Overview

Useful For
Influencing the target dose of methylphenidate treatment for patients with attention deficit/hyperactivity disorder

Determining possible cause for poor response to methylphenidate in treated patients with attention deficit/hyperactivity disorder

Genotyping patients who prefer not to have venipuncture done

Special Instructions
- Informed Consent for Genetic Testing
- Multiple Saliva Genotype Tests
- Informed Consent for Genetic Testing (Spanish)

Method Name
Polymerase Chain Reaction (PCR) Followed by Sizing Analysis

NY State Available
Yes

Specimen

Specimen Type
Saliva

Specimen Required
Multiple saliva genotype tests can be performed on a single specimen after a single extraction. See Multiple Saliva Genotype Tests in Special Instructions for a list of tests that can be ordered together.

Supplies: DNA Saliva Collection Kit (T651)

Container/Tube: Oragene DNA Self-Collection Kit (T651: fees apply)

Specimen Volume: Full tube

Collection Instructions:
1. Fill tube to line.
2. Send specimen in original container per kit instructions.

Forms
1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)
2. If not ordering electronically, complete, print, and send a Pharmacogenomics Test Request (T797) with the specimen.

**Specimen Minimum Volume**

1 mL

**Reject Due To**

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Temperature</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>Ambient</td>
<td></td>
</tr>
</tbody>
</table>

**Specimen Stability Information**

<table>
<thead>
<tr>
<th>Allele/Number of Repeats (R)</th>
<th>Allelic Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2R</td>
<td>8.8</td>
</tr>
<tr>
<td>3R</td>
<td>2.4</td>
</tr>
<tr>
<td>4R</td>
<td>65.1</td>
</tr>
<tr>
<td>5R</td>
<td>1.6</td>
</tr>
<tr>
<td>6R</td>
<td>2.2</td>
</tr>
<tr>
<td>7R</td>
<td>19.2</td>
</tr>
<tr>
<td>8R</td>
<td>0.6</td>
</tr>
<tr>
<td>9R</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>10R</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

The dopamine receptor D4 gene (DRD4) is located near the telomeric region of chromosome 11q and is a highly variable gene. A 48-base pair (bp) variable number tandem repeat (VNTR) polymorphism in exon 3 of DRD4, which ranges from 2 to 11 repeats, creates a 32- to 176-amino acid variation in the third intracellular loop on the dopamine receptor. The frequency of these alleles is shown in Table 1. The DRD4 7-repeat allele (7R) has functional consequences and is associated with lower affinity for dopamine receptor agonists and reduced signal transduction (eg, cAMP levels) compared to the more common DRD4 4-repeat allele (4R). The effect of other copy number repeats is not as well defined to date, however, and VNTRs with 6 or fewer repeats are grouped as 4R and those with 7 or more repeats as 7R.

Frequency of alleles with various DRD4 exon 3 48-bp repeats:
The DRD4 protein is expressed in a number of brain regions, with higher levels of expression in the prefrontal cortex, where animal models suggest that it inhibits neuronal firing.

Attention Deficit/Hyperactivity Disorder (ADHD):

Several studies have found associations between the DRD4 7R allele and ADHD.\(^{(1,2)}\) Similarly, a long form (240-bp variant) of a DRD4 promoter repeat polymorphism is associated with ADHD susceptibility, possibly due to linkage disequilibrium with the DRD4 7R allele.\(^{(3)}\)

Pharmacogenetics:

Several studies demonstrate that the presence of the DRD4 7R allele, alone or in combination with the SLC6A4 long/long promotor polymorphism of the serotonin transporter, is associated with lower responsiveness of ADHD to methylphenidate (eg, Ritalin, Concerta), the main treatment for ADHD.\(^{(4)}\) Methylphenidate dosage may have to be increased to effectively treat individuals with the DRD4 7R allele. Attempts to find an association between DRD4 genotype and the variability of response to antipsychotic drugs, especially clozapine, have been largely unsuccessful or have yielded conflicting results. A recent meta-analysis found that children with a 4R/4R genotype had a 66% greater chance of responding to methylphenidate than those with other genotypes. Nonsignificant results were obtained when comparing the 7R variant to other genotypes.\(^{(5)}\)

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

Cautions

Samples may contain donor DNA if obtained from patients who received heterologous blood transfusions or allogeneic hematopoietic stem cell transplantation. Results from samples obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell transplantation, a pretransplant DNA specimen is recommended for testing.

This test does not detect polymorphisms other than the exon 3 variable number tandem repeat (VNTR).

The DRD4 VNTR alleles are not correlated with the variability of antipsychotic drug response; this test should not be ordered for that purpose.

Clinical Reference


2004;9(7):711-717


Performance

Method Description
Genomic DNA is extracted from saliva. Genotyping for DRD4 polymorphisms utilizes PCR followed by a size assay of the amplicon performed on the Agilent Bioanalyzer 2100. Each sample is amplified in 1 PCR reaction. An aliquot of the PCR product is sized using an Agilent chip. Alleles are detected by comparing the sizes observed in the assay with known standards. Ambiguous assays are directly sequenced reflexively. Genotypes are assigned based upon the alleles detected. (Unpublished Mayo method)

PDF Report
No

Day(s) and Time(s) Test Performed
Friday; 8 a.m.

Analytic Time
1 day

Maximum Laboratory Time
10 days

Specimen Retention Time
Saliva: 2 weeks; Extracted DNA: 2 months

Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
81479
## LOINC® Information

<table>
<thead>
<tr>
<th>Test ID</th>
<th>Test Order Name</th>
<th>Order LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD4O</td>
<td>DRD4 Genotype, Saliva</td>
<td>In Process</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Result ID</th>
<th>Test Result Name</th>
<th>Result LOINC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>32982</td>
<td>48 BP Repeat Genotype</td>
<td>82939-0</td>
</tr>
<tr>
<td>32983</td>
<td>Reviewed by</td>
<td>18771-6</td>
</tr>
<tr>
<td>32984</td>
<td>Interpretation</td>
<td>69047-9</td>
</tr>
</tbody>
</table>