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Short communication

Screening for inborn errors of metabolism in psychotic patients using Next Generation Sequencing

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ABSTRACT

Inborn errors of metabolism (IEMs) are a group of rare genetic disorders which, when emerging later in life, are often characterized by neuropsychiatric manifestations including psychosis. This study aimed to determine whether it would be useful to screen patients presenting with a psychotic disorder for IEMs by a single blood sample using Next Generation Sequencing (NGS), in order to detect rare, treatable causes of psychotic disorders. Blood was drawn from 60 patients with a psychotic disorder, with a duration of illness of less than 5 years. Blood samples were screened for 67 genes using NGS (Illumina® MiSeq sequencing technique). The results were compared to the human reference genome (GoNL, n = 498). The identified variants were classified according to the ACMG classification. For the psychotic patients, 6 variants of a likely pathogenic (class 4, n = 2) or pathogenic (class 5, n = 4) origin were found. As all variants were heterozygous, no patients were considered to be affected by an IEM. For the GoNL control group, 73 variants of a likely pathogenic (class 4, n = 31) or pathogenic (class 5, n = 42) origin were found. All of these found variants were heterozygous. Therefore, these individuals from the control group were considered to be a carrier only. Thus, no patients were identified to have an IEM as an underlying disease using this approach. However, NGS may be useful to detect variants of genes associated with IEMs in an enriched subgroup of psychotic patients.

1. Introduction

Inborn errors of metabolism (IEMs) are a group of rare genetic disorders, characterized by a defect in specific metabolic enzymes or transport proteins. Consequently, the body is not able to turn food into energy properly (Saudubray and Garcia-Cazorla, 2018). IEMs may result in a wide variety of symptoms and may affect any organ at any age. However, from all the 750 IEMs that have been described so far, some IEMs may result in isolated neuropsychiatric symptoms before any somatic symptoms are present (Sedel et al., 2007). Furthermore, it is known that when IEMs manifest later in life, neuropsychiatric manifestations including psychosis are more prominent (Klunemann, H.H. et al., 2012). IEMs that are associated with neuropsychiatric symptoms include diseases of homocysteine metabolism, urea cycle disorders, porphyria, Wilson disease, cerebrotendinous xanthomatosis and Niemann-Pick disease type C (Sedel et al., 2007). In a cohort of 34 patients with Wilson's disease, 50% of these patients reported psychiatric symptoms and in some of these cases, psychosis was the only clinical manifestation for several months before any organic symptoms were reported (Rathbun, 1996). Additionally, neuropsychiatric symptoms are observed in 24–70% of the patients with acute porphyria (Goldberg, 1959; Stein and Tschudy, 1970). The emergence of neuropsychiatric symptoms may be due to the accumulation of substrates (and therefore, direct toxicity to neurons), a deficiency of products and/or the result of toxicity due to alternative metabolite production (Fekete and Decsi, 2010). Neurons are easily affected by disturbances in metabolic pathways, leading to neuronal damage and therefore, neuropsychiatric symptoms (Walterfang et al., 2013).

However, due to the rarity of the individual IEMs, only few psychiatrists are aware of psychotic symptoms due to underlying diseases as IEMs. Therefore, patients with psychotic symptoms due to IEMs may be misdiagnosed and miss the opportunity to receive appropriate treatment (Bonnot et al., 2014; Trakadis et al., 2018; Walterfang et al., 2013). For most IEMs treatment options, e.g. adjustment of diet or taking

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supplements, are available nowadays. Early treatment is of great importance because a delayed or no treatment can result in irreversible neurological damage and cognitive decline. Furthermore, treatment is most efficient when IEMs are detected early in disease development (Trakadis et al., 2018). Therefore, it is important to raise awareness for IEMs and its relationship with neuropsychiatric manifestations.

Standard diagnostic procedures for individual IEMs often involve several separate tests including multiple blood samples, a urine sample and sometimes cerebrospinal fluid draw and MRI scans as well. This makes the diagnosis for most IEMs invasive, time consuming and expensive, resulting in diagnostic delays. Next Generation Sequencing (NGS) however, can be used to screen for a large panel of genes by using only a single blood sample. For example, NGS can be used as a non-invasive method to screen for genes that are associated with treatable IEMs that may affect brain function and result in psychotic symptoms. IEMs that are associated with these genes include adrenoleukodystrophy, citrullinemia, coenzyme Q10 deficiency, coproporphyria, GLUT1 deficiency syndrome, Hartnup disease, homocystinuria, hyperphenylalaninemia, mannosidosis, maple syrup urine disease, methylmalonic acidemia, methylmalonic aciduria, molybdenum cofactor deficiency, mucopolysaccharidosis (Sanfilippo syndrome), Niemann-Pick Disease type C1, purine nucleoside phosphorylase deficiency, Tay-Sachs disease and Wilson's disease. The Amsterdam University Medical Centre developed a NGS panel that allows detection of 67 genes that are associated with 56 treatable IEMs that are present with neuropsychiatric symptoms. NGS is not used in routine clinical psychiatric practice yet because of its relatively high costs, and unknown diagnostic yield. However, compared to current routine diagnostics NGS might prove valuable to detect genetic hetero- or homozygous variants of genes related to IEMs. Therefore, this study aimed to determine whether it would be useful to screen patients with a recent onset psychotic disorder for IEMs with a novel NGS panel, in order to detect rare, treatable causes of psychotic disorders. Additionally, this study aimed to determine whether there would be a possible statistical difference between patients with a psychotic disorder and controls for being a carrier of a gene associated with an IEM.

2. Methods

A total of 60 patients with a psychotic disorder, within the early stages of illness and a minimum age of 16, were recruited through various psychiatric facilities in the Netherlands or patients were referred for clinical diagnostic testing by their psychiatrist. Patients with severe brain injury or trauma were excluded from the study. After receiving full information on the study, participants or their legal guardians gave written consent to participate in the study. The study was approved by the Medical Ethical Committee of Maastricht University and Amsterdam University Medical Centre. All procedures followed were in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration of 1975. The Comprehensive Assessment of Symptoms and History (CASH, (Andreasen et al., 1992)) was used to validate the diagnosis of a psychotic disorder. The Positive and Negative Syndrome Scale (PANSS, (Kay et al., 1987)) was conducted to measure psychotic symptoms severity. IQ was determined using a shortened version of the Wechsler Adult Intelligence Scale (WAIS III, (Velthorst et al., 2013)).

After blood draw, DNA was isolated from at least 7 ml of blood by using robot Gentra® AUTOPURE LS 98 or by isolating the DNA manually. NGS was used to determine the genotype of the patients of the following 67 metabolic genes: *ABCD1, ADCK3, ABCD2, ADCK4, ABCD3, ADCK5, ARG1, ARSA, ASL, ASS1, ATP7B, BCK- DHA, BCKDHB, CBS, COQ2, COQ9, CPOX, CPS1, CYP27A1, DBT, DDC, DLD, GAMT, GCDH, GCH1, GNS, HEXA, HGSNAT, HLCS, HPRT1, IDS, IDUA, IVD, LMBRD1, MAN2B1, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MOCS1, MOCS2, MTHFR, MTR, MTRR, MUT, NAGLU, NAGS, NPC1, NPC2, OTC, PCBD1, PCCA, PCCB, PDSS1, PDSS2, PNP, PNPO, PPOX, PTS, QDPR, SGSH, SLC2A1, SLC6A19* and *SPR*.

NGS was executed according to the Illumina® MiSeq sequencing technique. The results of this technique were compared to the DNA sequences of 498 Dutch individuals. These DNA sequences were obtained via the Genome of the Netherlands (GoNL), which consists of DNA sequences from 498 representative Dutch individuals, derived from 4 different biobanks in the Netherlands. The DNA sequences of all 498 individuals were included in the study. For the purposes of the study, the DNA sequences of these 498 individuals were reduced to the coding regions of the 67 metabolic genes.

The identified variants of the patients and control group were classified according to their predicted pathogenicity and were given a score between 1 and 5, based on the American College of Medical Genetics and Genomics (ACMG) classification and in silico predictions (Ellard et al., 2018; Richards et al., 2015). The classification was as followed: 1 as benign; 2 as likely benign; 3 as a variant of uncertain significance (VOUS); 4 as likely pathogenic and 5 as a pathogenic variant (Richards et al., 2015).

Statistical analysis was performed using SPSS (version 25). For the statistical analysis, Fisher's exact tests were executed to determine whether there was a statistically significant difference between the psychotic patients and control group for being a carrier of a gene of interest. Statistical significance was defined as a p-value <0.05.

3. Results

In total, blood samples from 60 patients with a diagnosis of a psychotic disorder were collected (Table 1). All blood samples were screened for 67 metabolic genes. In these patients, 6 variants of class 4 and 5 were found (Table 2). These variants were classified as likely pathogenic (class 4, n = 2) and pathogenic (class 5, n = 4). All variants were heterozygous. Therefore, no patients were considered to be affected by an IEM, but as carrier of a (likely) pathogenic mutation. For the control group, 73 variants of class 4 and 5 were found (Table 2). These variants were classified likely pathogenic (class 4, n = 31) and pathogenic (class 5, n = 42). Of these variants, 35 variants were missense mutations and 2 variants were single base changes in the intronic region. Furthermore, one stoploss, one stopgain and one frameshift deletion were found as well. All of these variants were heterozygous. Therefore, individuals from the control group were considered to be a carrier only and not affected by an IEM. There was no statistically significant difference in prevalence for the found variants between the psychotic patients and the control group ($p > 0.0592$).

Table 1
Demographic data, clinical information and diagnosis of included psychotic patients (n = 60).

		Psychotic patients		
		n	Mean	SD
Demographics	Male | Female (n)	60	28 | 32	
	Age (years)	60	29.18	8.06
	IQ	60	98.45	13.47
Clinical information	Number of episodes (n)	60	2.39	4.17
	Duration of illness (years)	60	5.18	4.98
		n	%	
Diagnosis	Psychotic Disorder NOS	21	35.0	
	Schizophrenia, Paranoid Type	15	25.0	
	Schizoaffective Disorder	13	21.7	
	Schizophreniform Disorder	4	6.7	
	Brief Psychotic Disorder	4	6.7	
	Schizophrenia, Undifferentiated Type	2	3.3	
	Schizophrenia, Disorganized Type	1	1.7	

Table 2
Class 4 and 5 variants in psychotic patients and controls.

Psychotic patients (n = 60)							
Patient number	Gene	Variant	RefSeq ID	Frequency	Homo- or heterozygous	Class	Described as
17	*PDSS1*	del	n/a	1	n/a	4	Likely pathogenic
29	*SLC6A19*	c.517G > A	NM_001003841.3	1	Heterozygous	5	Pathogenic
31	*PCCB*	c.932G > A	NM_001178014.1	1	Heterozygous	4	Likely pathogenic
49	*MMACHC*	c.276G > T	NM_015506.2	1	Heterozygous	5	Pathogenic
69	*CBS*	c.833T > C	NM_000071.3	1	Heterozygous	5	Pathogenic
70	*CBS*	c.833T > C	NM_000071.3	1	Heterozygous	5	Pathogenic
Control (n = 498)							
Mutation number	Gene	Variant	RefSeq ID	Frequency	Homo- or heterozygous	Class	Described as
1	*MMACHC*	c.276G > T	NM_015506.2	1	Heterozygous	5	Pathogenic
2	*MMACHC*	c.440G > C	NM_015506.3	1	Heterozygous	4	Likely pathogenic
3	*MMACHC*	c.482G > A	NM_015506.2	1	Heterozygous	5	Pathogenic
6	*CYP27A1*	c.1016C > T	Not described	1	Heterozygous	4	Likely pathogenic
7	*IDUA*	c.208C > T	NM_000203.5	4	Heterozygous	5	Pathogenic
10	*SLC6A19*	c.517G > A	NM_001003841.3	9	Heterozygous	4	Likely pathogenic
11	*ALDH7A1*	c.1279G > C	NM_001182.5	1	Heterozygous	5	Pathogenic
14	*MUT*	c.1106G > A	NM_000255.3	1	Heterozygous	4	Likely pathogenic
15	*MUT*	c.655A > T	NM_000255.3	1	Heterozygous	5	Pathogenic
16	*BCKDHB*	c.832G > A	NM_183050.3	1	Heterozygous	5	Pathogenic
18	*ASL*	c.35G > A	NM_000048.4	3	Heterozygous	5	Pathogenic
19	*ASL*	c.446+1G > A	NM_000048.4	1	Heterozygous	5	Pathogenic
21	*ATP7B*	c.4135C > T	NM_000053.4	1	Heterozygous	4	Likely pathogenic
22	*ATP7B*	c.3207C > A	NM_000053.4	2	Heterozygous	5	Pathogenic
26	*NPC2*	c.441+1G > A	NM_006432.4	5	Heterozygous	5	Pathogenic
27	*IVD*	c.941C > T	NM_002225.3	5	Heterozygous	5	Pathogenic
28	*HEXA*	c.805G > A	NM_000520.5	1	Heterozygous	5	Pathogenic
30	*NAGLU*	c.2021G > A	NM_000263.3	2	Heterozygous	5	Pathogenic
31	*SGSH*	c.734G > A	NM_000199.5	5	Heterozygous	5	Pathogenic
32	*SGSH*	c.220C > T	NM_000199.5	1	Heterozygous	5	Pathogenic
34	*CBS*	c.833T > C	NM_000071.3	18	Heterozygous	4	Likely pathogenic
36	*CBS*	c.146C > T	NM_000071.2	1	Heterozygous	5	Pathogenic
37	*ADSL*	c.1277G > A	NM_000026.4	4	Heterozygous	5	Pathogenic
39	*ARSA*	c.1283C > T	NM_000487.6	3	Heterozygous	5	Pathogenic

PDSS1 = Decaprenyl-diphosphate Synthase Subunit 1, *SLC6A19* = Solute Carrier Family 6 Member 19, *PCCB* = Propionyl-CoA Carboxylase Subunit Beta, *MMACHC* = Metabolism Of Cobalamin Associated C, *BCKDHB* = Branched Chain Keto Acid Dehydrogenase E1 Subunit Beta, *CBS* = Cystathionine Beta-Synthase, *CYP27A1* = Cytochrome P450 Family 27 Subfamily A member 1, *IDUA* = Alpha-L-iduronidase, *ALDH7A1* = Aldehyde Dehydrogenase 7 Family Member A1, *MUT* = Methylmalonyl Coenzyme A Mutase, *ASL* = Argininosuccinate Lyase, *ATP7B* = copper-transporting ATPase 2, *NPC2* = Niemann-Pick Disease Type C2, *IVD* = isovaleryl-CoA Dehydrogenase, *HEXA* = Beta-hexosaminidase A, *NAGLU* = Alpha-N-acetylglucosaminidase, *SGSH* = N-Sulfoglucosamine Sulfohydrolase, *ARSA* = Arylsulfatase A.

4. Discussion

In this study, we detected 6 heterozygous variants described as (likely) pathogenic in 6 patients with a recent onset of psychotic disorder. Furthermore, 73 heterozygous variants described as (likely) pathogenic were detected in 498 control individuals. Among these heterozygous mutations, a deletion of the *PDSS1* gene was found in a patient with a psychotic disorder and not in one of the control individuals. A homozygous mutation in the *PDSS1* gene is associated with coenzyme Q10 deficiency, which is observed in patients with schizophrenia (Maguire et al., 2018). Furthermore, a heterozygous variant of the *CBS* gene, associated with homocystinuria, was detected in several patients with a psychotic disorder and the control individuals. A homozygous mutation in the *CBS* gene has been associated with ocular abnormalities, skeletal deformities, intellectual disability, psychiatric disturbances and seizures (Gong et al., 2015). However, the mean urinary homocysteine excretion rate was significantly elevated in individuals with a heterozygous *CBS* mutation, compared to healthy controls (Guttormsen et al., 2001). This may suggest that mild disturbances in the homocysteine metabolism may still occur in case of a heterozygous mutation and this may be related to psychosis (Kinoshita et al., 2016; Trzesniowska-Drukala et al., 2019). Furthermore, a heterozygous variant of *SLC6A19* was observed in one patient and one control. A mutation in this gene is associated with Hartnup disorder, an IEM that is characterized by pellagra-like rash, ataxia and psychotic behavior (Cheon et al., 2010; Seow et al., 2004). Additionally, 3 control individuals were considered to be a carrier for the *ATP7B* gene. A homozygous mutation in the *ATP7B* gene is associated with Wilson's disease (Chang and Hahn, 2017). In some cases, low ceruloplasmin and serum copper levels, which are associated with Wilson's Disease, have been observed in psychiatric patients with a heterozygous variant of *ATP7B* gene (Demily et al., 2017). Furthermore, psychiatric symptoms and Parkinsonians tremors were described in case reports of patients with a heterozygous variant of the *ATP7B* gene (Gromadzka et al., 2010; Sechi et al., 2007). Although not screened for in this study, a homozygous mutation in the *GBA1* gene results in Gaucher's Disease. Additionally, a heterozygous variant of this gene is associated with Parkinsonism as well (Yanez et al., 2021). Heterozygous variants of the *NPC* gene were observed in patients with delirium or paranoid schizophrenia as well (Maubert et al., 2015). However, as the found variants are all heterozygous variants, it is not likely that these variants could result in an IEM although it may be possible that heterozygous variants result in mild symptoms or other neuropsychiatric disorders (Bonnot et al., 2014; Klunemann, H. H. et al., 2012). Furthermore, it is known that heterozygous compound mutations can result in IEMs, as observed in case of homocystinuria and Hartnup disease (Cheon et al., 2010; Gong et al., 2015; Lerner-Ellis et al., 2009). Additionally, it may be possible that these heterozygous variants result in increased vulnerability for psychotic and/or neurological disorders. Consequently, further research is necessary to study the effect of these heterozygous variants on neuropsychiatric manifestations.

As for limitations, the small number of included patients may contribute to the absence of affected patients. Previous research showed that an IEM may result in neuropsychiatric symptoms and that several

variants are significantly associated with schizophrenia (Trakadis et al., 2018). However, this study used a large sample of whole exome data of adults with psychotic disorder and unrelated controls, which increases the likelihood of detecting these rare genetic disorders. Additionally, it may be possible that the occurrence of a psychotic disorder in case of an underlying disease such as an IEM also depends on the degree to which the metabolic process is disrupted and to the presence of other biological or genetic factors (Trakadis et al., 2018). Screening in a large 'enriched, high risk' sample of patients only would be a next step for future research. These 'enriched, high risk' patients may present atypical psychotic symptoms, neurological symptoms, catatonia, cognitive decline, movement abnormalities, an intellectual disability or do not respond to treatment as expected (Bonnot et al., 2015; Lauterbach et al., 2008; Sedel et al., 2007; Trakadis et al., 2018). The presence of an underlying disease such as IEMs is probably higher in such patients and therefore, screening and clinical evaluation should be prioritized in these patients.

However, as screening for IEMs still requires invasive and time-consuming methods, this study showed that a NGS approach is a good, relatively cheap, alternative to using multiple blood samples, urine samples, cerebrospinal fluid and MRI scans to detect hetero- or homozygous variants of genes related to IEMs. Consequently, the detection of IEMs may be limited to the use of only one blood sample in the future.

Taken together, future research should focus on screening for genetic variants associated with IEMs in 'enriched, high risk' patients with the use of NGS.

Author contributions statement

Therese van Amelsvoort: Conceptualization, design, supervision and funding acquisition of the study, writing – reviewing and editing. Marcel Mannens: Conceptualization, design, supervision of the study. Pilar Martinez-Martinez: Conceptualization, design and supervision of the study. Silvana van Koningsbruggen: Conceptualization, design, data acquisition, data analysis, data interpretation and supervision of the study, writing – reviewing and editing. Nicole Leibold: Data interpretation, writing – reviewing and editing. Leonie Behrens: Data acquisition, data analyses and data interpretation. Nikita van de Burgt: Data analysis, data interpretation, writing – original draft preparation. All authors critically revised the manuscript before submission. TA acts as the guarantor.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.03.060.

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