High Yield of Deep Phenotyping and Long Read Whole Genome Sequencing in Treatment-Resistant Schizophrenia or Schizoaffective Disorder

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BACKGROUND

The **UBC MAGERS (Metabolic & Genetic Explorations in Refractory Schizophrenia)** is a pilot multimodal -omics and psychiatric genetic counselling project involving 50 participants with **deeply phenotyped, severe treatment-resistant schizophrenia (SCZ) or schizoaffective disorder (SZAD)** recruited from a tertiary inpatient adult refractory psychosis clinical and research unit in British Columbia, Canada. In our first 25 cases, 9 (36%) participants had a pathogenic/likely pathogenic (P/LP) rare or novel DNA sequence or structural variant (SV) relevant to their psychosis and/or neurodevelopmental (ND) phenotype(s). Pathogenic exonic and chromosomal variants from the second 25 MAGERS participants are highlighted here. We hypothesized individuals with "extreme phenotypes" of psychosis and poor treatment response are likely to harbour potent rare and/or novel genetic risk variants with potential precision medicine implications.

METHODS

Participants with SCZ and SZAD were enrolled in our pilot precision medicine study while admitted to the BC Psychosis Program, the tertiary inpatient adult refractory psychosis research and clinical care unit for the province of British Columbia, Canada. Phenotyping included structured birth histories and three-generation family histories, Mini-International Neuropsychiatry Interviews (M.I.N.I.), Childhood Trauma Questionnaires, neuropsychological assessment, physical exams, structured neurological and dysmorphological exams, and detailed reviews of medical records, labs, EEG, and imaging data. Standardized and extensive clinical-biochemical screening for psychosis-associated inborn errors of metabolism (IEMs) was completed. DSM-5 diagnoses were achieved by multidisciplinary consensus and M.I.N.I. Clinical chromosomal microarrays (CMAs) using Cytoscan HD arrays were performed at entry by clinical cytogeneticists. Long-read HiFi whole genome sequencing (WGS) on PacBio's Revio sequencer at ~30X coverage and whole blood RNA-Seq on llumina's NovaSeq (150 BP paired-end, 100M individual reads) were completed. Rare DNA sequence variants identified by DeepVariant were functionally annotated, filtered, and prioritized by Exomiser (v14.0.0) using VCF files and extensively HPO-coded phenotypes. Shortlisted P/LP variants were manually curated with multiple bioinformatic databases and tools (e.g. SCHEMA, Varsome, Franklin SZGR2, OMIM, UniProt, IDRBind, LIST-S2, Ricopili, MetaRNN, AlphaMissense), literature review, and correlated with clinical and phenotypic data. Short tandem repeat analysis was performed using Straglr and TRGT; RNA-Seq, SV, and epigenetic analyses from long read sequencing are in process. Clinically reportable copy number and single nucleotide variants (CNVs and SNVs) and pharmacogenomic analyses are returned to participants and families via psychiatric genetic counselling.

RESULTS

The second 25 participants (20 males and 5 females) were aged 18 - 65 (median age 31.7). Mean admission and discharge PANSS scores were 73.3 (n=24, SD 10) and 68.4 (n=23, SD 9) respectively. Co-morbid diagnoses included Catatonia (n=7), Intellectual Disability (n=4), Developmental Delay and/or Learning Disability (n=10), ADHD (n=9), Autism (n=6), Substance Use Disorder (n=4), and OCD (n=3).

CMAs detected SVs reported as clinically P/LP in 2 male participants. UBC-18 featured SZAD, speech and language delay, dysgraphia, and catatonia and a 906 Kb 16p13.11 duplication. The other, UBC-14, featured SZAD-BP, developmental speech and fine motor deficits, and an ~477 Kb 3p22.1 exonic deletion overlapping ULK4. In a third male participant UBC-22, a 206 Kb 8p22 deletion, reported as a VUS, was found to be *de novo* in a male proband with SZAD, ASD, and ADHD, without any compelling exonic variants and transmitted to his affected son.

The UBC-22 206 Kb 8p22 deletion involved only 1 OMIM gene, *TRMT9B* (*KIAA1456*), which has been found to regulate synaptic growth and function in a dosage-sensitive manner and is linked in GWAS to SCZ risk. We thus suspect the UBC-22 206 Kb 8p22 deletion to be pathogenic.

Exonic variants were preliminarily analyzed from 25 PacBio whole genomes. Exomiser and manual curation identified P/LP variants in 3/25 participants (12%), one each with heterozygous protein-truncating variants (PTVs) in *SETD1A* and *CACNA1C*, and one heterozygous missense variant in *ASH1L.* Straglr and TRGT found an additional potentially pathogenic pentanucleotide repeat expansion in *ATXN10* in a fourth participant. Exomiser-prioritized VUS with less compelling *in silico* predictions of pathogenicity and/or genotype-phenotype correlation included missense variants in *ZSWIM6*, *SYNE1, OCRL, MBD5,* and another in *ASH1L*. These less compelling variants were not found in the P/LP cases.

ASH1L and *SETD1A* are particularly strong SCZ risk genes, with odds ratios of ~ 18 and 20 respectively for PTVs in the SCHEMA consortium's meta-analysis, while *CACNA1C*, *ULK4, ZSWIM6, MBD5, SYNE1*, and *ATXN10* have been SCZ- and/or SZAD-associated.

Overall, 7/25 cases (28%) have a rare SV or sequence variant convincingly related to their neuropsychiatric phenotypes. P/LP variants in three ACMG secondary finding genes (v3.2) were also determined to be clinically relevant. Two cases with multiple rare variants in *HLA* genes encoding DQA1 and DQB1, with autoinflammatory and auto-immune phenotypes were also captured: UBC-10 with atopy, anti-gliadin antibodies, and a history of empyema (*HLA-DQA1*, *HLA-DQB1*) and UBC-23 with psoriasis, asthma, and pericarditis (*HLA-DQA1* only). Results from all 25 cases, including the *ATXN10* pathogenic repeat expansion missed by CMA, and case illustrations are presented.

Variant Type	Class	Number of Variants (class as % of total)	Number of Participants (Yield %)	Details
Clinically reportable CNVs	Variant of unknown significance	11/15 (73%)	10/15 (73%)	2 additional VUS-LB were found, not included in the total number of clinically reportable CNVs.
	Likely pathogenic	**4/15 (27%)**	**4/15 (27%)**	See Table 2 UBC- 14, 18, 21 22. One de novo 206 Kb 8p22 DEL, curated as VUS but suspected as pathogenic, see Results above.
Exonic DNA sequence variants	Moderate-high impact	143 (100%)	23/25 (92%)	Mean: 5.72 variants per participant . Range: 0-54 variants.
	Primary pathogenic or likely pathogenic	**3/143 (2%)**	**3/25 (12%)**	3 pt w/ pathogenic SNVs (***SETD1A, ASH1L, CACNA1C***), felt to be significant genetic contributors to their neuropsychiatric dx.
	Predicted loss-of-function	30/143 (21%)	21/25 (84%)	Only a few LoF variants were in OMIM Morbid disease genes. The remainder did not have a known mouse phenotype and were judged benign.
	Missense	95/143 (66%)	20/25 (80%)	As expected, the vast majority of missense variants, while rare and in LoF-intolerant genes, were clinically benign. Notable exceptions are referenced in Table 2.
	Impacting ACMG secondary finding gene	3/143 (2%)	3/25 (12%)	***APC*** pathogenic splice donor variant with high CADD and pathogenicity prediction scores. ***GJB2*** heterozygous missense variant clinically associated with hearing impairment in 44M with sensorineural hearing loss. ***BRCA2*** known clinVar pathogenic variant affecting splice acceptor site in exon 21; exon skipping disrupts reading frame with the transcript predicted to undergo NMD.

Table 1. Key findings in the second 25 participants

UBC ID	Sex, Age	Psych. Dx	Admission/ Discharge PANSS[1]	DD/ID/LD[2] (FSIQ)[2]	Relevant Family History	Chromosomal Microarray Results	Flagged Exonic Variants	Genome Sequencing Results (Some Highlights Listed)
1	M, 25	SCZ, ?ASD, AUD, CUD	84/87	DD, Language Disorder (105)	Paternal Hx of AUD Maternal aunt, great GM, and 2 nieces w/ SCZ Maternal uncle w/ DD/ID and ASD	Normal male microarray	3	**Pathogenic missense variant in *ASH1L* (p.Q2134H)** Missense VUS[3] in *SIN3A* (p.T1111A) **[9]Pathogenic APC splice donor variant**
2	M, 21	SCZ	74	ADHD (89)	Dizygotic twin brother w/ ADHD, OCD, SCZ vs substance-induced P Younger brother w/ MDD, anxiety, SCZ onset @ 18, polySUD Father w/ AUD, mother w/ MDD	117 Kb 15q21.3 DUP (VUS) partially overlapping 1 OMIM gene (*CGNL1*) and 2 RefSeq genes (*FLJ14957, KIAA1749*)	1	Missense VUS in *SETD4* (p.S179F)
3	M, 19	SCZ, ASD	53/57	Speech Delay, Language Disorder, ID (65)	Brother, sister w/ ADHD Mother w/ seasonal affective dis. Maternal uncle w/ MDD	Pat. transmitted 710 Kb 6p21.2 tandem triplication (VUS), incl. *MDGA1*	4	Missense VUS in *NSD1* (p.L1091I), *MADD* (p.D1298G)
4	M, 25	SCZ, ASD	82/81	?Language Disorder (88)	Mother w/ ASD Father w/ polySUD	Normal male microarray	1	**Pathogenic stopgain variant in *SETD1A* (p.R1227X)**
5	F, 65	PNOS[4], r/o ASD	62/65	DD/ID (61)	Mother w/ MDD Father died of colon cancer Mother w/ melanoma	Normal female microarray	1	Missense VUS in *EGFR* (p.S724G)
6	F, 32	SZAD-BP[5]	70/64	ADHD (101)	Maternal uncle w/ SCZ	Mat. transmitted 626 Kb 4q13.3 triplication (VUS) incl. *GSTT2B, GC, ADAMTS3*	2	ACMG Benign or Likely Benign variants only
7	M, 29	SCZ, CAT[7]	95/74	DCD[6], ADHD (96)	Mother w/ MDD (?BP), stimulant use Maternal GM w/ SCZ	Mat. transmitted 131 Kb 1p13.3 DUP (VUS) and 487 Kb 7q11.21 DEL (VUS-LB)	2	Missense VUS in *HTT* (p. E1114A), *ZSWIM6* (p.I1193T)
8	M, 61	SZAD	76/57	Speech delay, Language Disorder (FSIQ NA)	Father w/ AUD Monozygotic twin daughters w/ MDD	Normal male microarray	1	ACMG Benign or Likely Benign variants only.
9	M, 44	SCZ/ SZAD, CAT	112/70	None (86)	Sister w/ BP/SZAD Aunt w/ PNOS	Mat. transmitted 434 Kb Xp22.33 DUP (VUS) incl. *GSTT2,* also in sister	1	Missense VUS in *COL12A1* (p.N540S) **[9]Pathogenic het. missense variant in *GJB6* (p.V37I)**
10	M, 31	SZAD-BP, CAT, AUD	115/70	Speech and Sound Disorder, Dyslexia, ID (65)	Father w/ LD Maternal GF AUD	331 kb 7q11.22 DUP (VUS) incl. *GSTT2*	41	[8]11 Missense VUS in *HLA-DQA1* and 11 Missense VUS in *HLA-DQB1* Pt. has atopy, anti-gliadin Abs, Hx empyema
11	M, 36	SCZ, MNCD, CAT	87/61	FAS, ADHD, ID (64)	Mother, Father w/ AUD Brother w/ ADHD, "genetic syndrome"; niece w/ SCZ	443 Kb 7q11.21 DEL (VUS-LB) incl. *INTS4P1, ZNF92*	1	ACMG Benign or Likely Benign variants only
12	M, 22	SZAD	98/82	None (125)	Father w/ MDD	Mat. transmitted 439 Kb 6p22.2 DUP (VUS) incl. *CARMIL1, SCGN, HIST1H2AA, HIST1H2BA*	2	Missense VUS in *SRCAP* (p.T1680I), *NSD1* (p.K1339T)
13	M, 32	SCZ	76/64	ADHD (FSIQ NA)	Father w/ BD Maternal GF w/ PTSD	Normal male microarray	2	Missense VUS in *LRRC8A* (p.R262H)
14	M, 23	SZAD-BP, CAT, AUD	85/44	Dysgraphia, Language Disorder, ADHD (101)	Mother w/ MDD, ADHD, OCD Father w/ BRCA2 deletion, prostate, thyroid CA Maternal Uncle w/ ASD, MDD	**Mat transmitted 477 kb 3p22.1 deletion incl. ULK4 (LP)** and 109 Kb 7p22.3 DUP incl. MAD1L1 (VUS) Pat. transmitted 415 Kb 22q11.1 DUP (VUS)	1	Missense VUS in *MBD5* (p.D686H) **[9]Frameshift *BRCA2* splice donor site deletion predicted to undergo NMD (known pathogenic variant in ClinVar)[9]**
15	M, 22	SZAD, CAT	68/76	None (126)	Brother w/ MDD, substance use Paternal Uncle w/ young onset PD	Normal male microarray.	2	Missense VUS in *SYNE1* (p.R3430L)
16	M, 24	MDwP[10], AN-B[11], CUD	108/40	None (103)	Mother w/ BD1 w/ psychosis, Maternal aunt/GM rapid cycling BD, Paternal Hx of Depression	Normal male microarray	2	ACMG Benign or Likely Benign variants only
17	F, 62	SCZ	89/82	DD, DCD, Language Disorder (97)	Mother w/ AUD, Sister w/ psychosis onset in 30s OSA in sister, brother	Normale female microarray	3	Missense VUS in *GTF2IRD2* (p.R846W), *OCRL* (p.N366S)
18	M, 18	SZAD	101/61	None (76, estimated PMIQ 88)	Mother w/ unspecified anxiety disorder. Maternal GM treated w/ ECT	**906 kb 16p13.11 DUP (LP)** incl. *MIR6506, NDE1, MIR484, MYH11, FOPNL, ABCC1, ABCC6, NOMO3*	10	In-frame insertion in *ACAN* - no phenotypic correlate Missense VUS in *ACAN* (p.A1309V)
19	M, 19	SCZ, MDE, OCD	68/81	ADHD (FSIQ NA)	Mother w/ anxiety, mat. and pat aunt w/ BP Depression, mat. cousins w/ ASD	637 Kb 17q21.33 DUP (VUS) incl. *CACNA1G, LUC7L3*, and *TOB1*	3	Stopgain variant in *DST* (R.1156X) – recessive gene, phenotypically unrelated Missense VUS in *ASH1L* (p. p.R2208H)
20	M, 32	SCZ, ASD	94/63	None (80)	Father w/ PNOS, mother Cluster A Traits, jRA w/ rheumatic fever, MS, lung CA	Normal male microarray	0	ACMG Benign or Likely Benign variants only
21	M, 25	SCZ	62	None (FSIQ NA)	Mother w/ BD or SZAD	734 Kb 6p11.2 DEL (VUS) incl. *PRIM2* Not present in mother	1	**Pathogenic pentanucleotide repeat expansion in *ATXN10*** (1595 copies per TRGT, 1,882 per Straglr, IGV-verified)
22	M, 38	SZAD-BP, ASD, ADHD	84	Language Disorder, ID (68)	Mother, father w/ strong Hx of mood disorders, son w/ ASD, ADHD, and psychosis; maternal half-sister w/ AUD	**De novo 206 Kb 8p22 DEL, transmitted to affected son, deleting *TRMT9B (KIAA145)***	2	ACMG Benign or Likely Benign variants only
23	M, 57	SCZ, OCD	98/96	ADHD (81)	Paternal aunt w/ DD, Paternal 2nd cousin w/ SCZ	Normal male microarray	54	[8]27 Missense VUS in *HLA-DQA1*, 1 VUS frameshift insertion in *HLA-DQA1* (p.I98Sfs*4). Pt. has Hx of psoriasis, asthma and pericarditis
24	F, 53	SCZ, ASD, PTSD	93/66	Speech and Sound Disorder (107)	Father w/ SCZ, Maternal uncle w/ SCZ, sister w/ idiopathic insomnia	Normal female microarray	2	Missense VUS in *ARVCF* (p. R560W), *GTF2IRD2* (p. C82R)
25	F, 34	SCZ, CAT OCD		ADHD, Language Disorder, DCD (81)	GM w/ BD, Paternal great uncle w/ epilepsy and niece w/ epilepsy	Normal female microarray	1	**Pathogenic stopgain variant in *CACNA1C* (p.W1091X)**

Table 2. Clinical overview and notable variants in the second 25 participants

Potentially pathogenic (**P**) loss-of-function structural and exonic sequence variants are **bolded**.

[1]Positive & Negative Symptom Scale in Schizophrenia. [2]DD/ID/LD/FSIQ = Developmental Disorder, Intellectual Disability, Learning Disorder, Full Scale IQ. [3]VUS = Variant of Uncertain Significance. [4]PNOS = Psychosis Not Otherwise Specified. [5]BP = Bipolar Disease. [6]DCD= Developmental Coordination Disorder. [7]CAT= Catatonia [8]Incidental Finding. [9]ACMG Secondary Finding. [10]MDwP= Mood w/ Psychotic Features, [11]AN-B = Anorexia Nervosa, Bulimia Subtype.

CASE EXAMPLES

UBC-1 – *ASH1L* (p.Q2139H) 25M with SCZ harbouring predicted LoF pathogenic missense variant in *ASH1L. ASH1L* is a pleiotropic chromatin modifier encoding KMT2H, an ASH1-like histone lysine methyltransferase mediating H3K36 dimethylation. In the SCHEMA SCZ exomes meta-analysis, *ASH1L* has a predicted LoF protein-truncating variant (PTV) odds ratio of 18.1 (meta-analysis $P = 3.77\times10^{-5}$). *ASH1L* haploinsufficiency confers an increased risk of seizures, an autosomal dominant neurodevelopmental delay phenotype with speech delay, ASD, and behavioural abnormalities like hyperactivity, inattention, and obsessive behaviour. P1 had a R-sided motor seizure at 16 mo., after a fall resulted in an occipital skull fracture; a significant TBI was ruled out and brain MRI was normal. Encephalitis of unclear etiology was diagnosed at age 8. He began abusing cannabis and ethanol at age 13. Psychosis was diagnosed at age 16 on the background of suspected ASD and DD/ID, including language. At age 18 he received additional diagnoses of an unspecified anxiety disorder and MDD. Despite average intellectual functioning overall, his cognitive profile suggests ADHD and possible dyslexia; the pt did leave high school early on. Dysmorphic features include a widow's peak, a mildly broadened nasal bridge, low set right ear, an everted upper lip, a broad and shallow palatal arch, and a small chin.

UBC-4 – *SETD1A* (p.R1227X) 25M with SCZ harbouring a predicted LoF PTV in *SETD1A*, the most significant PTV-related risk gene in SCHEMA. *SETD1A* encodes the chromatin modifier KMT2F. *SETD1A* haploinsufficiency confers syndromic neurodevelopmental and psychiatric phenotypes, including DD (esp. speech/language and motor functions) and/or ID, ADHD, anxiety, behavioural problems, and sleep disturbances. P4 never crawled, but did walk at 18 months. ASD was diagnosed at age 8. He was preoccupied with pornography as a teen and accumulated gambling and credit card debts. Psychosis developed at age 21 with delusions, thought disorder, and AH (which he ingested cleaning solution and mouthwash to abate). Neuropsychological assessment revealed low average processing speed, working memory, verbal comprehension and WAIS-4 FSIQ (88), and impulsivity. A clear decline from previous testing was observed in learning and memory, and verbal and category fluencies. He endorsed narcoleptic features (sleep paralysis, hypnogogic/hypnopompic hallucinations/autoscopic phenomena, and napping), without cataplexy. Dysmorphic features included a longish triangular asymmetrical face with blepharophimosis, hooded upper eyelids and medial epicanthal folds (likely ethnicity-related), narrow auditory canals, a depressed nasal root and very wide nasal base, a short philtrum, a prominent cupid's bow upper lip, a high-arched narrow palate, and insloping mandibular teeth.

While rare in SCHEMA (15 PTVs/~25K cases), our first 25 cases featured 2 additional *SETD1A* hits (1 PTV, and 1 damaging missense variant), suggesting significant pathogenic variant enrichment in TRS cohorts. KMT2F mediates H3K4 tri-methylation. Targeting the corresponding demethylase (LSD1), which reversed working memory impairment in haplo-insufficient mice, is a potential precision medicine strategy.

CONCLUSIONS

- At least 7/25 (28%) of our participants harbour a rare or novel CNV or sequence variant likely to confer significant risk for SCZ or SZAD. Because of their potent effects on risk, identifying these variants may illuminate key pathogenetic mechanisms and inform development of precision medicine strategies. One of these structural variants, a pathogenic pentanucleotide repeat expansion in *ATXN10*, was likely only detectable by our long read sequencing approach.
- 3/7 (43%) of our participants do not have known co-morbid ID or ASD, with 2/7 (29%) lacking any comorbid neurodevelopmental disorders. Our results suggest that severe, treatment-resistant psychosis alone should be considered an indication for genomic sequencing, preferably with long read technologies that can detect pathogenic repeat expansions which can be missed by chromosomal microarrays, exome, and even short-read WGS.

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