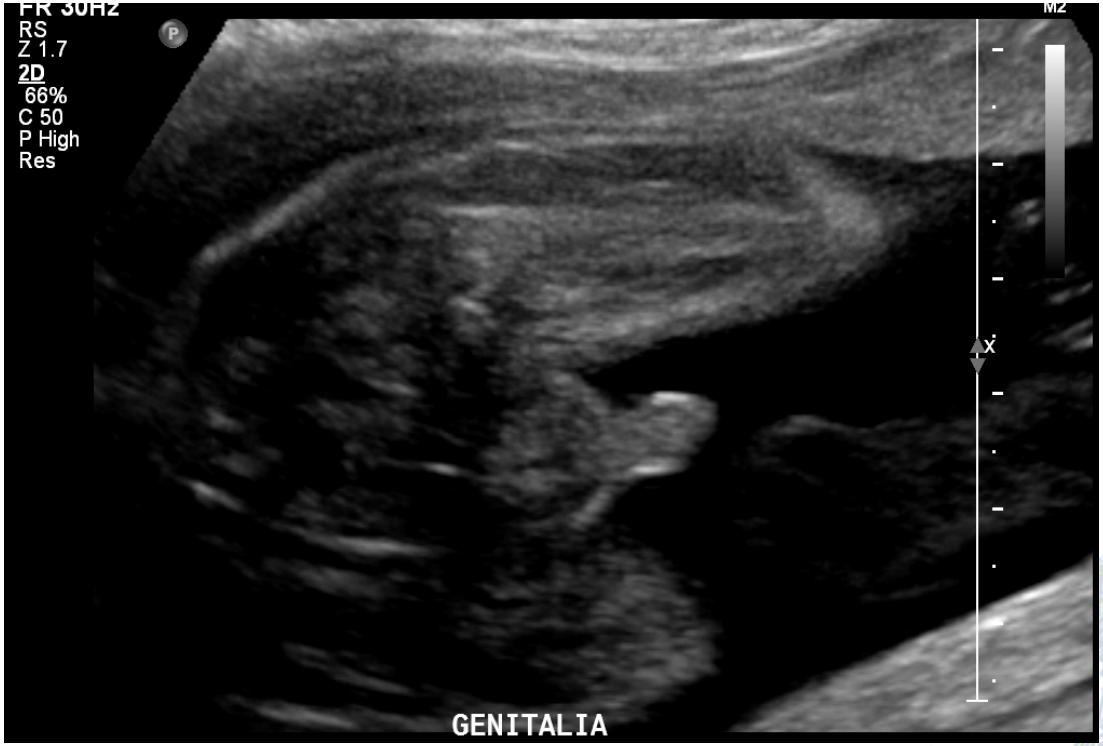
[1]Ross JL et al. NEJM. 2011;364:1230-42

Should NIPT be used to screen for SCAs?

- Potential benefit
  - Earlier diagnosis – optimize outcomes
  - Referral to genetics specialist - improve parental knowledge of pathology associated with SCA
- Potential negatives
  - Wide yet mild phenotypic spectrum
  - Possibility of uncovering a previously unknown aneuploidy in the mother
- Patient autonomy: women should have the option to separately accept or reject the sex chromosome analysis
- Quality of the counseling is critical

Case 6

- cfDNA: XX
- Second trimester US: male genitalia



Case 6

Amniocentesis: SRY translocation

- 46, X der(X)t(X;Y)(p22.3, p11.3)
- Array revealed no additional deletions

Case 7

- cfDNA: trisomy 18
- Patient declines invasive diagnostic testing and terminates the pregnancy
- Karyotype: 46,XY

Case 8……

- Normal cfDNA result
- Newborn diagnosed with:
  - Single gene disorder
  - Multifactorial disorder
  - Rare genetic syndrome……

Chromosomal Microarray Cases

Case 1: CVS performed for AMA

- Karyotype: 46,XY
- Microarray: 203 kb del 3p26.2
- Parental arrays done – maternal deletion confirmed

Case 1: Counseling Issues

- Gene for spinocerebellar ataxia 15 maps to this region
- Gene deletions associated with adult onset gait ataxia, slowly progressive
  - Autosomal dominant
  - Onset is between ages seven and 66 years, affected individuals remain ambulant for ten to 54 years after onset

Case 1: Counseling Issues

- Should we disclose CNVs associated with adult onset diseases (i.e. cancer risk, neuro-degenerative disorders)?
- Are parents prepared to receive genetic information that is relevant to their health?
- Should informed consent process include this information?

Incidental Discovery of Late-Onset Untreatable Disease

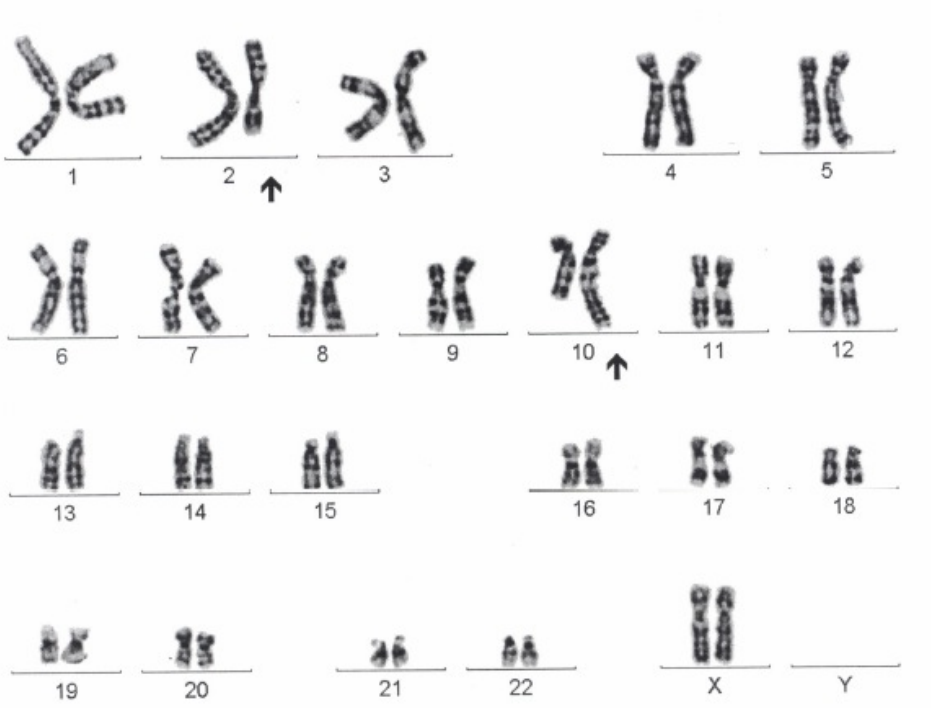
- Most labs do not report them in children and pre-symptomatic adults
- How should this be handled in prenatal cases?
  - Disorder can be prevented if parents choose the option of not continuing a pregnancy
  - Do we infringe autonomy by shielding information that may allow parents and young adults to make decisions about their future that take into consideration all aspects of their current or future health?

Incidental Discovery of Late-Onset Untreatable Disease

- Children should not undergo presymptomatic genetic testing for late-onset disorders for which no cure is available
- Preserves the child's right to an open future that is unbiased by the prior knowledge that there will be impairment in later adulthood

Case 2

- 40 year old G2P1- amniocentesis for AMA
- Cytogenetic analysis: 46,XX,t(2;10)(q31;q26)



Case 2

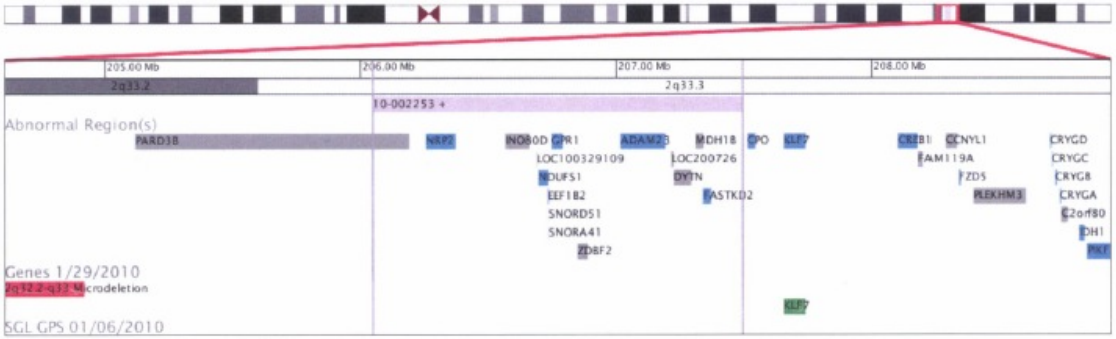
- Parental karyotypes – normal 46,XX and 46,XY
- Anatomy scan – no apparent anomalies
- Fetal echocardiogram – no apparent anomalies

Case 2

- 6.1% (10 of 163) of prenatally detected de novo balanced simple balanced reciprocal translocations were associated with serious congenital anomalies
- Microarray offered to detect a genomic gain or loss at the chromosome breakpoints involved in the translocation
  - Pathogenic gene disruption - (translocation breakpoint) in the middle of a gene
  - Cryptic intrachromosomal rearrangements which may exist in addition to the cytogenetically visible structural chromosome aberrations

ArrayCGH - 1.5 Mb duplication of 2q33.3

Genoglyphix Abnormality Summary SGL# 10-002253



Legend:

Abnormal Region(s): Copy-number alteration identified in this patient.

Genes: Protein-coding genes from the NCBI mRNA reference sequences (RefSeq) collection. Blue = genes present in the OMIM database. Gray = genes not present in OMIM.

SGL GPS: Signature Genomic Laboratories' Genome Positioning System = regions of the genome known to be associated with specific genetic conditions. Causative genes/developmental pathway genes are green.

Abnormality Details:

Copy Number:	Copy Gain
Chromosome Band:	2q33.3
Genomic Coordinates:	chr2:206048173-207493279
Estimated Minimum Size:	1.45 Mb
Estimated Maximum Size:	1.49 Mb
Gaps:	Start Gap: 30.06 kb Cen End Gap: 17.37 kb Tel

Syndromes in Region (0 Total):

OMIM Genes in Region (6 Total):
NRP2, NDUFS1, EEF1B2, GPR1, ADAM23, FASTKD2

Other Genes in Region (9 Total):
PARD3B, INO80D, LOC100329109, SNORD51, SNORA41, ZDBF2, LOC200726, DYTN, MDH1B

Case 2: Genetic Counseling

- *de novo* unbalanced translocation with a 1.5 Mb duplication of 2q33.3
- Review
  - Literature
  - Databases
  - OMIM
- Conclusion: duplication of uncertain clinical significance
- With a normal ECHO and US - 6% chance of negative effect on cognitive development, developmental delay, behavioral issues
- Couple chose to terminate

cfDNA:
Pre-test counseling and informed consent issues

- Scope and nature of disorders being tested
- Detection, false-positive and no call rates
- Explanation that false-positive results can be common (particularly when testing for rare disorders)
- Follow-up confirmatory studies are necessary for positive screening results
- Possibility of identification of genetic variants in mother
- Uncertainties associated with mosaicism, sex chromosome aneuploidy and unexpected findings

Microarray:

Pre-test counseling and informed consent issues

- Genetic principles of uncertainty
- Variable expressivity
- Lack of precise genotype-phenotype correlation
- Possibility of identification of genetic variants in a fetus and/or parent that may cause adult-onset disorders
- Benefits of a targeted array

Additional Informed Consent Issues

- ? Disclosure of genetic variants in a fetus and/or parent that may cause adult-onset disorders
- Opt in/opt out testing

Conclusions

- Increased genetic testing options with increased complexity
- Informed consent process/pre and post test counseling - critical
- Need to develop tools to optimize consent process for all stakeholders - patients, care providers and the labs

Discussion

- How can we improve the process of informed consent for prenatal testing?