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Original research

Clinical utility of genome sequencing in autism: illustrative examples from a genomic research study

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ABSTRACT

Background Genetics is an important contributor to autism spectrum disorder (ASD). Clinical guidelines endorse genetic testing in the medical workup of ASD, particularly tests that use whole genome sequencing (WGS) technology. While the clinical utility of genetic testing in ASD is demonstrated, the breadth of impact of results can depend on the variant and/or gene being reported.

Methods We reviewed research results returned to families enrolled in our ASD WGS study between 2012 and 2023. For significant results, we grouped the outcome of each genetic finding into three outcome categories: (1) genetic diagnosis, (2) counselling benefits and (3) support to family.

Results Out of 202 families who received genome sequencing results, 100 had at least one clinically relevant finding related to ASD. With detailed examples, we show that all significant results led to a genetic diagnosis and counselling benefits.

Conclusion Our findings show the relevance of genome sequencing in ASD and provide illustrative examples of how the information can be used.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The clinical utility of genome sequencing in autism spectrum disorder (ASD) is documented, but the uptake and perceived benefit is sometimes questioned due to a lack of examples of impact.

WHAT THIS STUDY ADDS

⇒ One hundred real-life examples of the downstream impact of receiving a genetic result from genome sequencing based on the gene involved in ASD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides data on how genomic information may be used by families, healthcare providers and researchers to better understand ASD.

INTRODUCTION

Autism spectrum disorder (ASD or autism) is a heterogeneous condition diagnosed through behavioural assessments focusing on social communication skills and restrictive or repetitive behaviours. The prevalence varies depending on ascertainment and assessment[1]; in Canada, it is seen in 1 out of 66 children, and in 1 out of 100 individuals globally.[1 2] The underlying aetiology of autism is complex, but genetics is a contributor.[3] Approximately 100 genes have been implicated in ASD and are used in genetic testing, and many of these are associated with known genetic conditions.[4–6]

Professional societies, including the American Academy of Child and Adolescent Psychiatry, the American College of Medical Genetics (ACMG) and the Canadian College of Medical Geneticists (CCMG), endorse genetic testing in the medical workup of children diagnosed with neurodevelopmental disorders (NDDs), which include autism.[7–9] As a first-tier diagnostic test, the ACMG and CCMG recommend chromosomal microarray analysis (CMA) to identify copy number variants. Additional genetic testing, including metabolic screening, fragile X testing and targeted gene tests/panels, are also suggested for individuals with a high suspicion of a genetic aetiology.[8 9] Now, exome and whole genome sequencing (WGS) in NDD is the standard due to increased clinical testing yields.[10 11] WGS uses next-generation sequencing technology to determine the DNA sequence of an individual's entire genetic material, enabling the identification of variants across coding and non-coding regions of the genome. The application of WGS in autism has a diagnostic yield ranging from 8% to 14%,[5 12 13] and these values increase considering individuals with profound autism with medical complications.[5 10 11]

The clinical utility of a genetic test, according to the ACMG, demonstrates an impact on 'therapeutic management, implications for prognosis, health and psychological benefits to patients and their relatives, and a broad economic impact on health-care systems'.[14] The benefit of uncovering a genetic aetiology in a NDD population is well documented and include informing medical management, providing gene-specific or condition-specific information, guiding genetic counselling and connecting families to tailored supports and research opportunities.[15 16] For autism specifically, studies have demonstrated that genetic testing has informed screening for

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co-occurring conditions, prompted/altered medical interventions, and ended the diagnostic odyssey (avoiding multiple investigations) for a subset of patients.[11 17–19]

While the clinical utility of genetic diagnosis is evident, its uptake for patients with autism can be limited.[20] Emerging data on the perspectives of some autistic adults suggest concern related to genetic testing and autonomy.[21] Moreover, some healthcare professionals and families have expressed scepticism regarding the practical benefits of understanding the genetic aetiology of autism.[20 22] Clinicians caring for individuals with autism reported a need to learn about the clinical utility of genetic testing and to better understand the genetics of autism.[3 23] These different perspectives highlight the need to demonstrate more clearly the relevance of genetic testing to effectively support healthcare providers in their decisions to order such testing for medical patients with autism and offer evidence for health insurance coverage for some families.[24] Additionally, more information will help families considering genomic testing to make informed decisions. Here, we present the results from a longitudinal WGS project to showcase the potential impact of genomic testing in individuals with autism and their families and highlight their perspectives. We also discuss our experience of how the impact of delivering genomic results can depend on the variant and/or gene involved, the stage of life of the participants and new scientific advances.

METHODS

Study cohort

Participants are enrolled in the Autism Speaks Genomics of Autism (MSSNG) research study across multiple sites (primary site, The Hospital for Sick Children (SickKids) in Toronto) which includes individuals from varying ancestries (see online supplemental table 1). The primary goal of this prospective cohort study is to identify genetic variants contributing to ASD and the cellular processes involved. Individuals with autism, as well as their immediate family members (eg, parents, siblings), are eligible to participate. Voluntary enrolment involves providing a biological sample for genomic analysis (ideally trio analysis, but can involve singleton and multiplex analysis) and completing standardised questionnaires to supply clinical presentation information (ie, phenotype data).[12 25] When the genomic analysis is complete, the results are disclosed to the family via the research study team. The consented genomic and phenotypic data are uploaded to the MSSNG database, which is a cloud-based controlled-access data repository that provides a power tool for genomic analysis across the autism study population.[12] The cohort described in this paper are those research families who underwent WGS analysis and received a genetic result from genetic counsellors or clinicians. All participants consented to be in the study which allows for publication of results.

Disclosure of research results process

The primary research findings generated from the WGS analysis are genetic variants related to autism or NDD. Variants are interpreted using the ACMG variant classification framework with five variant classifications: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign and benign.[26] The study reporting protocol focuses on genes associated/potentially associated with autism or NDD.[12] Since the genetic findings are not confirmed in a clinically certified laboratory prior to disclosure to participants, the ACMG variant classification terminology was modified to differentiate between research-grade and clinical-grade results: 'significant' replacing 'pathogenic'.[26] Research reports are generated if VUS, likely significant variants and significant variants are identified.

A research report is generated for the study participant with autism using a team of genetic counsellors, genomic analysts, investigators and a clinical laboratory geneticist. For the disclosure, the family is contacted by the recruiting site to offer either an in-person or videoconference meeting with the genetic counsellor or study clinician. The families are counselled about their genetic results using a previously outlined approach to communicating complex information.[3] It is emphasised that the research results and their interpretation are based on current technology and understanding. As new genomic tools and algorithms are developed and scientific knowledge advances, the family may get updated information about their WGS results, including changes to variant classifications and newly reported variants. During the result disclosure, the research genetic counsellors asked the participant and family how they felt about receiving the research results. Their response was noted in the research file as direct quotes and/or paraphrased and compiled for this manuscript during the chart review process. Following the disclosure of results, the genetic counsellors or study clinician facilitate referrals to genetics centres for clinical confirmation of any significant variants through a Clinical Laboratory Improvement Amendments (CLIA) or Accreditation Canada Diagnostics certified laboratory.

Timeframe of WGS results disclosure

We reviewed all disclosed WGS research reports from January 2012 (when WGS was first implemented) to November 2023; 202 families received results where a genetic variant was disclosed. Here, we describe individuals with autism who received likely significant or significant results relevant to ASD. In addition, we include a few examples of VUS findings that, based on clinical interpretation, are likely to be contributory but require additional supporting evidence.

Categorisation of clinical utility

Using the ACMG description of clinical utility of genetic testing[14] and related publications in the NDD/autism population,[11 17–19] we designated three outcome categories: (1) genetic diagnosis, (2) counselling benefits and (3) support to family. Descriptions of each category are provided in the Results section. For each family who received genomic sequencing results, we reviewed the research report and any available summary note from the result disclosure to determine if the result impacted each clinical utility category. A single genetic finding can have multiple downstream outcomes; therefore, it can count towards more than one category. Two of the researchers (TS, NH) independently categorised each case to ensure reliability.

RESULTS

Of the 202 WGS results returned, 100 (49%) had at least one (likely) significant genetic variant relevant to ASD (table 1). It is important to note that this should not be interpreted as the cohort's diagnostic yield for WGS, which for this study has been previously published[12] and is discussed below. The demographic data for the 202 individuals with autism included 76.7% males and 23.3% females (see online supplemental table 1). The age at enrolment ranged from 11 months to 49 years and 8 months, with a mean age of 10 years 2 months and a median age of 7 years 9 months. The genetic ancestry of the 202 families consisted of 73.7% European, 5.9% South Asian, 2.5% Admixed American, 1.5% African and 1.5% East Asian.

Table 1 List of (likely) significant genomic findings in individuals with autism returned to families

Family number	Relevant ASD-related gene or locus	Mode of inheritance of associated condition	Inheritance	Presumed mechanism	Genetic diagnosis	Counselling benefits	Support to family	Additional reported findings
1	*CHD8*	AD	De novo	LoF	Y	Y		*LAMC3**
2	7q11.23 del	AD	De novo	Haploinsufficiency	Y	Y		*BRCA2*†
3	*MYT1L*	AD	De novo	LoF	Y	Y		NA
4	*KMT2A*	AD	De novo	LoF	Y	Y		NA
5	*WDFY3*	AD	De novo	LoF	Y	Y		*PER2, EIF4E, GAMT, COMT, TMLHE*
6	*SLC6A1*	AD	De novo	LoF	Y	Y		NA
7	*CASK*	XL	Unknown	LoF	Y	Y		*CLTC, TMLHE*
8	*CHD8*	AD	De novo	LoF	Y	Y		*CNTNAP4*
9	*PTEN*	AD	De novo	LoF and dominant-negative	Y	Y		NA
10	*TET3*	AD	Unknown	LoF	Y	Y		NA
11	*MBD5*	AD	De novo	LoF	Y	Y		NA
12	*CAPRIN1*	AD	De novo	LoF	Y	Y	Y	NA
13	1q21.1-1q21.2 del	AD	De novo	Haploinsufficiency	Y	Y		6q13 dup
14	*SCN2A*	AD	De novo	LoF and GoF	Y	Y		*ZBBX, TTN*
15	15q11.2-q13.1 dup	AD	Paternal	Triplosensitivity	Y	Y		NA
16	*SCN2A*	AD	Paternal (mosaic)	LoF and GoF	Y	Y		*RELN*
17	*SHANK3*	AD	De novo	LoF	Y	Y	Y	*AGBL1*
18	*DNMT3A*	AD	De novo	LoF	Y	Y		NA
19	*GRIN2B*	AD	De novo	LoF and GoF	Y	Y		*ATRX*
20	*MTSS2*	AD	Unknown, present in affected siblings	unknown	Y	Y		NA
21	3q29 del	AD	De novo	Haploinsufficiency	Y	Y		*ANK2, HCN1,* 3q29 dup
22	*ASXL3*	AD	De novo	LoF	Y	Y		NA
23	*NLGN3*	XL	Maternal	LoF	Y	Y		NA
24	*NLGN3*	XL	Maternal	LoF	Y	Y		*SCN2A*
25	*RORB*	AD	De novo	LoF	Y	Y		NA
26	22q11.21 dup	AD	Paternal	Triplosensitivity	Y	Y		*LZTR1*
27	*SHANK3*	AD	De novo	LoF	Y	Y	Y	NA
28	*NAA15*	AD	De novo	LoF	Y	Y		*RBM10, PCDH19*
29	*NRXN1*	AD and AR	De novo	LoF	Y	Y		NA
30	*CHD8, KMT2E*	AD, AD	De novo, de novo	LoF, LoF	Y	Y		NA
31	*KMT2A*	AD	De novo	LoF	Y	Y		NA
32	16p11.2 del	AD	De novo	Haploinsufficiency	Y	Y		*FXN* repeat
33	*CHD8*	AD	De novo	LoF	Y	Y		NA
34	*SCN2A*	AD	De novo	LoF and GoF	Y	Y		*SNTG2*
35	*PTEN*	AD	De novo	LoF and dominant-negative	Y	Y		NA
36	*SLC6A1*	AD	De novo	LoF	Y	Y		NA
37	*NF1*	AD	Unknown	LoF	Y	Y		NA
38	*CTNNB1*	AD	De novo	LoF	Y	Y		NA
39	*ARID1B*	AD	De novo	LoF	Y	Y		NA
40	*SHANK3*, 16p13.11–16p12.3 dup	AD, AD	De novo, paternal	LoF, triplosensitivity	Y	Y		NA
41	*SOX5*	AD	De novo	LoF	Y	Y		10q11.2-10q11.23 dup
42	*SYNGAP1*	AD	Unknown	LoF	Y	Y		NA
43	*CUL3*	AD	De novo	LoF	Y	Y		NA
44	*KMT2E*	AD	Unknown	LoF	Y	Y		*MAP1A*
45	*TRIP12*	AD	De novo	LoF	Y	Y		*FGA*†
46	*PTEN*	AD	De novo	LoF and dominant-negative	Y	Y		*CLN8**
47	*KMT2A*	AD	De novo	LoF	Y	Y	Y	*ADORA2A, ARNT2*
48	8q22.1 del	AD	De novo	Haploinsufficiency	Y	Y		1q21.1 dup, *GPHN*
49	*EHMT1*	AD	De novo	LoF	Y	Y		*MYH4*

Continued

Table 1 Continued

Family number	Relevant ASD-related gene or locus	Mode of inheritance of associated condition	Inheritance	Presumed mechanism	Genetic diagnosis	Counselling benefits	Support to family	Additional reported findings
50	*FMR1*	XL	Maternal	LoF	Y	Y		NA
51	*TLK2*	AD	De novo	LoF	Y	Y		NA
52	*SHANK3*	AD	De novo	LoF	Y	Y	Y	NA
53	*ZEB2*	AD	De novo	LoF	Y	Y		NA
54	*ASH1L*	AD	De novo	LoF	Y	Y		NA
55	*WAC*	AD	De novo	LoF	Y	Y		*CEP135**
56	*FOXP1*	AD	De novo	LoF	Y	Y		NA
57	*NF1*	AD	De novo	LoF	Y	Y		NA
58	*SMARCC2*	AD	De novo	LoF	Y	Y		NA
59	*NF1*	AD	De novo	LoF	Y	Y		*TCF12*
60	*CHD8*	AD	De novo	LoF	Y	Y		NA
61	*KDM3B*	AD	De novo	LoF	Y	Y		NA
62	*CHD2*	AD	De novo	LoF	Y	Y		NA
63	*NF1*	AD	Unknown	LoF	Y	Y		NA
64	*SCN2A*	AD	De novo	LoF and GoF	Y	Y		*ANK3*
65	*NLGN4X*	XL	Maternal	LoF	Y	Y		NA
66	22q11.2 dup	AD	Unknown	Triplosensitivity	Y	Y		*TMLHE*
67	*ADNP*	AD	De novo	LoF	Y	Y		NA
68	*MECP2*	XL	De novo	LoF	Y	Y		NA
69	*POGZ*	AD	Unknown	LoF	Y	Y		NA
70	*NEXMIF*	XL	De novo	LoF	Y	Y		*RFX3*
71	*KMT2A*	AD	De novo	LoF	Y	Y	Y	NA
72	*CNOT3*	AD	De novo	LoF	Y	Y	Y	*KDM6B*
73	*SHANK2*	AD	De novo	LoF	Y	Y	Y	*ATP1A3*
74	*SET*	AD	De novo	LoF	Y	Y		NA
75	*TCF12*	AD	De novo	LoF	Y	Y		NA
76	*DDX3X*	XL	De novo	LoF and dominant-negative	Y	Y		NA
77	*CHD8*	AD	De novo	LoF	Y	Y		*TAOK2*, *KIF1A*
78	*SCN2A*	AD	Unknown	LoF and GoF	Y	Y		NA
79	*PTEN*	AD	De novo	LoF and dominant-negative	Y	Y		NA
80	*KDM6A*	XL	De novo	LoF	Y	Y		NA
81	*KCNQ2*	AD	De novo	LoF, GoF, and dominant-negative	Y	Y		NA
82	*CDC42*	AD	De novo	LoF, GoF, and dominant-negative	Y	Y		*STXBP5*
83	17q11.2 dup	AD	Paternal	Triplosensitivity	Y	Y		20q11.21 dup, *TRAPPC9*, *OPHN1*, *PCDH15*
84	*NSD1*	AD	Unknown	LoF	Y	Y		NA
85	*NLGN4X*	XL	De novo	LoF	Y	Y		*TMLHE*
86	*TLK2*	AD	Unknown	LoF	Y	Y		*DYRK1A*
87	*SLC6A1*	AD	Unknown	LoF	Y	Y		*POMT1**
88	*ANKRD11*	AD	Unknown	LoF	Y	Y		NA
89	*ASH1L*	AD	De novo	LoF	Y	Y	Y	NA
90	22q11.21 dup	AD	Paternal	Triplosensitivity	Y	Y		NA
91	*SHANK3*	AD	De novo	LoF	Y	Y		NA
92	*KCNB1*	AD	De novo	LoF and dominant-negative	Y	Y		*KDM5B*
93	*PTEN*	AD	De novo	LoF and dominant-negative	Y	Y		*VIL1*
94	*ASH1L*	AD	De novo	LoF	Y	Y	Y	*POLA2*, 9q34.11q34.12 dup
95	*CHD8*	AD	De novo	LoF	Y	Y		NA
96	*CHD2*	AD	De novo	LoF	Y	Y		NA
97	22q11.2 del	AD	De novo	Haploinsufficiency	Y	Y		*F9*†

Continued

Table 1 Continued

Family number	Relevant ASD-related gene or locus	Mode of inheritance of associated condition	Inheritance	Presumed mechanism	Genetic diagnosis	Counselling benefits	Support to family	Additional reported findings
98	*ASH1L*	AD	De novo	LoF	Y	Y	Y	*TSHZ3, TNR*
99	*MEIS2*	AD	Unknown	LoF	Y	Y		*KCNC1*
100	*TRRAP*	AD	De novo	Unknown	Y	Y		*PKP2*†, 9q34.11 dup

*Carrier status result not relevant to ASD.
†Significant incidental finding unrelated to ASD or NDD.
AD, autosomal dominant; AR, autosomal recessive; ASD, autism spectrum disorder; del, deletion; dup, duplication; GoF, gain-of-function; LoF, loss-of-function; NA, not applicable; NDD, neurodevelopmental disorder; XLD, X-linked dominant; XLR, X-linked recessive; Y, yes.

In 12.4% of families, the ancestry analyses from two genomic prediction tools were discordant, and no self-reported ancestry data were available, so the ancestry was categorised as 'Other.' Two per cent were ADMIXED ancestry, where the parents are of different genetic ancestries, and for one family, the ancestry data were not available (see online supplemental table 1). Among the 100 families, all results had an impact on outcome categories 1 and 2: genetic diagnosis and counselling benefits. In 11% of families, the genetic results also provided support to the family by providing them with a gene name to form social support networks and connect with scientists and gene-specific research.

Category 1: genetic diagnosis

Receiving a genetic diagnosis that ends the diagnostic odyssey, informs medical management and prognosis, and treatment is a potential benefit of genetic testing in autism.

De novo *SHANK3* variant–NM_001080420.1: c.3727dup (p.Ala1243Glyfs*69)

In an 18-year-old male patient with autism, intellectual disability, seizures and generalised anxiety disorder, clinical CMA and gene panel testing were uninformative. When he was 23 years old, WGS analysis through this study identified a de novo, recurrent frameshift variant in *SHANK3* (MIM: 606230) associated with Phelan-McDermid syndrome (PMS (MIM: 606232)). The research result was clinically confirmed and provided a unifying diagnosis for the participant's clinical presentation. This genetic diagnosis provided guidance on how to monitor and manage associated features. For instance, a consensus guideline recently published advised on the diagnosis and treatment of seizures in patients with PMS.[27] This includes recommendations for brain imaging (eg, MRI) for every individual with PMS having neurological symptomology. In this participant, his seizures were already evident, and he is regularly followed up by his neurologist. For some seizure conditions, condition/gene-specific information regarding medication effectiveness may be available. For PMS, the guidelines recommend general seizure treatment protocols as there is currently no evidence of a specific medication that works best for all patients with PMS and no contraindicated drugs. The parents expressed that receiving a genetic diagnosis helped them understand their child better. Prior to the diagnosis, they felt they were 'floating with nothing to hold on to and with this diagnosis, they now have a starting point.' They expressed that this knowledge gave them a sense of control prompting them to plan their child's future differently, especially financially.

De novo *ARID1B* variant–NM_001346813.1: c.1044_1068del (p.Ala350Metfs*11)

After exhausting all clinically available tests (CMA, fragile X testing and *MED12* (MIM: 300188) gene sequencing), a participant with high suspicion of an underlying genetic aetiology was enrolled. The 15-year-old male patient presented with a provisional diagnosis of autism with a history of developmental delay, speech delay, febrile seizures, sensory hypersensitivity and strong food preferences. WGS identified a de novo variant in *ARID1B* (MIM: 614556), associated with Coffin-Siris syndrome (MIM: 135900). Following results disclosure, the participant was reassessed by a clinical geneticist, and the *ARID1B* variant was confirmed clinically to be pathogenic, providing the family with a new clinical and molecular diagnosis. As a result, the clinical team reviewed the clinical management guidelines for Coffin-Siris syndrome and ordered screening for associated symptoms, including abdominal imaging to rule out associated renal anomalies. For this participant, the ultrasound came back normal, but could have uncovered a hidden feature of the condition. With this molecular diagnosis, the primary care provider can use anticipatory guidelines (eg, vision, dental, scoliosis) to monitor the general health and well-being of this patient. Here, having a genetic diagnosis can inform additional surveillance and assessments, primarily unrelated to ASD but still impactful to the well-being of the participant.

De novo *GRIN2B* variant–NM_000834.3: c.2515G>A (p.Glu839Lys)

In a 31-year-old male patient with autism, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder with Tourette syndrome and intellectual disability, WGS analysis identified a de novo missense variant in *GRIN2B* (MIM:138252). Variants in *GRIN2B* are associated with *GRIN2B*-related neurodevelopmental disorder (MIM: 613970, 616139), which is characterised by variable intellectual disability, muscle tone and motor differences, and behavioural differences including autism. Approximately 50% of individuals also have seizures.[28] Over several years, this participant was noted to have episodes of incontinence, not being able to chew and appearing slow and tired. He was assessed by a neurologist, but the underlying aetiology of these episodes was not identified. After receiving this result, the participant was assessed by a clinical geneticist, and the *GRIN2B* variant was clinically confirmed. In addition, the participant's neurologist was notified of the new genetic diagnosis as the additional *GRIN2B*-related information may help clarify the seizure query. Whether these episodes are confirmed to be seizures or another clinical feature, this participant contributes to the growing knowledge about the presentation

of *GRIN2B*-related disorder. Emerging research on therapies for *GRIN*-related disorders showed promise with dietary supplementation. For some patients with variants in *GRIN2B*, taking L-serine supplements improved behaviour, development and/or seizure frequency, but additional clinical trials are needed to fully understand the benefits and safety of this therapy.[29]

De novo *CNOT3* variant–NM_014516.3: c.1473_1474del (p.Gly493Thrfs*21)

After being part of the study for 13 years, a male participant with autism, developmental delay/intellectual disability, limited verbal communication, obesity, macrocephaly, distinctive facial features and hypothyroidism received a genetic diagnosis at age 18. The WGS analysis identified a novel de novo frameshift variant in *CNOT3* (MIM: 604910), a gene implicated in a newly recognised condition called *CNOT3*-associated neurodevelopmental syndrome (MIM: 618672). The condition was first characterised in 2019 where 16 patients with a similar presentation were described with de novo variants in *CNOT3*.[30] This participant's neurodevelopmental phenotype is explained by this finding. However, it is not currently clear whether this finding fully explains his other features such as macrocephaly and hypothyroidism. As more individuals with *CNOT3* variants are described, we may learn of more associated features. This story highlights that even with newer technology like WGS to uncover previously unidentifiable variants, the immediate medical impact for this family is limited. However, families like this one, where the participant is now an adult, are valuable contributors to the growing understanding of gene-specific conditions as autistic children age. The parents expressed that this result provided closure, ending their diagnostic odyssey.

Category 2: counselling benefit

Given that the aetiology of autism is multifactorial, with many genes implicated, and varying levels of contribution, knowing the individual variant involved is helpful in all aspects of genetic counselling.

ASXL3 variant inherited from mosaic mother–NM_030632.1: c.4678C>T (p.Arg1560*)

A family with a 10-year-old male child diagnosed with autism, global developmental delay, hypotonia and photorefractive keratectomy enrolled looking for an underlying aetiology for their son's constellation of symptoms. Clinical genetic examination including CMA and fragile X testing was negative. WGS identified a nonsense variant in *ASXL3* (MIM: 615115), a gene where loss-of-function variants cause Bainbridge-Ropers syndrome (MIM: 615485). The variant was present in a mosaic state in the mother, who had no reported clinical diagnoses, but did have a history of speech delay. Given the inheritance and reportedly discordant clinical presentation, the variant was reported out by the research team as a VUS, but a referral for clinical follow-up was suggested. On assessment by a clinical geneticist, the participant's clinical features aligned with Bainbridge-Ropers syndrome, and the *ASXL3* variant was clinically confirmed and classified as pathogenic. Knowing the Bainbridge-Ropers syndrome diagnosis allowed the clinical team to counsel the family on the likelihood of recurrence based on a mosaic inheritance model. Since the proportion of gametes in the mother that carry this variant is unknown, the family was counselled that the chance of having another child with Bainbridge-Ropers syndrome is up to 50%.

EP300 deletion inherited from mother with autism–NC_000022.11: g.41113623_41129006del

When a child is diagnosed with autism in our study, some parents pursue an autism assessment for themselves. Here, the mother received an autism diagnosis following her daughter's diagnosis. WGS analysis of the 19-year-old daughter with autism, ADHD, mild Tourette syndrome and chronic ankle weakness identified a 15 kb deletion impacting multiple exons of *EP300* (MIM: 602700). The deletion in the daughter was maternally inherited; however, this same deletion was found to be a de novo event in the mother (ie, not inherited). Variants in *EP300* are associated with Rubinstein-Taybi syndrome (MIM: 613684). Individuals with this condition have a range of clinical presentations including short stature, distinctive facial features and autism. This research finding prompted assessments to look for features associated with Rubinstein-Taybi syndrome in both the mother and daughter. Follow-up clinical testing confirmed this deletion as pathogenic in both the proband and mother, and a geneticist assessment found that they both do not have the typical features associated with Rubinstein-Taybi syndrome. The knowledge that this deletion is pathogenic and likely contributed to the autism in the family provides the daughter with refined genetic counselling information. The de novo status in the mother provides insights for other family members as well.

Category 3: support to family

Having a genetic diagnosis allows families to connect with one another and build a social support network to share experiences. Identifying families with rare variants in shared genes also allows researchers to uncover biologically relevant pathways and develop molecular intervention targets.

De novo *ASH1L* variant–NM_018489.2: c.4902_4903del (p.Ser1635Cysfs*18)

WGS of a 7-year-old male child with autism, oromotor apraxia and history of hypotonia, delayed fine and gross motor skills identified a de novo variant in *ASH1L* (MIM: 607999). The reported associated features included intellectual disability, autism and a broad range of additional manifestations. The limited resources prompted the mother to seek out other families with this *ASH1L*-associated condition. She wanted to learn what this would mean for her young son and meet other individuals with *ASH1L* variants. The family formed a non-profit organisation connecting *ASH1L* families from around the world, as well as researchers studying the gene (https://www.care4ash1l.com/). The organisation's goal is to advance the understanding of the molecular mechanism of *ASH1L* to develop tailored therapeutics. Beyond creating an online community to share personal experiences and resources, the organisation has raised funds to support additional research, including stem cell studies, clinical phenotype and natural history studies, and functional work.

De novo *SHANK2* variant–NM_012309.5: c.2521C>T (p.Arg841*)

In an 18-year-old male patient with autism, WGS identified a de novo nonsense variant in *SHANK2* (MIM: 607999). This gene is a member of the *SHANK* family, which encodes synaptic proteins with important roles in the signalling pathway in the brain. Following the finding of *SHANK3* in idiopathic autism,[31] our research group followed to implicate *SHANK* genes in the susceptibility to autism.[32 33] For this family, the variant was clinically confirmed and provided an answer for why their son had autism. The question of how *SHANK2* variants impact neuron

biology remained unclear, which our team investigated using induced pluripotent stem cells (iPSCs). The family consented to participate in this iPSC study and provided blood samples, which were used to generate nerve cells with and without the *SHANK2* variant. The functional impact of the variant on neuronal structure, function and signalling was measured. Along with a different *SHANK2* variant contributed by another research family, the study found that neurons from participants with *SHANK2* variants were overconnected (increased dendrite length and complexity, and synapse number) and overactive (increased frequency of spontaneous excitatory postsynaptic currents) compared with control neurons.[34] This study provides insight into the pathophysiology of *SHANK2* variants in neurodevelopmental conditions, which may inform research into targeted supports for these families.

De novo *AMOTL1* variant–NM_130847.2: c.470G>A (p.Arg157His)

For some individuals with ASD and a known genetic syndrome, undergoing genomic analysis can uncover additional genetic contributions and prompt research. This was the case for a 7-year-old female child with Beckwith-Wiedemann syndrome (BWS (MIM: 130650)) due to hypomethylation on chromosome 11p15.5 at IC2. Her clinical team felt that her complex medical history and uncharacteristic clinical presentation was not fully explained by the BWS diagnosis. Research WGS analysis identified a de novo missense variant in *AMOTL1* (MIM:614657), which was of uncertain significance at the time. There were three reports in the literature of patients with missense variants in *AMOTL1*, including the specific variant identified in our participant.[35–37] The phenotype described in the three patients overlapped with our participant, prompting us to reach out to the researchers and contributing to a case series characterising a new Mendelian condition in patients with variants in *AMOTL1*.[38] These cohort studies also inform the development of management guidelines. For individuals with *AMOTL1* variants, several screening recommendations were suggested: examination for evidence of orofacial clefting and velopharyngeal insufficiency, regular eye examinations to evaluate for myopia, audiology examinations for hearing loss, echocardiograms and ECG for congenital heart disease and arrhythmia, screening for and aggressively treating constipation, evaluation of liver function, scoliosis and obtaining a developmental assessment.

DISCUSSION

We present examples of the clinical utility of genetic testing in autism. Many of the individuals we highlighted received results in adulthood. These individuals may have been assessed in a genetics clinic during childhood but did not receive a genetic diagnosis, possibly due to fewer genetic testing options or limited genetics knowledge available at the time. The advent of sequencing technologies has improved diagnostic rates for the broader NDDs (including ASD). The diagnostic yield ranges from 5% to 25% for CMA,[9] 30–43% for exome sequencing[11] and 30–50% for WGS.[13] Studies focusing on the autism population specifically have shown that WGS has a conservative diagnostic yield of 14%[12] or a diagnostic rate twofold more than CMA and threefold more than WES.[13] Although the implementation of WGS has been shown to streamline genetic diagnostic workflow and reduce the diagnostic odyssey, it is not yet established as the first-tier test for NDDs and is primarily offered in research settings.[12 39–41] As illustrated by the examples presented here, WGS is a comprehensive test capable of detecting a range of diagnostic variants, providing clinical utility to families and should be considered as a genetic test for patients with autism. Moreover, through our examples, we show the benefit of receiving a genetic diagnosis in adulthood not only for improved medical management but also for improved understanding of the natural history and variable presentation of a genetic condition.

Based on a 2022 review by Stafford and Sanchez-Lara, several studies have demonstrated that results from genetic testing in patients with autism, primarily using CMA results and WES, have provided a genetic diagnosis, which informed screening for co-occurring conditions and prompted medical interventions.[17] In some cases, by identifying a genetic aetiology, unnecessary medical assessments and interventions can be avoided.[8 42 43] In three of the illustrative cases presented (*GRIN2B*, *CNOT3*, *EP300*), the individuals are contributing to a better understanding of the phenotypic spectrum of their associated conditions. For rare genetic conditions or newly described associations, management guidelines and prospective information are likely unavailable. As the number of individuals with shared genetic findings is identified, there is an opportunity to collect more phenotypic data to better understand the clinical expression as individuals age. This underscores the importance of capturing the phenotypic expression of a genetic variant in a 'bonafide' ASD-relevant gene. To address the need for a standardised approach for autism gene curation, a team of multidisciplinary experts in autism and clinical genetics developed the EAGLE (Evaluation of Autism Gene Link Evidence) framework that uses and expands on ClinGen's pre-existing gene-disease curation process.[44] This framework was developed to evaluate the relevance of variations in a specific gene to the autism phenotype.[4] It combines reported genotype and phenotype information including the specific assessments used to diagnose autism.

Autism has substantial phenotypic and genetic heterogeneity as our examples illustrate. Many studies have shown that autism results from a combination of individually rare, underlying genetic aetiologies.[5 11 12 45] This makes genetic counselling in the autism context complex.[3] Knowing the specific genetic aetiology can inform genetic counselling about inheritance patterns, variability, expressivity and prognosis. Having gene-specific information can help clinicians connect families to available interventions (eg, screening, treatment) and clinical trials. For families, this information allows them to connect to community networks and support groups to learn about new research and therapies for their specific genetic diagnosis. For autism, early intervention has been shown to improve outcomes,[46] and the early identification of genetic variants can enable preparation for both families and healthcare providers. Having genetic information is important for informed decision-making not only for the individual but also for extended family members.[8 43 47] When no significant variants are identified or VUS findings are disclosed, the underlying genetic contribution to the autism in the family remains unclear. This is common and underscores the complexity inherent in autism.[3] In these situations, clinicians can rely on empirical studies to provide families with additional information. The identification of VUSs provides an opportunity for clinicians to collect additional phenotypic data and/or prompt additional research (eg, functional analysis, iPSC studies) to clarify the significance of the findings.

One way to look at the clinical utility of genetic testing is to evaluate treatment options that ultimately improve health outcomes among the autism population. The discovery of rare genetic variants associated with genetic conditions is the essential first step in developing novel therapies for precision medicine.[48 49] Currently, numerous clinical gene therapy trials

are underway for NDD/ASD-related conditions. In Angelman syndrome (MIM: 105830), antisense oligonucleotide (ASO) therapy called GTX-102 has been designed to decrease expression of *UBE3A-AS* and reactivate expression of paternal *UBE3A* (MIM:601623). Data from the Phase I/II suggested functional gain over time and multidomain improvement in the Bayley-4 and Angelman Severity Assessment measures in treated individuals. ASO-based and adeno-associated virus-9 (AAV9)-based therapies for Dravet syndrome (MIM: 607208) are also underway. Phase I/II study data for ASO-based therapy, called STK-001, indicate a reduction in seizure frequency and improvements in various measures of cognition and behaviour. Among others, gene therapies for Rett syndrome (MIM: 300005) and other developmental and epileptic encephalopathies including *CDKL5* deficiency disorder (MIM: 300672), *STXBP1*-related disorder (MIM: 612164) and *SCN2A*-related disorder (MIM: 613721, 607745) are also in development.

Limitations of this study

We evaluated genetic results for clinical utility and benefit to an individual family. We did not assess the potential harms of receiving these findings (noting, however, no overt harm was observed). Most individuals who received results were of European ancestry (expected proportion of individuals of this background in Ontario is 66%), although other ancestry groups were represented. We did not explore potential cultural differences in response to genetic findings. While we share some family perspectives on receiving results, we did not systematically collect these experiences from all families that received results.

Summary

We present examples of families who have received a genetic diagnosis and discuss our experiences of genetic testing in the autism population. As our understanding of the genetic contributions to autism grows, there is potential to aid in early detection, inform the development of targeted supports and therapies, and provide improved care and outcomes for individuals with autism and their families.

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Contributors TS and NH compiled, reviewed and categorised all genetic results shared with research families and selected examples to illustrate clinical utility for each category. TS, NH and ES produced table 1. TS, NH, ES and SWS wrote the manuscript. All authors reviewed, provided revisions and approved the final manuscript. SWS is the guarantor.

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