Predicting the Challenges of Prenatal Microarray from the Postnatal Experience

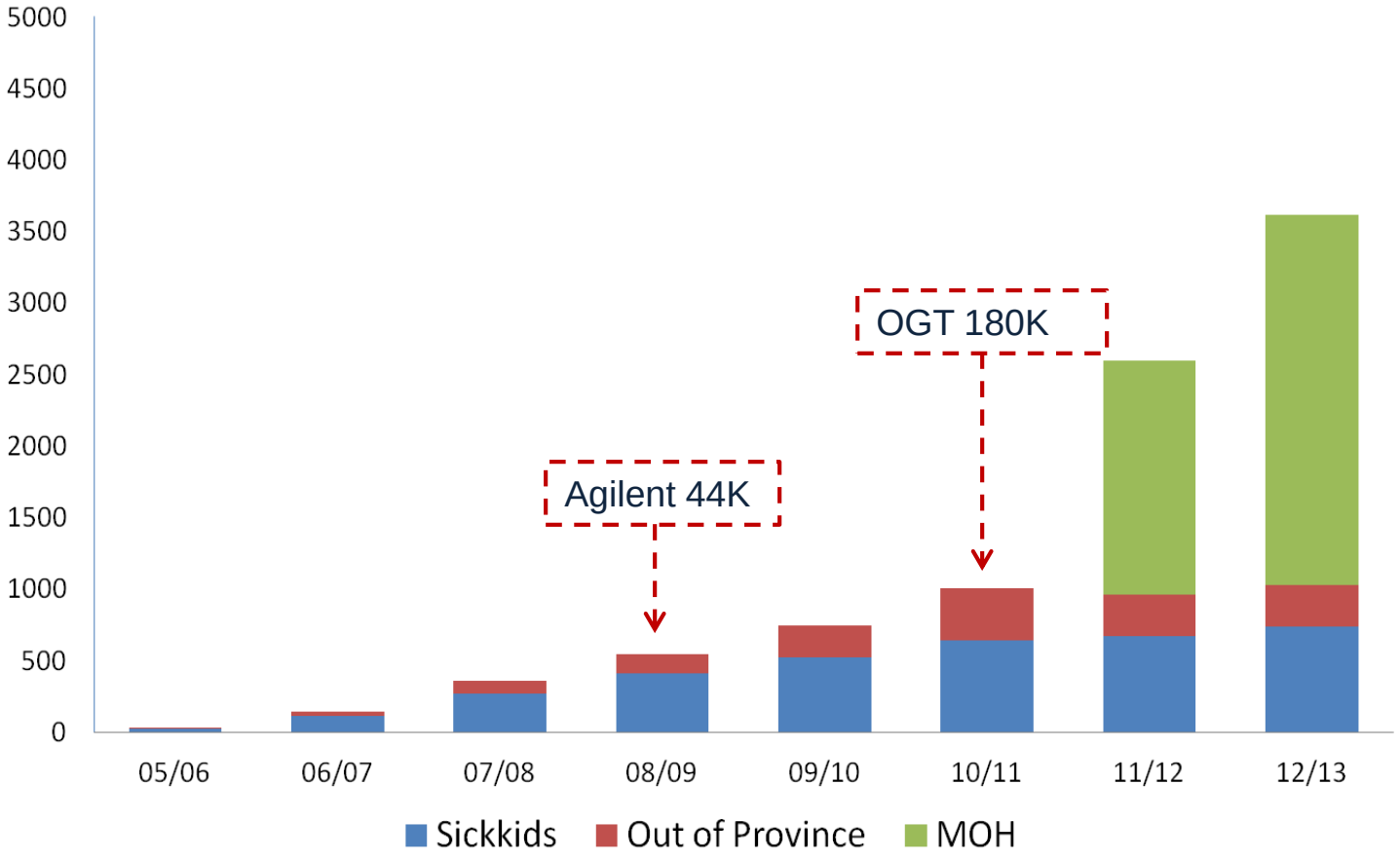
Abdul Noor, PhD

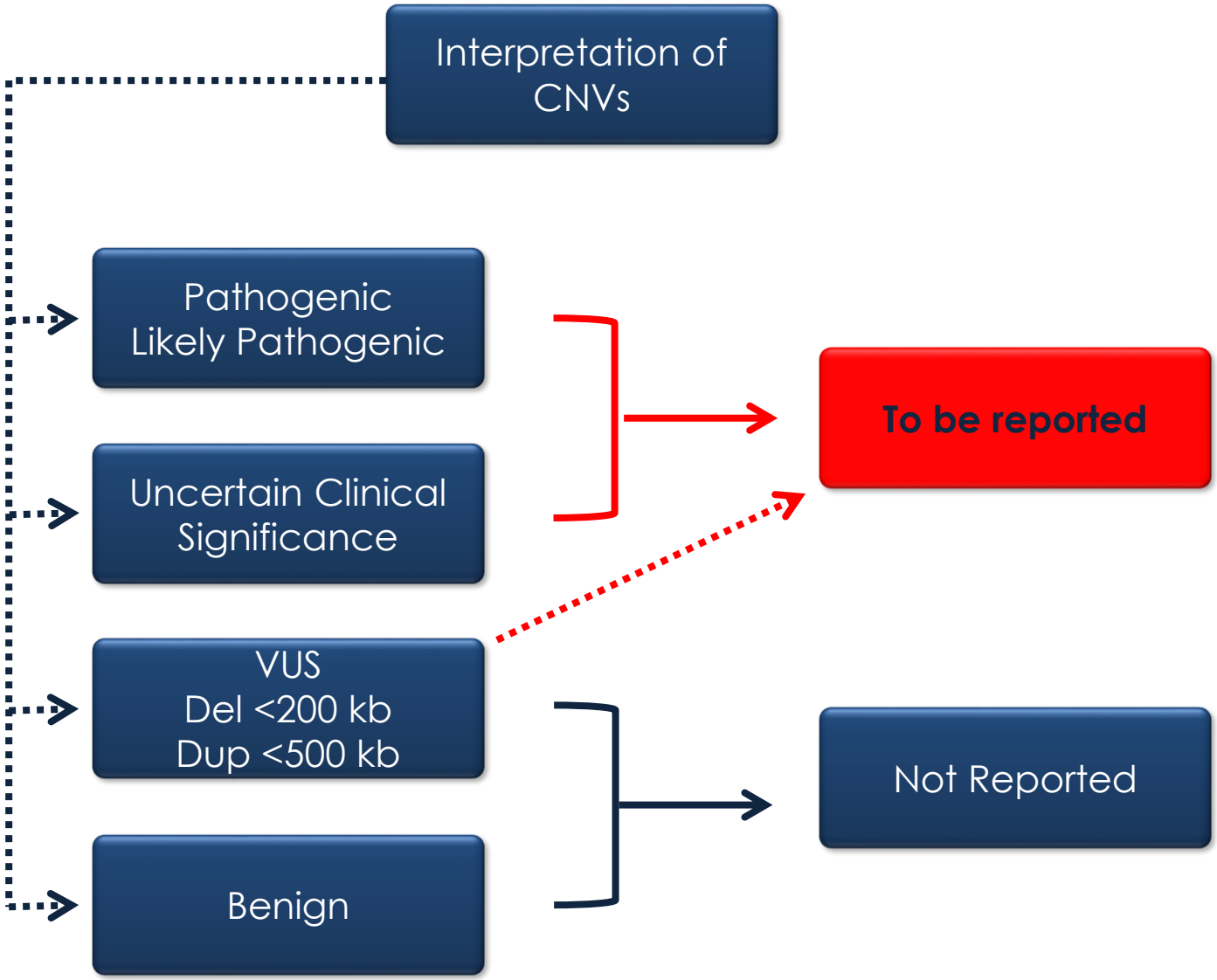
Clinical Cytogenetic Fellow (CCMG)
The Hospital for Sick Children
Toronto, ON

SickKids

Microarray Service at SickKids

Annual Microarray Test Volumes




Interpretation of CNVs
Pathogenic
Likely Pathogenic
Uncertain Clinical Significance
VUS
Del <200 kb
Dup <500 kb
Benign
To be reported
Not Reported

Diagnostic Yield

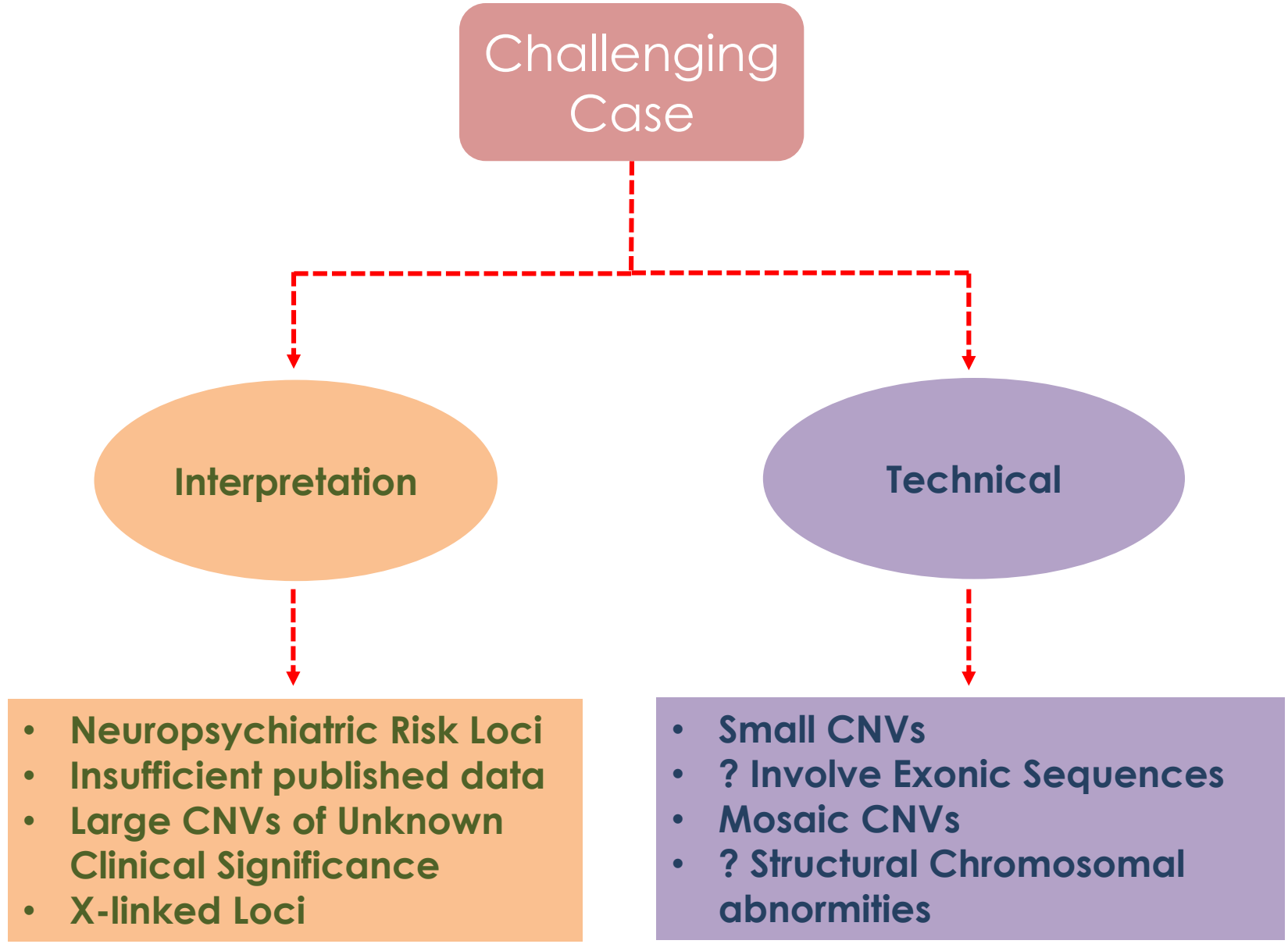
- Pathogenic = 10%
- Variants of Uncertain Significance = 16%

SickKids

- Pathogenic = 9%
- Variants of Uncertain Significance = 14%

CVH

Challenging Cases


Challenging Case
Interpretation
Technical
• Neuropsychiatric Risk Loci
• Insufficient published data
• Large CNVs of Unknown Clinical Significance
• X-linked Loci
• Small CNVs
• ? Involve Exonic Sequences
• Mosaic CNVs
• ? Structural Chromosomal abnormities

Neuropsychiatric Risk Loci

CNV	Initial identification	Subsequent neurodevelopmental associations	Other non-behavioural phenotypes
del3q29	MR (Rossi et al., 2001)	ASD (Willatt et al., 2005); schizophrenia (Mulle et al., 2010) BPD (Bailer et al., 2002)	Eye abnormalities (Tyshchenko et al., 2009); cardiac defect (Li et al., 2009)
del7q31	ASD and language disorders (IMGSAC, 2001)	Speech and language development (Marshall et al., 2008); TS (Sundaram et al., 2010)	–
dup7q36.3	ID (Tyson et al., 2005)	Schizophrenia (Kirov et al., 2009a, b)	Triphalangeal thumb and polysyndactyly phenotype (Klopocki et al., 2008)
dup15q11–q13	Autism (Gillberg et al., 1991)	IGE (Bundey et al., 1994); developmental delay (Mohandas et al., 1999); schizophrenia (Kirov et al., 2008; Ingason et al., 2011)	–
del15q11.2	ID, ADHD (Murthy et al., 2007)	Schizophrenia (Stefansson et al., 2008; ISC, 2008); ASD (Doornbos et al., 2009); IGE (de Kovel et al., 2010)	–
del15q13.3	ID, seizures (Sharp et al., 2008)	Schizophrenia (Stefansson et al., 2008; ISC, 2008); ASD (Miller et al., 2009); IGE (Helbig et al., 2009); BPD (Miller et al., 2009)	Cardiac defects (van Bon et al., 2009)
dup16p11.2	Autism (Weiss et al., 2008)	Schizophrenia (Walsh et al., 2008; McCarthy et al., 2009); ADHD, microcephaly (Shinawi et al., 2010)	Syringomyelia (Schaaf et al., 2011)
del 16p11.2	Cardiac defects and unilateral multiple renal cysts (Hernando et al., 2002)	Mild MR (Ghebranious et al., 2007); Autism (Weiss et al., 2008; Kumar et al., 2008)	Flat facies, hypotonia, short stature (Ballif et al., 2007a, b); obesity (Walters et al., 2010)
del16p13.1	ID (Ullmann et al., 2007)	IGE, microcephaly (Hannes et al., 2009); schizophrenia (Ingason et al., 2009); IGE (de Kovel et al., 2010)	–
dup16p13.1	ASD (Ullmann et al., 2007)	MR (Hannes et al., 2009); schizophrenia (Ingason et al., 2009)	Congenital anomalies (Hannes et al., 2009)

Variable phenotype, penetrance and expressivity.

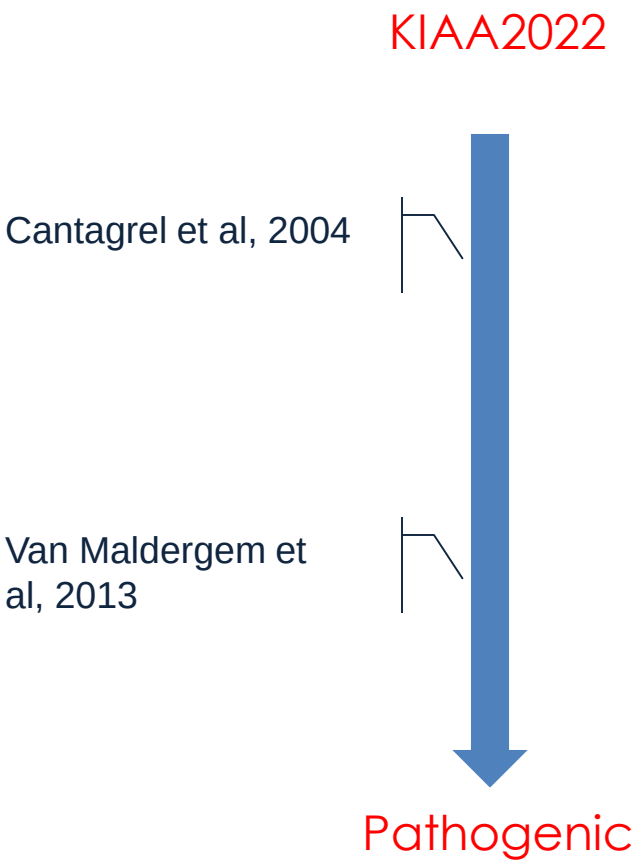
Insufficient Published Data

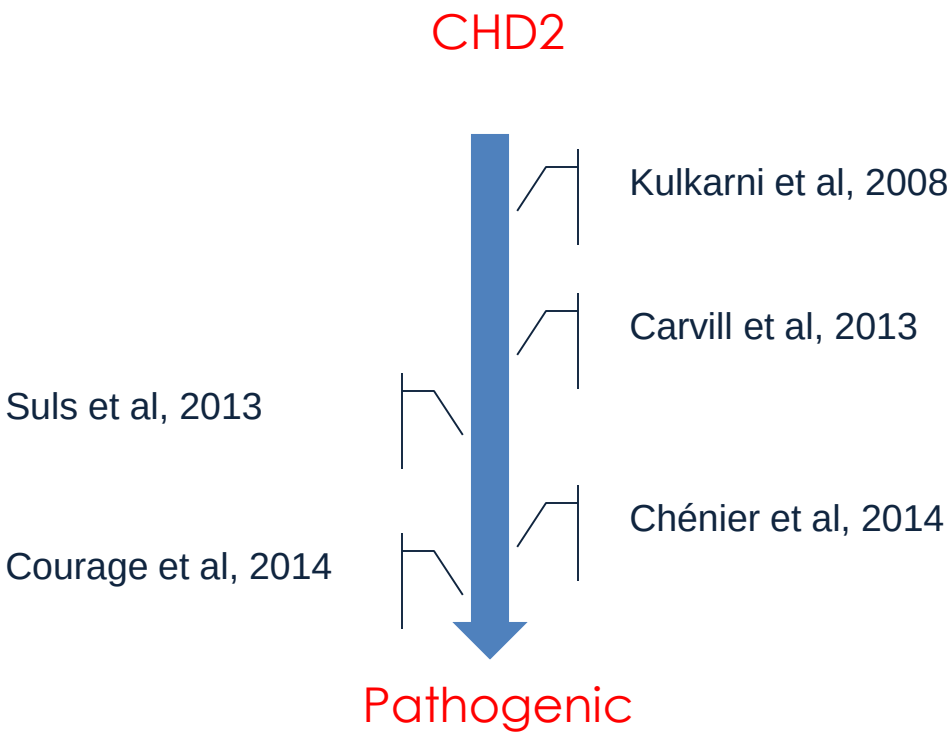
- 77 Kb deletion, Xq13.3, exonic deletion of KIAA2022. In one published report disruption of KIAA2022 gene has been reported in two related males with intellectual disability.

- 191 Kb deletion, 15q26.1, four RefSeq genes including CHD2. Disruption of CHD2 gene by a de novo translocation in one patient (Kulkarni et al, 2008).

Clinical significance not established.

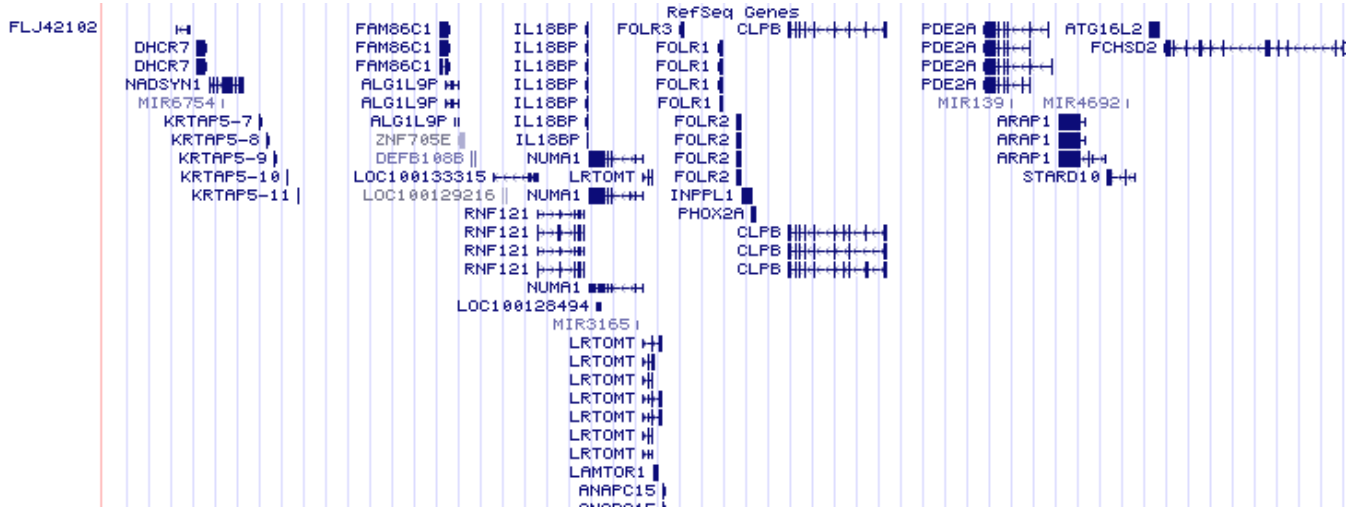
Insufficient Published Data





Large CNVs of Unknown Clinical Significance

- 1.8 Mb deletion, 11q13.4. Involves 32 RefSeq genes, 05 OMIM Morbid Map genes.



Size and number of genes suggest to be Pathogenic
No published evidence

X-linked Loci

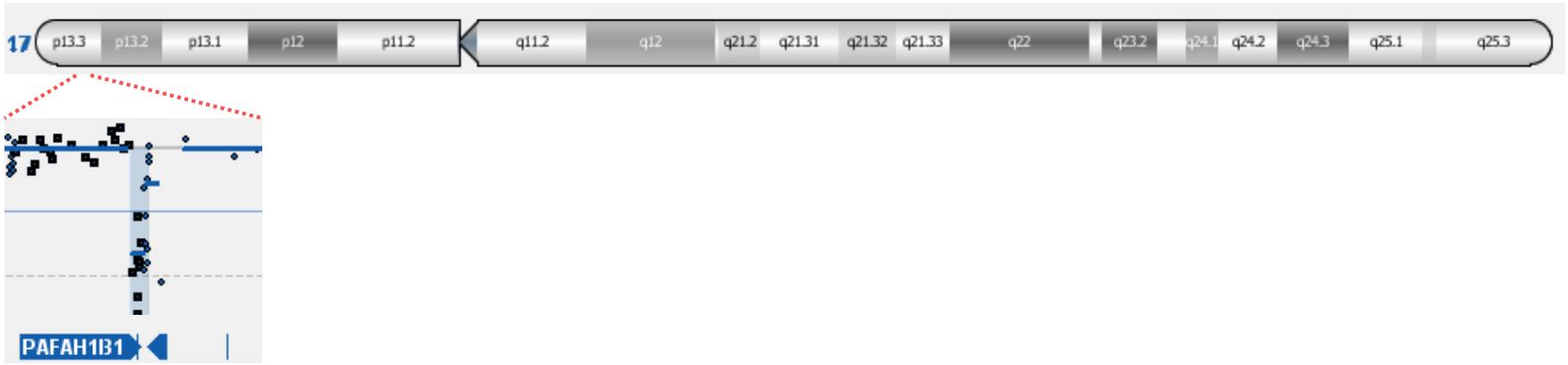
- DMD deletions in females

- 6.708 Mb deletion, Xq27.3-q28, 39 RefSeq genes, 03 OMIM Morbid Map genes FMR1, FMR2 and IDS.

Unpredictable phenotype in females due to X Chromosome inactivation pattern and location of CNV

Very Small CNVs

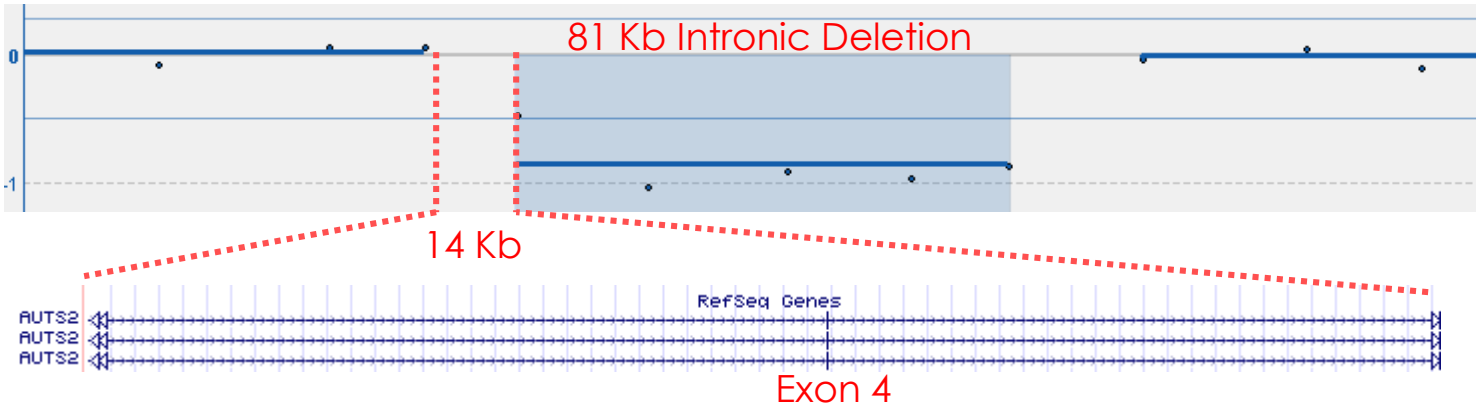
- 9 Kb deletion, 17p13.3, Exons10-11, PAFAH1B1(LIS1).



Confirmation by other methods is required

? Involve Exonic Sequences

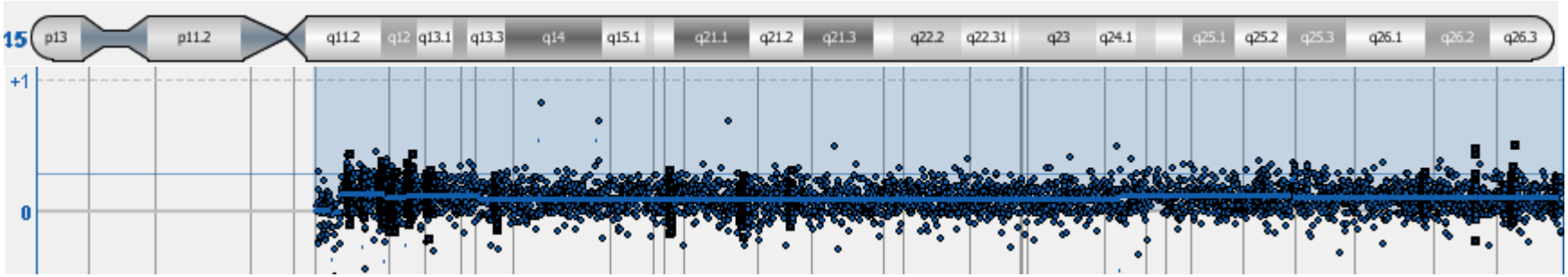
- 81Kb intragenic deletion, OMIM Morbid Map gene AUTS2. Exon 4 is deleted**?**



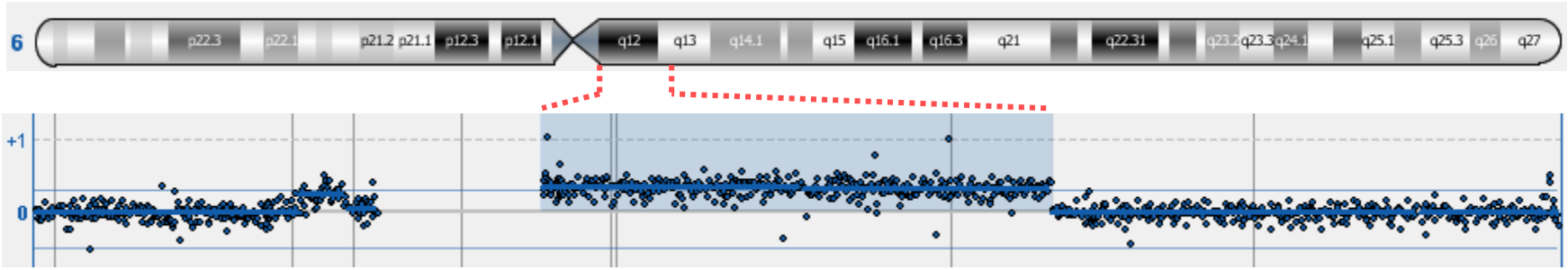
Confirmation by other molecular methods is required

Mosaic CNVs

- Trisomy 13, 15, 18, X, Y



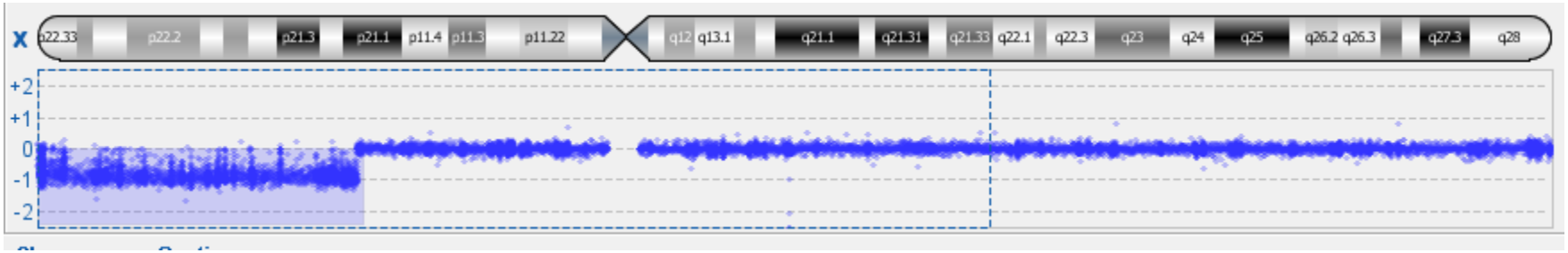
- Mosaic Deletions and Duplications of Large Segments
  - 15 Mb del at 20q11.21-q13.12, 10 Mb dup at 6q11.1-q13



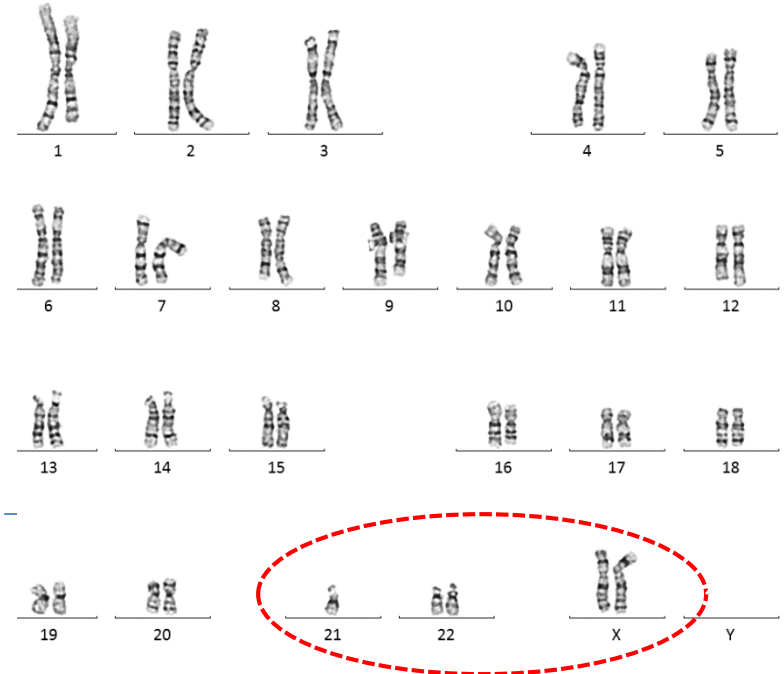
G-banding and FISH testing to determine the level of mosaicism

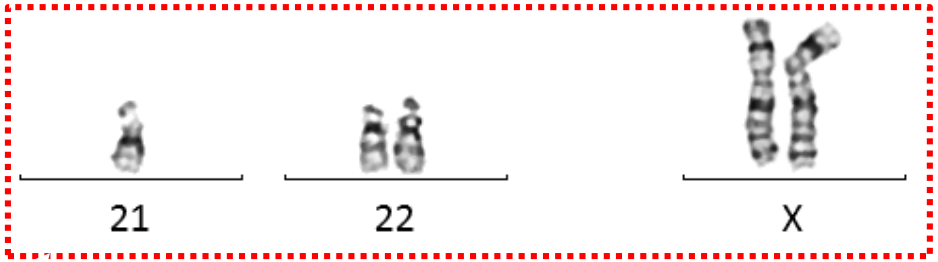
? Structural Chromosomal Abnormities

- 32 Mb terminal deletion, Xp22.33-p21.1



G-banding, 45,X,dic(X;21)(p21.1;p11.2)





Reporting Challenging Cases

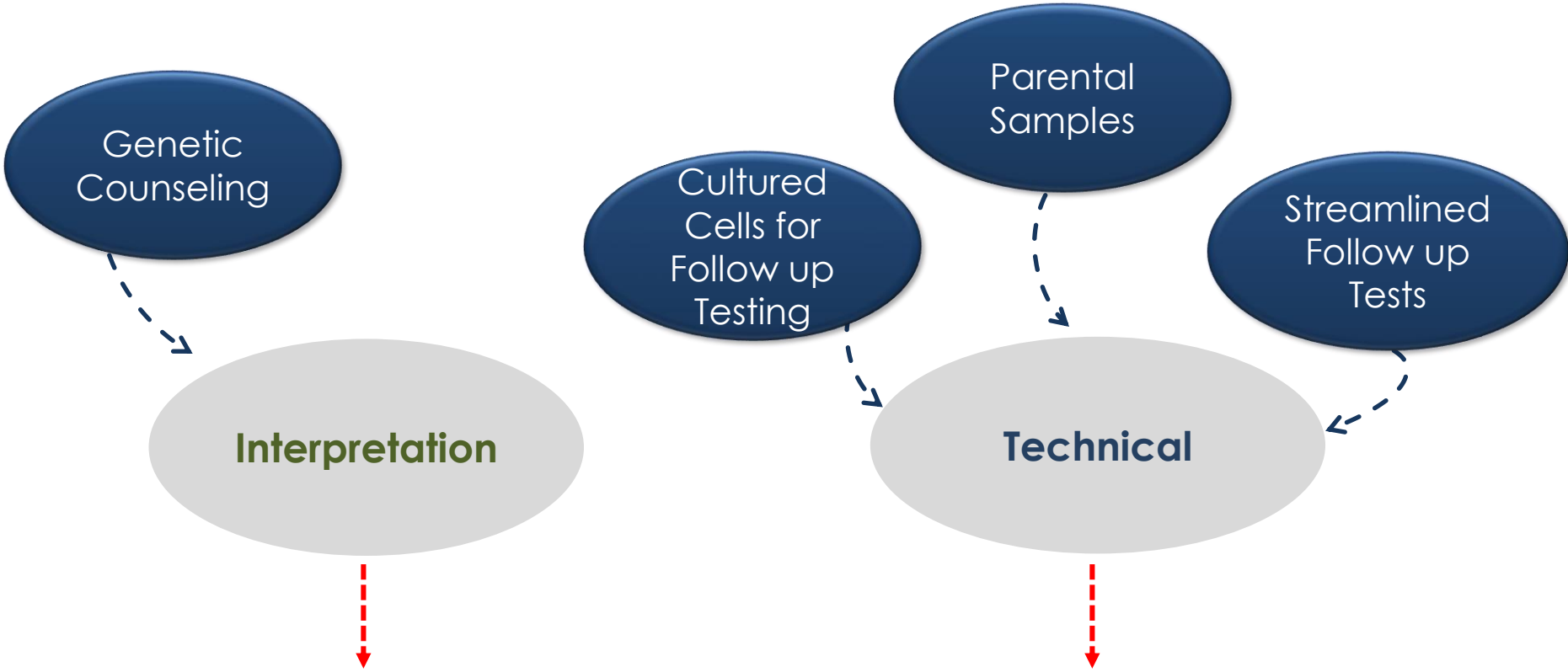
Interpretation

- Clinical correlation
- Parental testing
- Internal database

Technical

- qPCR
- FISH
- G-banding

Considerations for Prenatal Microarray



Acknowledgements

- Dr. James Stavropoulos (SickKids)
- Dr. Mary Shago (SickKids)
- Dr. Mary Ann George (SickKids)
- Dr. Elena Kolomietz (MSH)
- Dr. Kathy Chun (NYGH)

Ontario

Ministry of Health and Long-Term Care

Ministère de la Santé et des Soins de longue durée