Using exome analysis as a tool for genetics acquaintance in a psychiatry residence program

Usando a análise exoma como ferramenta para conhecimento de genética em um programa de residência psiquiátrica

Uso del análisis del exoma como herramienta para el conocimiento genético en un programa de residencia en psiquiatría

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Aldo Ferreira Castello Branco Vilar
Medical Residency in Psychiatry
Institution: Universidade Federal de Pernambuco (UFPE)
Address: Av. Prof. Moraes Rego, 1235, Cidade Universitária, Recife - PE, CEP: 50670-901
E-mail: aldocbvilar@gmail.com

Danyllo Felipe de Oliveira
Doctor of Genetics
Institution: Instituto de Biociências (USP)
Address: Rua do Matão, 277, Cidade Universitária, São Paulo - SP, CEP: 05508-090
E-mail: oliveira.danyllo@gmail.com

Jose Brasileiro Dourado Junior
Master in Collective Health
Institution: Hospital das Clínicas (UFPE)
Address: Av. Prof. Moraes Rego, 1235, Cidade Universitária, Recife - PE, CEP: 50670-901
E-mail: drjosebrasileiro@gmail.com

Mayana Zatz
Doctor of Genetics
Institution: Instituto de Biociências (USP)
Address: Rua do Matão, 277, Cidade Universitária, São Paulo - SP, CEP: 05508-090
E-mail: mayazatz@gmail.com

João Ricardo Mendes de Oliveira
Postgraduate degree in Neuropsychiatry and Behavioral Sciences, MD PhD in Biological Sciences
Institution: Universidade Federal de Pernambuco (UFPE)
Address: Av. Prof. Moraes Rego, 1235, Cidade Universitária, Recife - PE, CEP: 50670-901
E-mail: joao.ricardo@ufpe.br

ABSTRACT
Objective: In this paper, a residency program at a Brazilian University Hospital shares its experience with a genetic screening test during the investigation of an inpatient with schizophrenia features. Method: A whole exome sequencing study investigation of a clozapine-
refractory patient with schizophrenia served as a facilitator for mastering skills in genetics. Results: During the hospitalization of a 26-year-old patient with clozapine-refractory schizophrenia, the medical residency team noted syndromic features, such as retrognathia, large ear pinnae, pectus excavatum, and a longer wingspan relative to height. These findings led to an interest in genetic evaluation using exome sequencing. The exam showed variations in TMEM106B, IRF2BPL, and ALKBH8, leading to the hypothesis of polygenic heritage. The variations found are previously linked to a wide variety of neuropsychiatric syndromes. Conclusions: Clinical practice in modern psychiatry demands deep knowledge in genetics as genetic and pharmacogenetic tests become more accessible. Genetic training is imperative for the 21st-century psychiatric resident so that one can critically assess this field of knowledge. In this paper, a residency program at a Brazilian University Hospital shares its experience in genetics learning.

Keywords: genetics/genomics, schizophrenia spectrum and other psychotic disorders, education, antipsychotics.

RESUMO
Objetivo: Neste artigo, um programa de residência em um Hospital Universitário Brasileiro compartilha sua experiência com um teste de triagem genética durante a investigação de um paciente internado com características de esquizofrenia. Método: todo um estudo de sequenciamento de exoma investigação de um paciente resistente à clozapina com esquizofrenia serviu como facilitador para o domínio de habilidades em genética. Resultados: Durante a hospitalização de um paciente de 26 anos com esquizofrenia refratária à clozapina, a equipe de residência médica notou características sindrômicas, como retrognatia, grande orelha de pinagem, pectus excavatum e uma maior envergadura em relação à altura. Esses achados levaram ao interesse na avaliação genética por meio do sequenciamento de exomas. O exame mostrou variações em TMEM106B, IRF2BPL e ALKBH8, levando à hipótese de herança poligênica. As variações encontradas estão previamente ligadas a uma grande variedade de síndromes neuropsiquiátricas. Conclusões: A prática clínica na psiquiatria moderna exige um profundo conhecimento da genética à medida que os testes genéticos e farmacogenéticos se tornam mais acessíveis. O treinamento genético é imperativo para os residentes psiquiátricos do século 21 para que se possa avaliar criticamente esse campo do conhecimento. Neste artigo, um programa de residência em um Hospital Universitário Brasileiro compartilha sua experiência no aprendizado de genética.

Palavras-chave: genética/genômica, espectro esquizofrênico e outros transtornos psicóticos, educação, antipsicóticos.

RESUMEN
Objetivo: En este trabajo, un programa de residencia en un Hospital Universitario Brasileño comparte su experiencia con una prueba de detección genética durante la investigación de un paciente hospitalizado con características de esquizofrenia. Método: Un estudio de secuenciación del exoma completo de un paciente refractario a clozapina con esquizofrenia sirvió como facilitador para dominar las habilidades en genética. Resultados: Durante la hospitalización de un paciente de 26 años con esquizofrenia refractaria a la clozapina, el equipo de residencia médica observó características sindrómicas, como retrognatia, pinnas de oído grandes, tórax excavado y una envergadura alar más larga en relación con la altura. Estos hallazgos llevaron a un interés en la evaluación genética utilizando la secuenciación del exoma. El examen mostró variaciones en TMEM106B, IRF2BPL y ALKBH8, lo que llevó a la hipótesis de herencia poligénica. Las variaciones encontradas están vinculadas previamente a
Genetic comprehension of mental illnesses is taking place in clinical practice. Genetic tests are recommended for most patients with autism spectrum disorder, intellectual disabilities, and developmental delay (1), although these tests are not always available. Specialized centers in Brazil already show advancements in accessing genetic analyses in neuropsychiatric conditions (2). Some pharmacogenetic tests are commonly used, mainly by private health providers, despite the need for better evidence for their clinical use. Genetic training is imperative for the 21st-century psychiatric resident so that this field of knowledge can be critically assessed (3).

Institutions are facing this challenge for a better medical education. In 2015 The International Society of Psychiatric Genetics Committee on Resident Education established learning objectives for all psychiatrists. Against that, Brazilian Minimum Program for Medical Residency in Psychiatry still does not have specific learning goals in the field. In this paper, we present our experience as a residency program at a Brazilian University Hospital, specifically at the Federal University of Pernambuco.

We report the case of a 28-year-old male who was admitted to the Clinical Hospital at the Federal University of Pernambuco with chronic delusions and hallucinations. The patient had no neurodevelopmental abnormalities except for difficulty in socialization dating from early childhood. There were no reports of intercurrences during pregnancy or labor. He has a grandmother and a granduncle, from his mother's genealogy, with the diagnosis of schizophrenia. He had 12 years of formal education but has had no occupation since then.

By the age of 16, he had his first psychotic episode after prodromal symptoms such as social withdrawal and hypobulia. At that time, the patient presented paranoid delusions, auditory hallucinations, and severely disorganized speech and behavior. He was treated with haloperidol, risperidone, and olanzapine, without response. His first hospitalization occurred at
the age of 26, when clozapine was introduced. He developed clozapine-refractory schizophrenia, with chronic delusions and disorganized thoughts.

The patient was submitted to a second hospitalization one year later due to psychomotor agitation. Chronic symptoms remained unchanged. For a better assessment of the case, the patient underwent an MRI and blood tests, both of which showed no abnormalities.

At that time, syndromic stigmata were noted, such as retrognathia, large ear pinnae, pectus excavatum, and a longer wingspan compared to height. These findings led to an interest in genetic evaluation. The patient underwent exome sequencing in order to assess differential diagnosis and better understand the refractoriness.

Exome sequencing showed rare mutations in TMEM106B, IRF2BPL, and ALKBH8, leading to the hypothesis of polygenic inheritance. Results were subsequently confirmed by Sanger sequencing in samples from the patient and his parents. Family segregation studies revealed that one mutation came from his mother and two mutations came from his father, both of whom are healthy individuals.

All mutations found in both studies have been reportedly associated with different phenotypes of psychiatric diseases, as shown in Table 1. A family tree describing the main family history linked to schizophrenia spectrum disease is shown in Figure 1.

Table 1 - Details on the main variations found at the patient and his parents, including positioning, population frequency, inheritance pattern, pathogenic predictions and previously linked phenotypes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Exon</th>
<th>Variant</th>
<th>Frequency</th>
<th>Zygosity</th>
<th>Classification</th>
<th>Inheritance pattern</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMEM106B (NM_001134232.2)</td>
<td>4</td>
<td>c.295A&gt;G;p.(Met99Val)</td>
<td>0%</td>
<td>Heterozygous</td>
<td>Variant of uncertain significance</td>
<td>AD</td>
<td>Leukodystrophy hypomyelinating 16 (OMIM 617964)</td>
</tr>
<tr>
<td>IRF2BPL (NM_024496.4)</td>
<td>1</td>
<td>c.731G&gt;A;p.(Gly244Asp)</td>
<td>0.0005%</td>
<td>Heterozygous</td>
<td>Variant of uncertain significance</td>
<td>AD</td>
<td>Neurodevelopmental disorder with regression, abnormal movements, loss of speech, and seizures; (OMIM 618088)</td>
</tr>
<tr>
<td>ALKBH8 (NM_138775.3)</td>
<td>3</td>
<td>c.367+1G&gt;T;p. (?)</td>
<td>0.006%</td>
<td>Heterozygous</td>
<td>Variant of uncertain significance</td>
<td>AR</td>
<td>Intellectual developmental disorder, autosomal recessive 71 (OMIM 618504)</td>
</tr>
</tbody>
</table>

Source: The Authors.
Figure 1 - Family tree of index patient describing the main family history linked to schizophrenia spectrum disease.

Source: The Authors.

Leukodystrophy hypomyelinating is associated with cognitive and speech impairment. Case reports describe a comorbid motor syndrome characterized by ataxia, dysmetria, and tremor. Other mutations in TMEM106B have also been described with a higher susceptibility for Frontotemporal Dementia and other neurodegenerative diseases. This gene encodes a lysosomal transmembrane protein, of which different expressions can lead to altered neuron proportions and pathological brain aging (4,5). Our index patient has not shown motor symptoms, but cognitive impairment is clearly established.

In turn, IRF mutations are associated with a neurodevelopmental disorder characterized by regression, abnormal movements, loss of speech, and seizures. This gene encodes a transcriptional modulator, and a range of different phenotypes have been reported. Speech impairment seems to be severe and highly prevalent (6). As for our patient, the MOCCA test shows a disproportionate loss of speech compared to other domains.

ALK gene encodes dioxygenases involved in the formation of tRNA. There are few case reports of ALK mutations, usually associated with global cognitive impairment manifested during neurodevelopment. Dysmorphic signs have been described, including large ears and a long face, but no clear pattern has yet been defined (7).

All these findings reinforce the hypothesis of a genetic comorbidity with overlapping risks stemming from different gene mutations, providing a final clinical profile compatible with the schizophrenia spectrum.

This case demonstrates that whole exome sequencing studies can contribute to elucidating the severity and refractoriness in schizophrenia. Though it doesn’t have practical
contributions to therapeutics yet, large studies are mapping the genetic risks of developing mental illnesses. As different populations have distinct pools of genes, understanding local heritage is fundamental to keeping up with the state of the art in molecular psychiatry. Case reports like this can contribute to a better understanding of local heritage.

Genetic exams are not available for most patients, and access to these exams might be challenging, especially in developing countries such as Brazil. Teaching Hospitals should incorporate this practice, as modern psychiatry requires knowledge in genetics.

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