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Guy's and St Thomas' NHS
NHS Foundation Trust

Updating penetrance estimates for syndromes with variable phenotypic manifestation

ACGS
Association for Clinical Genomic Science

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Background

- Array CGH has led to increased identification of copy number variants (CNVs)
- Our understanding of the role of CNVs in disease is improving
- Identified a number of fully penetrant, clinically recognisable syndromes e.g. 15q11.2-q13 deletion Prader-Willi / Angelman syndrome
- Many others associated with early-onset neurodevelopmental disorders have incomplete penetrance and variable phenotypic manifestation
- Examples include 1q21.1 del/dup, 16p11.2

Challenges

Clinician

Extended family

Genetic counsellor

Patient

Carrier parent

Need for clarity concerning risk

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Estimating penetrance

Genetics inMedicine | BRIEF REPORT

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Estimates of penetrance for recurrent pathogenic copy-number variations

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Purpose: Although an increasing number of copy-number variations are being identified as susceptibility loci for a variety of pediatric diseases, the penetrance of these copy-number variations remains mostly unknown. This poses challenges for counseling, both for recurrence risks and prenatal diagnosis. We sought to provide empiric estimates for penetrance for some of these recurrent, disease-susceptibility loci.

Methods: We conducted a Bayesian analysis, based on the copy-number variation frequencies in control populations ($n = 22,246$) and in our database of >48,000 postnatal microarray-based comparative distal deletions and duplications, 17q12 deletions and duplications, and 22q11.21 duplications.

Results: Estimates for the risk of an abnormal phenotype ranged from 10.4% for 15q11.2 deletions to 62.4% for distal 16p11.2 deletions.

Conclusion: This model can be used to provide more precise estimates for the chance of an abnormal phenotype for many copy-number variations encountered in the prenatal setting. By providing the penetrance, additional, critical information can be given to prospec-

*Rosenfeld et al, Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med. 2013 Jun;15(6):478-81.

Guy's array cohort

- Comparable cohort size 31,269 postnatal specimens received for aCGH between 2008-2017.
- Penetrance estimates calculated for the same 13 susceptibility regions
- Samples were tested on Agilent custom design arrays median resolution 125kb
- Referral indications included developmental delay, intellectual disability, epilepsy, congenital malformations and dysmorphism
- Same control cohort of 22,246 individuals that were used in the Rosenfeld study

Penetrance calculation

Incidence of CNV in cases

Incidence in population

Penetrance

$$P(D \mid G) = \frac{P(G \mid D)\,P(D)}{P(G \mid D)\,P(D) + P(G \mid \overline{D})\,P(\overline{D})}$$

Incidence of CNV in controls

Proportion of population unaffected

Incidence

Region	Copy number	Coordinates (hg19)	Freq. aCGH cases Rosenfeld	Freq. aCGH cases Guy's
Proximal	Dup	145386506-	0.17%	0.11%

- Population

Region	Copy number	Coordinates	Freq. Rosenfeld	Freq. Guy's
Region	Copy number	Coordinates	Freq. Rosenfeld	Freq. Guys
Distal 1q21.1 (GJA5)	Deletion	146533376-147883376	0.29% (97/33,226)	0.12% (39/31,269)
Distal 1q21.1 (GJA5)	Duplication	146533376-147883376	0.20% (68/33,226)	0.06% (18/31,269)
22q11.2 (TBX1)	Duplication	19009792-21452445	0.28% (136/48,637)	0.16% (50/31,269)
16p13.11 (MYH11)	Deletion	14986684-16486684	0.15% (50/33,226)	0.07% (21/31,269)
Proximal 16p11.2 (TBX6)	Deletion	29606852-30199855	0.44% (146/33,226)	0.32% (99/31,269)
17q12 (*HNF1B*)	Dup	34815072-36215917	0.11% (37/33,226)	0.09% (29/31,269)
22q11.2 (*TBX1*)	Dup	19009792-21452445	0.28% (136/48,637)	0.16% (50/31,269)

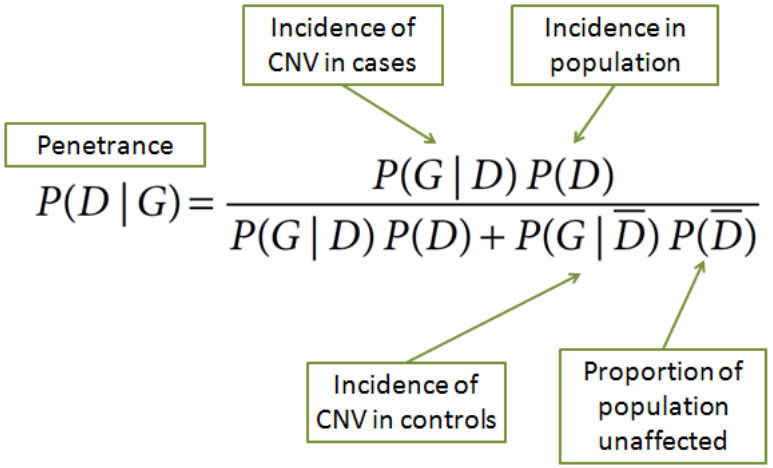
Penetrance estimates

Region	Coordinates	Penetrance estimate Rosenfeld	Penetrance estimate Guy's
16p12.1 (del)	21946524-22467284	12.3 (7.91–18.8)	13.7 (7.1-24.6)
17q12 (del)	34815072-36215917	34.4 (13.7-70.0)	24.6 (5.3-95.0)
Prox. 16p11.2 (del)	29606852-30199855	46.8 (31.5-64.2)	38.8 (19.3-62.6)
Distal 16p11.2 (del)	28822499-29042499	62.4 (26.8-94.4)	54.3 (12.9-99.0)

Region	Freq. Rosenfeld	Freq. Guys	Freq. controls	P value Rosenfeld	P value Guy's	Penetrance Rosenfeld	Penetrance Guy's
Distal 1q21.1 (Dup)	0.29% (97/33,226)	0.12% (39/31,269)	0.03% (6/22,246)	<<0.0001	0.0749	29.1 (16.9–46.8)	10.3 (3.2-28.4)
16p13.11 (Del)	0.15% (50/33,226)	0.07% (21/31,269)	0.05% (12/22,246)	<0.0005	0.3335	13.1 (7.91–21.3)	6.3 (2.5-15.2)
Distal 16p11.2 (Dup)	0.11% (35/33,226)	0.06% (18/31,269)	0.04% (10/22246)	<0.01	0.3310	11.2 (6.26–19.8)	6.5 (2.3-16.8)

Limitations

- Population prevalence (prior risk) ~5% based on data from a study carried out between 1952-83
- Wide range of phenotypes, differing severity considered together
- Separation may give a more accurate estimation of population incidence



- Some patients will have multiple CNVs
- No stratification based on ancestral substructure within the population – larger sample size needed
- Cannot guarantee that control population was unaffected
- Still a relatively small sample size when considering rare CNV

Collaboration Needed

Ideally we would collect data from a range of centres to improve the estimates

More robust picture of CNV incidence

Improve feasibility of stratification

Acknowledgements

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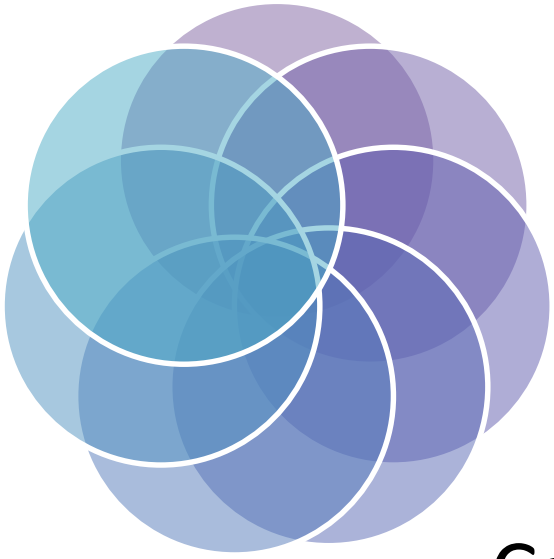

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