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Chromosomal microarray analysis

- a routine clinical genetic test for patients with schizophrenia

Kate Baker MRCPCH PhD[1]

Gregory Costain PhD[2]

Wai Lun Alan Fung MD ScD [2,3,4]

Anne S. Bassett MD FRCPCP [2,3,4]

[1]Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, United Kingdom.

[2] Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

[3] The Dalglish Family Hearts and Minds Clinic for Adults with 22q11.2 Deletion Syndrome, University Health Network, Toronto, Ontario, Canada

[4] Department of Psychiatry, University of Toronto Faculty of Medicine, Toronto, Ontario, Canada.

Corresponding authors: Kate Baker, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, United Kingdom, E-mail: kb488@cam.ac.uk and Anne S. Bassett, Centre for Addiction and Mental Health, 33 Russell Street, Room 1100, Toronto, Ontario, Canada M5S 2S1, E-mail: anne.bassett@utoronto.ca

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Aetiological diagnosis for patients with schizophrenia was long thought to be impossible. However, genomic abnormalities with clear causal relevance can now be identified in a consistent minority of cases using chromosomal microarray analysis (CMA; also known as array Comparative Genomic Hybridization or array-CGH). Analogous to a karyotype but with dramatically improved genome-wide resolution, CMA can inform diagnosis and clinical management by identifying sub-microscopic segments of missing (deleted) or additional (duplicated) chromosomal material known as copy number variants (CNVs). CMA is sensitive, reliable, and widely available in clinical laboratories around the world, including major medical centres in the developing world. Costs are competitive with other investigations such as neuroimaging. CMA is now a standard first-line diagnostic test for intellectual disability and autism where 10-20% of affected individuals have a clinically-relevant deletion or duplication (1). Widespread application of CMA testing in these populations has increased confidence in diagnostic interpretation, enhanced the prognostic evidence base, and facilitated research progress (2). In our view, the time has come to translate replicated research findings with proven clinical utility into routine diagnostic practice for patients with schizophrenia.

The rationale for chromosomal microarray testing in schizophrenia

Clinically-relevant deletions or duplications are present amongst individuals with schizophrenia with a collective prevalence of 5% or more (3-5). These encompass three broad groups of CNVs, each of which can occur *de novo* or can be inherited: (A) 22q11.2 deletions (~1% of schizophrenia; lifetime schizophrenia risk amongst deletion carriers ~25% (6)); (B) other recurrent deletions and duplications associated with schizophrenia, e.g. 1q21.1 deletions, 15q11-q13 duplications (~3-4% collectively of schizophrenia); (C) other

individually rarer abnormalities. The first study of CMA application in a community-based sample of schizophrenia showed that 1 in 13 patients within a single geographical catchment had a clinically-relevant deletion or duplication: diagnostic yield 8.1% (95% CI 5.2–12.2%)(7). Those with pathogenic genetic anomalies diagnosed via CMA were indistinguishable from the remainder of patients with respect to basic clinical variables. Hence, if CMA is only offered to patients with additional features such as intellectual disability or dysmorphology, many individuals with clinically-significant deletions or duplications will remain undiagnosed.

Maximising clinical utility

Identification of a pathogenic CNV can improve holistic physical and mental health care for patients with schizophrenia. Taking the example of 22q11.2 deletion syndrome, there are clinical practice guidelines to aid lifetime management (8). These include clear recommendations for baseline medical assessments (e.g. cardiac and immunological assessments) and annual checks (e.g. thyroid function tests and serum calcium monitoring). These CNV-specific assessments frequently uncover hidden health problems in adult patients, leading to a range of interventions from dietary advice to pharmacological treatments which significantly improve well-being and reduce risk of serious complications. Diagnosis of 22q11.2 deletion syndrome can also influence psychiatric treatment: antipsychotic choice may be modified according to safety profiles; seizure risk can be reduced by early use of anticonvulsants and by identifying and treating hypocalcaemia. For other recurrent schizophrenia-associated CNVs, there are systematic efforts to establish similar evidence bases (9-11). Genetic counselling after diagnosis of any clinically-significant

deletion or duplication is important because offspring are at 50% risk of inheriting the CNV, with inherent medical, neurodevelopmental and psychiatric implications.

Recognising limitations

Genomic abnormalities interact with biological and social factors to mediate psychiatric risk, and an overly reductionist approach is unrealistic. However, this complexity is not unique to psychiatric illness or schizophrenia. As for most genetic diagnoses, the clinical problems associated with pathogenic deletions and duplications vary from person to person, even within families. Variable expression encompasses physical manifestations, cognitive impairments and psychiatric symptoms, and it is difficult to predict which individuals with clinically-significant CNVs will experience specific problems in each area. For very rare CNVs, limited prognostic information will be available until more cases are diagnosed. A further limitation is that some CMA findings will be reported as variants of uncertain significance (VUS) when there is insufficient current evidence to classify a CNV as either benign or pathogenic.

Practicalities of chromosomal microarray testing for patients with schizophrenia

CMA testing and genetic diagnosis have been shown to be desirable and acceptable amongst patients with schizophrenia and their families, even amongst the majority who did not receive a genetic diagnosis (12;13). The process of obtaining informed consent is in essence no different for patients with schizophrenia than for any other population, once capacity has been evaluated. A simple pre-test discussion should outline the purposes, benefits and limitations of testing (Table 1). It is desirable to involve family members so that awareness is shared amongst individuals for whom test results are potentially relevant.

However, lack of availability of family members should not preclude testing that may be of great individual benefit.

Looking ahead

A genetic diagnosis can have multiple practical and psychological values for patients, their partners, relatives, clinicians and wider society. Further research that integrates CNV diagnosis with cognitive neuroscience has the potential to illuminate diverse pathways from risk to symptoms (14, 15). The benefits of genetic diagnosis and risks inherent in under-investigation considerably outweigh limitations of CMA testing. CMA is a natural step in the evolution of biologically-informed clinical management of schizophrenia – clinical exome and whole genome sequencing is on its way (16). This eventuality mandates a concerted effort to address knowledge gaps, remove discriminatory barriers, and increase opportunities for individualized care for adults with severe mental illness.

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TABLE 1: CMA testing for patients with schizophrenia – aims, benefits, limitations, strategies

AIMS	Identification of causal factors	Awareness of associated medical risks	Tailored psychiatric care	Genetic counselling
Potential benefits	• Detection of clinically-significant deletion or duplication (CNV) in 5-8% of patients with schizophrenia	• Surveillance and interventions for treatable conditions e.g. cardiac, endocrine, neurological • Reduction in health inequalities, improvement in quality of life	• Enhanced understanding of the patient's illness • Improved safety and effectiveness of treatments for schizophrenia	• Individualised, evidence-based counselling • Education and empowerment • Genetic testing options for at-risk relatives
Limitations and challenges	• No clinically-significant CNV in the majority of cases • Variants of uncertain significance • Incidental findings	• Limited evidence base for rare CNVs • Variability in clinical expression	• Few specific treatment recommendations for rare CNVs	• Adjustment of patient, family and clinician to new knowledge • Questions around childhood testing and prenatal testing
Strategies	• Submission of CNV data to international databases to enhance interpretation of variants • Genome sequencing to increase diagnostic yield	• Submission of phenotype data to international databases to enhance prognostic evidence base • Research into medical comorbidities, surveillance approaches, interventions and outcomes	• Continue standard treatments unless change indicated • Research into psychiatric presentations, treatment responses and outcomes • Potential for new aetiology-specific, mechanism-informed therapies	• Enhanced liaison between psychiatry and clinical genetics • Clinician education to increase confidence in initiating testing, pre-test discussion, managing results