Copy number variation in ID psychosis

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Disclosures

• I am not a psychiatrist of Intellectual Disabilities
Chromosomes and DNA
DNA sequence

Sequence = sequence of bases along the DNA strand

The totality of DNA sequence = human genome
Human genome >3 billion base pairs
DNA variation

- Large range in size of variation
- **Molecular level:**
  - Single base pair (SNP and SNV)
  - Multiple base pair changes <1000 bp - e.g. repeat sequences
- **Sub-microscopic level:**
  - Structural variations > 1000 < ~ 5,000,000 bp in size - e.g. Copy number variation (CNVs)
- **Microscopic/chromosomal/cytogenetic level**
  - Large structural re-arrangements > ~5,000,000 bp
  - Aneuploidies
The Copy Number Variation story: From new technology to new ID syndromes
Submicroscopic deletions and duplications: Copy Number Variation (CNV)

Deletion
- 1 copy

Normal
- 2 copies

Duplication
- 3 copies

1kb to a few Mb

Inherited or de novo
Microarray technology
Large-Scale Copy Number Polymorphism in the Human Genome

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lafrate et al. Detection of large-scale variation in the human genome. Nat Genet. 2004
Examples of the (not so) new developmental delay/MCA CNV syndromes


1q21.1 deletion/duplication syndrome (*Sharp et al* Nature Genetics 2006)

15q13.3 deletion syndrome (*Sharp et al* Nature Genetics 2008)
CNV syndromes identified in children with developmental delay

Refining analyses of copy number variation identifies specific genes associated with developmental delay

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A Copy Number Variation Morbidity Map of Developmental Delay

Gregory M. Cooper, Stephanie Morgan, Cantor Crispin, Jill A. Rosenfeld, Tiffany Vu, Carl Baker, Charles Williams, Heather Staker, Rizwan Hamidi, Vickie Hanning, Hoda Abdol-Hamid, Patricia Bader, Elizabeth McCracken, Dmitriy Myasoiev, Kathleen Lepeschkin, Heidi Thies, Marybeth Hummer, Nora Alexander, Jerome Gorski, Jennifer Kusamenn, Vandana Shashidhar, Krys Johnson, Catherine Nehder, Blake C. Bell, Lisa G. Shaffer, and Evan E. Eichler

Refining analyses of copy number variation identifies specific genes associated with developmental delay


Copy number variants (CNVs) are associated with many neurocognitive disorders; however, these events are typically large, and the underlying causative genes are unclear. We created an expanded CNV morbidity map from 29,085 children with developmental delay in comparison to 19,504 healthy controls, identifying 70 significant CNVs. We resequenced 26 candidate genes in 4,216 additional cases with developmental delay or autism and 2,193 controls. An integrated analysis of CNV and single-nucleotide variant (SNV) data pinpointed 10 genes enriched for putative loss of function. Follow-up of a subset of affected individuals identified new clinical subtypes of pediatric disease and the genes responsible for disease-associated CNVs. These genetic changes include haploinsufficiency of SETBP1 associated with intellectual disability and loss of expressive language and truncations of ZMPEN1 in individuals with autism, aggression and complex neuropsychiatric features. This combined CNV and SNV approach facilitates the rapid discovery of new syndromes and genes involved in neuropsychiatric disease despite extensive genetic heterogeneity.
New DD CNV syndromes – pleiotropic effects on neurodevelopment?

3q29 Deletion syndrome
– Schizophrenia (Levinson et al Am J Psychiatry 2011)

1q21.1 Deletion syndrome
– Schizophrenia (ISC Nature. 2008)
– ASD (Mefford et al NEJM 2008)

15q13.3 Deletion
– Epilepsy (Helbig et al Nat Genet 2009)
– ASD (Miller et al J Med Genet. 2009)
– Schizophrenia (Costain et al Hum Mol Genet. 2013)
Questions

• Do some adults with idiopathic ID have the “new” developmental delay CNV syndromes?
• Are adults with ID and mental disorders/challenging behaviour at higher risk for neuro-pathogenic CNVs?
• What is the medical/psychiatric prognosis for children being diagnosed with new developmental delay CNV syndromes?
• Can novel neuro-pathogenic CNVs be found?
Chromosomal microarray testing in adults with intellectual disability presenting with comorbid psychiatric disorders

Kate Wolfe*\(^1\), André Strydom\(^1\), Deborah Morrogh\(^2\), Jennifer Carter\(^2\), Peter Cutajar\(^3\), Mo Eyeyoibo\(^4\), Angela Hassiotis\(^1\), Jane McCarthy\(^5\), Raja Mukherjee\(^6\), Dimitrios Paschos\(^7\), Naganan Perumal\(^8\), Stephen Read\(^9\), Rohit Shankar\(^10\), Saif Sharif\(^11\), Suchithra Thirulokachandran\(^12\), Johan H Thygesen\(^1\), Christine Patch\(^13\), Caroline Ogilvie\(^13\), Frances Flinter\(^13\), Andrew McQuillin\(^1\) and Nick Bass\(^1\)
Participants

Recruited from caseloads of ID Psychiatrists:

Adults (over 18) with a ID of unknown cause* and co-morbid mental health problem or severe challenging behaviour

Participants without capacity to consent included

* unknown to treating team
Recruitment Sites

[Map showing various recruitment sites across England, Scotland, and Ireland, with key indicating approved sites in green, training provided awaiting approval in orange, and set up stage in blue.]
Meeting with Participant

- Picture vocabulary test

- Observations and measurements photograph, height and head circumference
Meeting with Informant

• Informant: family member, carer, Psychiatrist, GP.

• Medical/Psychiatric and family history of participant.

• Behavioural (BPI-S) and mental health assessment (PAS-ADD).
Biological samples for DNA extraction
CMA testing
Categorisation of CNVs

1. Likely clinically significant (pathogenic): known locus or large CNV predicted to disrupt function of many genes, **feedback to clinician where requested**.

2. VOUS (possibly pathogenic) CNV harbours gene(s), strongly implicated in ID/mental disorders, attempt to follow up result.

3. VOUS (likely benign) CNV harbours gene(s) of potential interest but insufficient evidence for follow up.

4. CNV (benign) a) common CNVs b) No genes within CNV or no implication in ID/mental disorders.
Headline findings

- **202** participants
- 63% males
- mean age 37 years (range 18-78 years)
- **11% (22) likely clinically significant** (pathogenic) CNVs
- **19% (38) VOUS** (possibly pathogenic) CNVs that impact psychiatric or ID relevant genes
CNVs in neurodevelopmental genes
- NRXN1 deletion (n=1, 0.5Mb, Exon 1)
- GRIN2B duplication (n=1, 9Kb, Exon 9)

Chromosomal abnormalities
- Unbalanced translocation - 6p25.3 duplication (7.2Mb) + 18p11.32 deletion (6.8Mb) (n=1)
- XXY syndrome (n=1)

Emerging rare neurodevelopmental CNVs
- 2q13 deletion (n=1, 1.7Mb)
- 4p16.3 duplication (n=1, 2.4Mb)
- 12q21.2-21.31 deletion (n=1, 5Mb)
- 13q32.3-13q33.3 duplication (n=1, 9.1 Mb)
- 19q13.32 deletion (n=1, 1.5Mb)
- Xq24-25 duplication (n=1, 4.4Mb)

CNVs at recurrent loci
- 15q11.2 microdeletion syndrome (n=1, 0.3Mb, BP1-2)
- Angelman syndrome type 2 (n=1, 4.8Mb, BP2-3)
- 15q11.2-13.1 duplication syndrome (n=1, 4.7Mb, BP2-3)
- 15q11.2 deletion (n=1, 2.9Mb)
- 15q13.3 microdeletion syndrome (n=1, 2.3Mb, BP4-5)
- 16p11.2 microduplication syndrome (n=4, 0.4-0.7Mb)
- 16p11.2 microdeletion syndrome (n=1, 0.4Mb)
- 16p13.11 microdeletion (n=1, 1.7Mb)
- NF1 Microdeletion syndrome type 2 (n=1, 1.2Mb)
Recurrent pathogenic CNVs observed

• Mainly “new” recurrent pathogenic CNVs/developmental delay CNV syndromes observed

• Most frequently observed CNVs:
  16p11.2 (4 gains, 1 loss)
  15q11.2-15q13.3 region (5 different CNVs)*
Prevalence of 16p11.2 duplications in different conditions

- Atypical Rolandic Epilepsy ~1.3% (Reinthaler et al. Hum Mol Genet. 2014)
- ASD ~1% (Weiss et al. NEJM 2008)
- Schizophrenia ~0.3% (Rees et al. BJP 2014)
- DD ~0.2% (Cooper et al. Nature Genetic 2011)
- Controls ~0.02% (Cooper et al. Nature Genetic 2011)
Does rare matter? Copy number variants at 16p11.2 and the risk of psychosis: A systematic review of literature and meta-analysis

Giovanni Giaroli a, b, c, Nicholas Bass a, André Strydom a, Khadija Rantell a, Andrew McQuillin a, *.

Micro duplications at 16p11.2 - disease versus control

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walsh (2008)</td>
<td>4.75 (0.22, 100.62)</td>
<td>12.49</td>
</tr>
<tr>
<td>Vacic (2011)</td>
<td>8.37 (0.45, 155.70)</td>
<td>12.82</td>
</tr>
<tr>
<td>Vacic (2011)</td>
<td>16.12 (2.15, 120.75)</td>
<td>26.16</td>
</tr>
<tr>
<td>Zheng (2013)</td>
<td>7.63 (0.39, 147.28)</td>
<td>11.88</td>
</tr>
<tr>
<td>Zheng (2013)</td>
<td>5.96 (0.29, 124.29)</td>
<td>11.31</td>
</tr>
<tr>
<td>Priebe (2013)</td>
<td>2.98 (0.12, 73.20)</td>
<td>12.44</td>
</tr>
<tr>
<td>Rees (2014)</td>
<td>50.58 (3.09, 830.83)</td>
<td>12.89</td>
</tr>
<tr>
<td>Walsh (2008)</td>
<td>(Excluded)</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Overall (I² = 0.0%, p = 0.82?)
14.37 (5.19, 39.75) 100.00

Schizophrenia OR 14.37
16p11.2 duplications

1 person: epilepsy
2 people: ASD
2 people: schizophrenia
3 people: affective disorders (diagnosed or met PAS-ADD thresholds)
16p11.2 CNVs: other associated phenotypes

Deletions – obesity, hyperphagia and increased head circumference

Duplications – reduced BMI, selective and restrictive eating behaviours, reduced head circumference
15q11.2-15q13.3: a very confusing region
1: 15q11.2 neurosusceptibility locus deletion
1: Angelman syndrome
1: Angelman/PWS duplication
1: Atypical deletion partially overlapping BP2–BP3 region
1: 15q13.3 neurosusceptibility locus deletion
Novel pathogenic CNVs were identified

- 3 novel pathogenic CNVs identified:
  - duplication at Xq24-25
  - deletion at 12q21.2-21.31
  - duplication at 13q32.3-13q33.3
Clinical predictors of pathogenic CNV carriers: Post hoc analysis

• Univariate analyses were conducted using binary logistic regression for clinical and psychiatric predictor variables.
Conclusions/Limitations

• High diagnostic yield from CMA
• “New” CNV syndromes and novel CNVs
• No clear clinical predictors of pathogenicity
Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders


N= 599
Results: Headline

- **13.0% (10.5%–16.0%)** likely clinically significant (pathogenic) CNVs
- **21.5% (18.4%–25.1%)** VOUS (possibly pathogenic) CNVs
- Recurrent VOUS CNVs:
  
  Exonic duplications in CNTN6 (3p26.3) 9q21.32q21.33 duplications (including SLC28A3 and NTRK2 genes.)
  exonic CNVs in CHD8 gene (14q11.2)
  exonic CNVs in CHD2 gene (15q26.1)
Results: Recurrent ID associated CNVs

- Rees E et al. Analysis of intellectual disability copy number variants for association with schizophrenia. JAMA Psychiatry 2016

- 23 /63 CNVs observed
Rate of recurrent ID associated CNVs by cohort

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample size</th>
<th>Rate of the 63 neurodevelopmental disorder loci, %</th>
<th>Rate difference, % (95% CI),</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy control</td>
<td>26628</td>
<td>1.2</td>
<td>8.8 (6.3–11)</td>
<td>2.8 × 10^{-7}</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>20403</td>
<td>3.1</td>
<td>7 (4.5–9.5)</td>
<td>9.7 × 10^{-2}</td>
</tr>
<tr>
<td>Intellectual disability/autism spectrum disorder</td>
<td>29085</td>
<td>6.5</td>
<td>3.5 (1–6)</td>
<td>8.4 × 10^{-4}</td>
</tr>
<tr>
<td>GENIMI</td>
<td>599</td>
<td>10.0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

a. Rate percentage differences, 95% CI and P-values for rate comparisons are indicated.
Fig 1. Neurodevelopmental disorder copy number variant frequencies in the GEnetics of Mental disorders in Intellectual Disability (GEnIMD) sample compared with frequencies in healthy controls (n = 26,038), intellectual disability/autism spectrum disorder (ID/ASD) (n = 29,085) and schizophrenia (n = 20,403) cohorts as reported by Rees et al. Rates for deletions extend down from the centerline, and duplications extend upwards.
Clinical predictors of CNV pathogenicity

- ID, psychiatric diagnoses
Conclusions/Limitations

• High diagnostic yield from CMA
• No clear clinical predictors of pathogenicity
• Are adults with ID and mental disorders/challenging behaviour at higher risk for neuro-pathogenic CNVs?
Delineating the psychiatric and behavioral phenotype of recurrent 2q13 deletions and duplications

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Himanshu Goel9,10 | Sara Loddo2 | Deborah Morrogh11 |
Anne-Laure Mosca-Boidron12 | Antonio Novelli2 | Laurence Olivier-Faivre13 |
Jennifer Parker11 | Michael J. Parker14 | Christine Patch15,16 | Anna L. Pelling17 |
Thomas Smol3,6 | Zeynep Tümer8 | Olivier Vanakker18 | Arie van Haeringen19 |
Clémence Vanlerberghe5,6 | André Strydom1,20 | David Skuse21 | Nick Bass1
2q13 CNVs

- Deletions and deletions observed
- Both very rare
- Susceptibility locus
- Little psychiatric of behavioural phenotyping
2q13 CNV associations

• DD/ID (Rudd et al. 2009 and Cooper et al. 2011)

• Deletions - cardiovascular disorders

• Duplications - craniofacial features

• ASD 3/5 or ADHD ? 1/5 (Yu et al. 2012)

• Schizophrenia (Costain et al. 2013 n=3) ….not supported by subsequent studies
Recruitment and phenotyping

• Unique & Regional Genetics Centres (n=10) Mini PAS-ADD, ChA-PAS and BPI-S

• DECIPHER database (n= 15) Structured questionnaire

• Combined with reports from literature (n=52)
Sample characteristics

• median age = 9 years, (92% <18 years, range 4–42 years).
• 21 deletion carriers, 4 duplication.
• 36% inheritance status unknown, 20% \textit{de novo}, 28% paternally inherited, 8% maternally inherited, 8% inherited but parent of origin unknown
FIGURE 2  Clinically diagnosed psychiatric disorders and behavioral phenotypes in 2q13 deletion (n = 21) and duplication (n = 4) carriers. Y axis: percentage of participants with the diagnosis or behavior; X axis: ADHD—attention deficit hyperactivity disorder, Aggressive—aggressive behaviors, Anxiety—anxiety disorder, Autism—autism spectrum disorder, ODD—oppositional defiant disorder, Self-injurious—self-injurious behaviors [Color figure can be viewed at wileyonlinelibrary.com]
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>2q13 deletions</th>
<th>2q13 duplications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DD/ID</td>
<td>31/39 (79%)</td>
<td>14/20 (70%)</td>
</tr>
<tr>
<td>ASDs</td>
<td>9/27 (33%)</td>
<td>2/12 (17%)</td>
</tr>
<tr>
<td>ADHD</td>
<td>12/25 (48%)</td>
<td>3/5 (60%)</td>
</tr>
<tr>
<td>Dysmorphic features</td>
<td>33/41 (80%)</td>
<td>9/10 (90%)</td>
</tr>
<tr>
<td>Heart defect</td>
<td>11/35 (31%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>15/34 (44%)</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>8/31 (26%)</td>
<td>0/10 (0%)</td>
</tr>
<tr>
<td>Macrocephaly</td>
<td>10/35 (29%)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>8/35 (23%)</td>
<td>2/7 (29%)</td>
</tr>
</tbody>
</table>

For each phenotype the number of patients with the diagnosis is displayed alongside the number of patients for which the phenotype was assessed. Thus, the denominator differs due to the varying availability of phenotypic information in published case studies. Percentages are provided for each individual phenotype. ADHD = attention deficit hyperactivity disorder; ASDs = autism spectrum disorders; DD = developmental delay; ID = intellectual disabilities.
• 117 ID psychiatrists, 166 child and adolescent psychiatrists and 97 geneticists/genetic counsellors took part in the survey.
Attitudes towards genetic testing

- Respondents were asked to estimate the percentage of people with intellectual disability for whom genetic factors make a significant contribution towards the cause of their intellectual disability.

Estimates from child psychiatrists (Mean = 42%, SD = 24.7, \textbf{Range = 2-100%}) were comparable to those of intellectual disability psychiatrists (Mean = 39.6%, SD = 23.1, \textbf{Range=3-90%})

- However, estimates by both child and intellectual disability psychiatrists of the percentage of patients on their caseloads with an established genetic diagnosis were much lower.

- Intellectual disability psychiatrists estimated a higher percentage of their own patients to have an established genetic diagnosis (\textbf{Median} = 10%, \textbf{Range = 0-70%}) compared to child psychiatrists (\textbf{Median}=5%, \textbf{Range = 0-100%})
Ordering of genetic tests

• More intellectual disability psychiatrists (77%), compared with child psychiatrists (56%), had ordered a genetic test in the last 10 years
Related work
Acknowledgements

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Dr. Andrew McQuillin, Associate Professor

Dr. Johan Thygesen, Postdoc

Professor Andre Strydom