Schizophrenia Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The translation of psychiatric genetic findings to the clinic

Kimberley Marie Kendall [a,*], Donna Duffin [b], Joanne Doherty [a], Rachel Irving [b], Annie Procter [b], James Tynan Rhys Walters [a]

[a] Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff CF24 4HQ, United Kingdom
[b] All Wales Medical Genomics Service, Heath Park, Cardiff CF14 4XW, United Kingdom

ARTICLE INFO

Keywords:
Schizophrenia
CNV
Translation
Genomics

ABSTRACT

Mental health and neurodevelopmental disorders are highly heritable and can affect morbidity and mortality. A large, growing body of evidence has implicated both common and rare variation in the risk of these disorders. Testing for rare variants, such as copy number variants, has been available in clinical practice for some time in the context of developmental disorders. However, until recently, individuals with mental health and neurodevelopmental disorders in the UK have not tended to access genetic counselling and testing. Here, we describe the development of the All Wales Psychiatric Genomics Service, a collaborative effort between psychiatric and clinical genetics services and the first of its kind in the UK. We provide an overview of the structure and function of the service, our referral criteria, a summary of the 40 referrals we have received to date and our future plans.

1. Introduction

Mental health and neurodevelopmental disorders, such as schizophrenia, are highly heritable with complex genetic architecture (Hilker et al., 2018; McGuffin et al., 2003; Sullivan et al., 2000; Gratten et al., 2014). Genetic risk for these disorders is conferred by common variation of small effect, namely single nucleotide polymorphisms, and rare variation of large effect, including copy number variants (CNV) and rare coding variants (Gratten et al., 2014). Our knowledge of genetic risk factors for mental health and neurodevelopmental disorders is increasing rapidly due to the work of large international consortia (Trubetskoy et al., 2022; Singh et al., 2022; Levey et al., 2021; Rees et al., 2014).

In the UK, genetic counselling and testing for individuals with physical health problems have been available within the National Health Service (NHS) for some time - for example, for cancer and cardiovascular risk factors like hypercholesterolaemia. Testing for rare CNVs has been available for individuals with intellectual disability and syndromic presentations for a considerable period. Yet, despite a growing body of research findings, individuals with mental health and neurodevelopmental disorders in the UK have not routinely accessed the same levels of healthcare. Many of these CNVs have potentially treatable physical health implications. For example, deletions at the 22q11.2 locus increase the risk of schizophrenia and physical health problems, including congenital cardiac malformations, immune deficiency, and hypocalcaemia (Bassett et al., 2023). Our desire to improve healthcare and genetic counselling and testing for individuals with mental health and neurodevelopmental disorders and their families led us to set up the All Wales Psychiatric Genomics Service (AWPGS), the first service of its kind in the UK.

2. Aims and objectives of the All Wales Psychiatric Genomics Service

Our core aim is to provide comprehensive, multidisciplinary advice, genetic information and, where appropriate, genetic testing for individuals with concerns about a genetic predisposition to mental health and neurodevelopmental disorders.

Our objectives are to provide input for individuals and families with questions about i) the contribution of genomic variants to mental health or neurodevelopmental disorders, ii) genetic risk in the context of a family history of a mental health disorder, including preconception and perinatal genetic risk advice, and iii) risk of developing a mental health disorder associated with a known neuropsychiatric genetic risk variant (s) ascertained via NHS genetic testing or from specific research studies. We also provide consultations to healthcare professionals seeking advice on patients from our multidisciplinary expert team and provide training for clinicians interested in learning more about the use of psychiatric

* Corresponding author.
E-mail addresses: kendallkm@cardiff.ac.uk (K.M. Kendall), Donna.duffin@wales.nhs.uk (D. Duffin), dohertyjl@cardiff.ac.uk (J. Doherty), Rachel.irving@wales.nhs.uk (R. Irving), waltersjt@cardiff.ac.uk (J.T.R. Walters).

https://doi.org/10.1016/j.schres.2023.10.024
Received 29 June 2023; Received in revised form 6 October 2023; Accepted 24 October 2023

genetic findings in clinical care.

3. Structure and function of the All Wales Psychiatric Genomics Service

The AWPGS was officially launched in June 2022 with initial funding from Genomics Partnership Wales. The service is a collaboration between four organisations from Cardiff University and the NHS - the Centre for Neuropsychiatric Genetics and Genomics (CNGG), National Centre for Mental Health (NCMH), All Wales Medical Genomics Service (AWMGS) and Cardiff and Vale University Health Board.

Our core team comprises two adult psychiatrists, a consultant clinical geneticist, a principal genetic counsellor and a consultant child and adolescent psychiatrist. We run a clinic fortnightly, offering remote and in-person appointments at our clinical facility at Cardiff University. All patients referred to the service are offered an appointment run jointly between mental health and clinical genetics team members, with further appointments arranged as required. A monthly multidisciplinary team meeting attended by psychiatrists, clinical and laboratory geneticists, genetic counsellors, social scientists, and other researchers from throughout Wales underpins our work. At these meetings, there is a discussion of patients' clinical presentation, family history, psychosocial factors and laboratory results. Central to these discussions is a focus on the patient's interests and questions or, where appropriate, the family's questions on the patient's behalf. Healthcare professionals attend to request advice for their patients and to learn more broadly about genetics in psychiatric healthcare.

The AWPGS accepts referrals from healthcare professionals. Our referral criteria are:

1. A diagnosis or family history of a neuropsychiatric CNV, or
2. A diagnosis of a psychotic disorder, plus
   a) Treatment resistance, or
   b) A personal history of a neurodevelopmental disorder (such as intellectual disability, autism spectrum disorder or epilepsy), or
   c) A personal history of congenital anomaly (such as cleft lip/palate or a congenital heart defect), or
   d) A family history of a psychotic disorder (first and second-degree relatives), or
   e) A family history of a neurodevelopmental disorder (first and second-degree relatives), or
   f) A family history of a congenital anomaly.

4. Rare copy number variants and their phenotypic associations

Our first line genetic test is SNP array testing for rare CNVs. Further testing, including sequencing, is also available based on clinical need. Rare CNVs are associated with the risk of intellectual disability, autism spectrum disorder, attention deficit hyperactivity disorder, schizophrenia, schizoaffective disorder and major depressive disorder (Rees et al., 2014; Coe et al., 2014; Girirajan et al., 2011; Williams et al., 2012; Charney et al., 2019; Kendall et al., 2019). Rare CNVs often have large effects on disorder risk - for example, the twelve individual CNVs associated with the risk of schizophrenia have odds ratios of around 3–60 (Rees et al., 2014; Rees et al., 2016). However, lower risks were reported in a population study (Calle Sánchez et al., 2022). Most individuals attending the AWPGS have mental health or neurodevelopmental disorders, so discussions concerning disorder risk tend to focus on their family members.

Importantly, rare CNVs are associated with physical health problems which may be treatable or preventable. In some instances, this allows us to suggest investigations based on genetic findings, and on this, we are directed by the All Wales Medical Genomics Service. For example, individuals carrying duplications at 16p13.11 have an increased risk of thoracic aortic aneurysm, so they may be advised to consider an echocardiogram. In addition, some CNVs, such as the 22q11.2 deletion, have been studied sufficiently for consortia to develop detailed recommendations for clinical care (Fung et al., 2015).

5. Our work to date

Since the inception of the AWPGS, we have received 40 referrals - 28 from the NHS and 12 from NCMH research studies. NHS referrals have been received from i) adult psychiatric services, including community mental health teams, inpatient psychiatric services, early intervention in psychosis services, rehabilitation psychiatry and integrated autism services, ii) child and adolescent psychiatric services, iii) medical genetics, and iv) general practice. We have also provided input directly to healthcare professionals for several patients on whom they sought our advice. Individuals referred from NHS services have had a range of mental health diagnoses, as shown in Table 1. To date, seven individuals referred by the NHS have proceeded with genetic testing with three negative results, three results awaited and a positive result of a deletion at 22q11.2.

Twelve individuals were referred by the National Centre for Mental Health (NCMH). NCMH is a cohort of individuals recruited from community, inpatient and voluntary sector mental health services in the UK. During the consent process, individuals recruited to NCMH were asked if they wished to be informed about genetic findings with potential implications for their health or that of their family. Individuals who wished to learn more about their genetic results were required to participate in genetic counselling and confirmatory genetic testing, all of which fall under the remit of the AWPGS. Ten confirmatory tests in individuals referred by NCMH found copy number variant losses at *NRXN1*, 15q13.3, 16p13.11 and 22q11.2 and gains at 16p13.11, 17q12 and 22q11.2 (Table 1).

All individuals with genetic results were provided with a follow-up appointment so that the result and its potential implications could be

Table 1
Characteristics of the 40 individuals referred to the AWPGS. n - number.

	NHS referrals n = 28	NCMH referrals n = 12
Age, mean (range)	39 (13–75)	51 (26–80)
Sex, % female (n)	29 (8)	58 (7)
Mental health or neurodevelopmental disorder diagnoses[a]		
Psychosis	14	1
Bipolar disorder	4	3
Major depressive disorder	1	3
Anxiety disorder	1	2
Obsessive compulsive disorder	2	0
Post-traumatic stress disorder	0	2
Emotionally unstable personality disorder	1	1
Substance misuse	1	2
Intellectual disability	3	1
Autism spectrum disorder	5	1
Attention deficit hyperactivity disorder	3	1
No diagnosis	4	1
Genetic tests conducted	7	10
Negative results	3	0
Results awaited	3	0
Positive result (n)	22q11.2 deletion (1)	*NRXN1* deletion (1) 15q13.3 deletion (1) 16p13.11 deletion (2) 16p13.11 duplication (2) 17q12 duplication (1) 22q11.2 deletion (1) 22q11.2 duplication (2)

[a] Diagnoses are not mutually exclusive.

explained in more detail, including signposting to relevant third-sector organisations such as the charity Unique. In the case of several CNVs, we could refer the individual to a specialist service (e.g. specialist 22q11.2 clinic) or to recommend appropriate physical health investigations (e.g. echocardiogram for individuals with 16p13.11 duplication).

All individuals seen by the service are asked to complete a Genetic Counselling Outcome Scale before their first appointment and at their follow-up appointment (McAllister et al., 2011). As complete data are available for only seven individuals, we cannot perform a formal statistical analysis of the results. A feedback survey revealed several themes, including that individuals i) felt supported, ii) appreciated information provided about their mental and physical health, iii) found it helpful to understand how genetic factors have contributed to their difficulties, and iv) felt more informed and reassured about future reproductive choices.

6. Discussion and plans

The All Wales Psychiatric Genomics Service is a clear example of how psychiatric genetic research findings may be brought to the clinic via collaborative and multidisciplinary working. Patient evaluation surveys have revealed that patients seen in our service have valued the opportunity to discuss the aetiology of their disorders, something in keeping with the literature (Austin, 2020). Several have received genetic results, which have provided valuable information to improve their understanding of the aetiology of their illness. In some cases, this has provided the information needed to tailor their physical health care. We are in the process of seeking long-term funding for the running of the service by presenting a business case to the Welsh Government. We plan to continue our work with clinicians in Wales and to expand our work with young people with mental health disorders.

Further information on our service can be found at https://medicalgenomicswales.co.uk/index.php/health-professional-information/all-wales-psychiatric-genomics-service.

Role of funding source

Initial funding for the All Wales Psychiatric Genomics Service was provided by Genomics Partnership Wales. Genomics Partnership Wales had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors did not use any AI tools. The authors take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Initial funding for the All Wales Psychiatric Genomics Service was provided by Genomics Partnership Wales.

References

Austin, J.C., 2020. Evidence-based genetic counseling for psychiatric disorders: a road map. Cold Spring Harb. Perspect. Med. 10 (6) https://doi.org/10.1101/cshperspect.a036608 (Internet, Jun 1).

Bassett, A., Oskarsdottir, S., Boot, E., McDonald-McGinn, D., 2023. P112: updated clinical practice guidelines for managing children and adults with 22q11.2 deletion syndrome. Genet. Med. Open 1 (1), 100141.

Calle Sánchez, X., Helenius, D., Bybjerg-Grauholm, J., Pedersen, C., Hougaard, D.M., Børglum, A.D., et al., 2022. Comparing copy number variations in a Danish case cohort of individuals with psychiatric disorders. JAMA Psychiatry 79 (1), 59–69 (Jan 1).

Charney, A.W., Stahl, E.A., Green, E.K., Chen, C.Y., Moran, J.L., Chambert, K., et al., 2019. Contribution of rare copy number variants to bipolar disorder risk is limited to schizoaffective cases. Biol. Psychiatry 86 (2), 110–119 (Jul 15).

Coe, B.P., Witherspoon, K., Rosenfeld, J.A., van Bon, B.W., Vulto-van Silfhout, A.T., Bosco, P., et al., 2014. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat. Genet. 46 (10), 1063–1071.

Fung, W.L.A., Butcher, N.J., Costain, G., Andrade, D.M., Boot, E., Chow, E.W.C., et al., 2015. Practical guidelines for managing adults with 22q11.2 deletion syndrome. Genet. Med. 17 (8), 599–609 (8).

Girirajan, S., Brkanac, Z., Coe, B.P., Baker, C., Vives, L., Vu, T.H., et al., 2011. Relative burden of large CNVs on a range of neurodevelopmental phenotypes. PLoS Genet. 7 (11), e1002334.

Gratten, J., Wray, N.R., Keller, M.C., Visscher, P.M., 2014. Large-scale genomics unveils the genetic architecture of psychiatric disorders. Nat. Neurosci. 17 (6), 782–790.

Hilker, R., Helenius, D., Fagerlund, B., Skytthe, A., Christensen, K., Werge, T.M., et al., 2018. Heritability of schizophrenia and schizophrenia spectrum based on the Nationwide Danish Twin Register. Biol. Psychiatry 83 (6), 492–498 (Mar).

Kendall, K.M., Rees, E., Bracher-Smith, M., Legge, S., Riglin, L., Zammit, S., et al., 2019. Association of rare copy number variants with risk of depression. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2019.0566 (Internet, Apr 17).

Levey, D.F., Stein, M.B., Wendt, F.R., Pathak, G.A., Zhou, H., Aslan, M., et al., 2021. Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. Nat. Neurosci. 24 (7), 954–963 (Jul).

McAllister, M., Wood, A.M., Dunn, G., Shiloh, S., Todd, C., 2011. The Genetic Counseling Outcome Scale: a new patient-reported outcome measure for clinical genetics services. Clin. Genet. 79 (5), 413–424 (May).

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., Cardno, A., 2003. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch. Gen. Psychiatry 60 (5), 497–502.

Rees, E., Walters, J.T., Georgieva, L., Isles, A.R., Chambert, K.D., Richards, A.L., et al., 2014. Analysis of copy number variations at 15 schizophrenia-associated loci. Br. J. Psychiatry 204 (2), 108–114.

Rees, E., Kendall, K., Pardiñas, A.F.F., Legge, S.E.E., Pocklington, A., Escott-Price, V., et al., 2016. Analysis of intellectual disability copy number variants for association with schizophrenia. JAMA Psychiatry 73 (9), 963–969.

Singh, T., Poterba, T., Curtis, D., Akil, H., Al Eissa, M., Barchas, J.D., et al., 2022. Rare coding variants in ten genes confer substantial risk for schizophrenia. Nature 604 (7906), 509–516 (Apr).

Sullivan, P., Neale, M., Kendler, K., 2000. Genetic epidemiology of major depression: review and meta-analysis. Am. J. Psychiatry 157 (10), 11.

Trubetskoy, V., Pardiñas, A.F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T.B., et al., 2022. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604 (7906), 502–508 (Apr).

Williams, N.M., Franke, B., Mick, E., Anney, R.J., Freitag, C.M., Gill, M., et al., 2012. Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3. Am. J. Psychiatry 169 (2), 195–204.