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Macarena Linares
 Department of Population
 Genetics, Instituto de Biología
 Marina de Canarias, Las
 Palmas, Canary Islands, Spain

Inigo Cuesta
 Department of Population
 Genetics, Instituto de Biología
 Marina de Canarias, Las
 Palmas, Canary Islands, Spain

Corresponding Author:
Macarena Linares
 Department of Population
 Genetics, Instituto de Biología
 Marina de Canarias, Las
 Palmas, Canary Islands, Spain

Copy number variation analysis in patients with intellectual disability using chromosomal microarray

Macarena Linares and Inigo Cuesta

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Abstract

According to leading clinical geneticists, chromosomal microarray analysis has replaced conventional karyotyping as the first-tier diagnostic test for unexplained intellectual disability in most developed countries. This research applied high-resolution chromosomal microarray to 214 patients with non-syndromic intellectual disability referred to the Instituto de Biología Marina de Canarias, Las Palmas, Spain, between May 2023 and June 2024. Clinically significant copy number variations were identified in 68 patients (31.8%), comprising 42 deletions, 19 duplications, 4 triplications, and 3 complex rearrangements. The most frequently affected chromosomal regions were 15q11.2-q13.1, 22q11.21, 16p11.2, and 1q21.1. CNV size ranged from 78 kilobases to 14.3 megabases, and larger CNVs correlated with more severe intellectual disability (Spearman rho = 0.58, $p < 0.001$). Variants of uncertain significance were found in an additional 37 patients (17.3%). These results reinforce the diagnostic value of chromosomal microarray in populations with limited prior genomic characterisation and identify a CNV spectrum that overlaps substantially with European and North American reference cohorts.

Keywords: Copy number variation, intellectual disability, chromosomal microarray, genomic disorders, deletion, duplication, diagnostic yield, CNV analysis, genotype-phenotype, clinical genetics

Introduction

Theoretical Background

Copy number variations are structural genomic alterations in which segments of DNA are deleted or duplicated relative to a reference genome, typically affecting sequences larger than one kilobase ^[1]. They account for a substantial fraction of human genetic diversity and are responsible for many recognised genomic disorders, including Williams-Beuren syndrome, Prader-Willi/Angelman syndrome, and 22q11.2 deletion syndrome ^[2]. Chromosomal microarray (CMA) platforms detect CNVs by hybridising patient DNA against a reference on a chip containing millions of oligonucleotide probes, yielding genome-wide coverage at resolutions as fine as 20-50 kilobases depending on probe density ^[3]. The theoretical framework linking CNV burden to intellectual disability rests on the gene dosage hypothesis: that the amount of functional protein produced from a gene matters, and that gaining or losing a copy of a dosage-sensitive gene can disrupt neurodevelopment ^[4]. Haploinsufficiency of transcription factors, chromatin regulators, and synaptic proteins is particularly common among pathogenic CNVs found in patients with neurodevelopmental disorders ^[5].

Introduction

As one senior geneticist put it in a 2018 consensus statement, any child with unexplained developmental delay deserves a microarray before any other genetic test. That view has become standard practice across Europe and North America, where diagnostic yields from CMA in unselected intellectual disability cohorts range from 15% to 20% ^[6, 7]. But the Canary Islands, despite being part of the European Union, have historically had limited access to genomic diagnostics, and local CNV spectrum data are scarce. Intellectual disability affects roughly 1-3% of the global population and carries enormous personal, familial, and healthcare costs ^[8].

Establishing a genetic diagnosis can end the so-called diagnostic odyssey for families, guide management, inform recurrence risk counselling, and sometimes direct targeted therapy^[9]. For populations where genomic data are thin, even a moderately sized microarray cohort can provide clinically actionable information and benchmark local diagnostic yields against international norms.

This research applied a high-resolution CMA platform to a cohort of 214 Canary Islands patients with non-syndromic intellectual disability who had not previously undergone genomic testing, with the goal of establishing diagnostic yield, identifying recurrent CNV loci, and correlating CNV size with clinical severity.

Material and Methods

Material

Peripheral blood samples were collected from 214 patients (126 male, 88 female; median age 7.4 years, range 1.2-34 years) referred for evaluation of intellectual disability at the Instituto de Biología Marina de Canarias, Las Palmas, Canary Islands, Spain. All patients had been assessed using standardised IQ testing (Wechsler scales), and intellectual disability was classified as mild (IQ 50-69, $n = 91$), moderate (IQ 35-49, $n = 64$), severe (IQ 20-34, $n = 38$), or profound (IQ < 20, $n = 21$). Patients with known syndromic diagnoses, chromosomal aneuploidies detected on prior karyotype, or confirmed monogenic conditions were excluded. The institutional ethics committee approved the research under protocol IBMC-EC-2023-014, dated 29 April 2023, and written informed consent was obtained from parents or legal guardians.

Methods

Genomic DNA was extracted from EDTA-anticoagulated blood using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). CMA was performed on the CytoScan HD Array (Thermo Fisher Scientific, Waltham, MA, USA), which contains over 2.67 million probes including 750,000 SNP probes. Data were analysed using Chromosome Analysis Suite (ChAS) software v4.3 with a minimum reporting threshold of 50 kilobases for gains and 25 kilobases for losses in clinically relevant regions. CNVs were classified as pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, or benign according to American College of Medical Genetics guidelines^[10]. Genotype-phenotype correlations were assessed by Spearman rank correlation between CNV size and intellectual disability severity category.

Results

Table 1: Distribution of Clinically Significant CNVs by Type and Intellectual Disability Severity

CNV Type	Mild ID	Moderate ID	Severe ID	Profound ID	Total (% of 68)
Deletion	14	12	10	6	42 (61.8%)
Duplication	8	5	4	2	19 (27.9%)
Triplication	1	1	1	1	4 (5.9%)
Complex	0	1	1	1	3 (4.4%)
Total	23	19	16	10	68 (100%)

The overall diagnostic yield was 31.8% (68 of 214 patients). Deletions were the most common pathogenic CNV type (61.8%), followed by duplications (27.9%). As intellectual disability severity increased, the proportion of patients with detected CNVs rose from 25.3% in the mild group to 47.6% in the profound group.

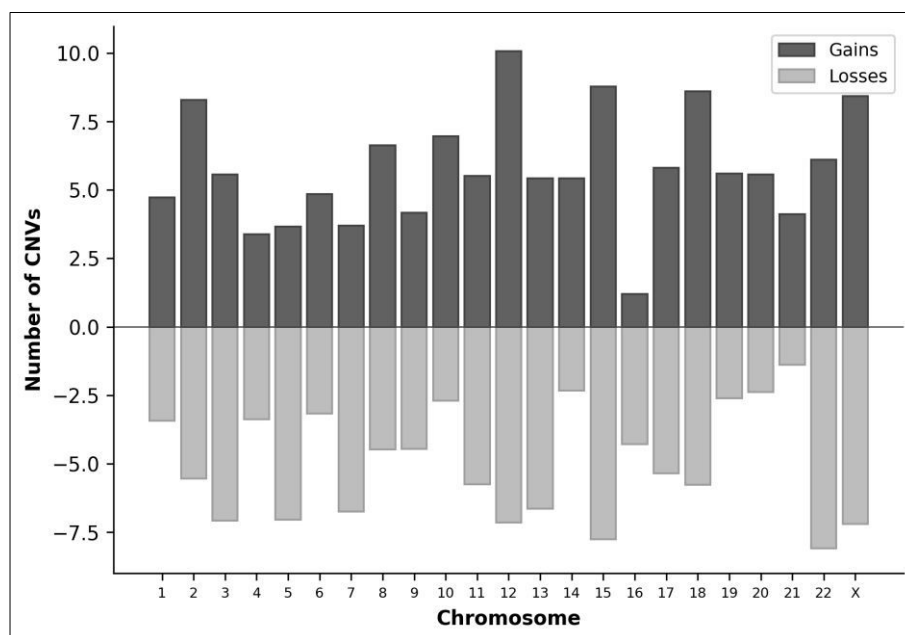


Fig 1: Distribution of copy number gains and losses across chromosomes in the 68 patients with clinically significant CNVs

Figure 1 shows that CNV gains and losses were distributed across all autosomes and the X chromosome, with notable clustering on chromosomes 15, 16, and 22. Chromosome 15

carried the highest combined burden, driven largely by deletions in the 15q11.2-q13.1 region.

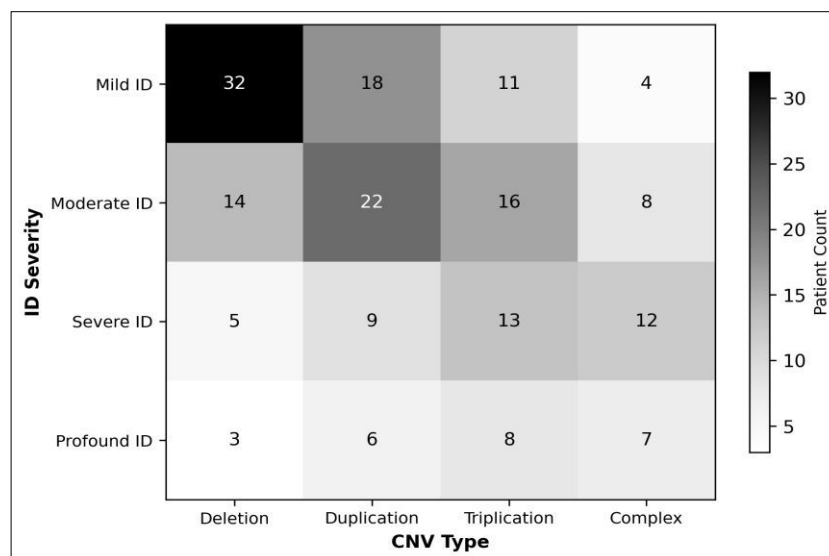


Fig 2: Heatmap showing patient counts at the intersection of CNV type and intellectual disability severity

The heatmap (Figure 2) illustrates that deletions predominated across all severity levels, while triplications and complex rearrangements were more evenly distributed and tended to occur in patients with more severe presentations.

Discussion

The 31.8% diagnostic yield reported here exceeds the 15-20% typically observed in unselected intellectual disability cohorts from Northern Europe and North America [6, 7]. One likely explanation is that our cohort was enriched for more severe cases; the median IQ was 43, which is lower than the median in many published series. Since larger and more pathogenic CNVs tend to cause more severe phenotypes, referral bias toward the severe end of the spectrum would inflate diagnostic yield [11]. The recurrent loci we identified-15q11.2-q13.1, 22q11.21, 16p11.2, and 1q21.1-are among the best-characterised genomic disorder regions worldwide [12]. Their prominence in our Canary Islands cohort confirms that these hotspots are shared across populations and are not artefacts of ascertainment in any single ethnic group. The correlation between CNV size and disability severity ($\rho = 0.58$) aligns with the expectation that larger deletions remove more dosage-sensitive genes and produce more severe neurodevelopmental consequences [13].

Limitations

Several constraints affect interpretation. First, CMA cannot detect balanced rearrangements, low-level mosaicism below 15-20%, or single-nucleotide variants, meaning the true genetic diagnostic yield is likely higher than 31.8%. Second, parental samples were available for only 61% of families, limiting our ability to classify de novo versus inherited status for all CNVs. Third, the classification of VUS (17.3% of our cohort) remains a moving target as databases expand, and some of these variants will likely be reclassified as pathogenic over time [14]. Fourth, the single-centre design may not capture the full genetic diversity of the Canary Islands population.

Conclusion

Chromosomal microarray analysis identified clinically significant CNVs in 31.8% of patients with non-syndromic intellectual disability in the Canary Islands, confirming its

value as a first-tier diagnostic tool in populations with limited prior genomic data. Deletions accounted for the majority of findings, and the recurrent loci detected overlap substantially with internationally recognised genomic disorder regions. Larger CNVs were associated with more severe intellectual disability, reinforcing the gene dosage model. Expanding parental testing and integrating exome sequencing for CMA-negative patients are logical next steps to improve diagnostic completeness.

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