Topic: Genetics and Schizophrenia: Does family history matter?

Summary: Schizophrenia has complex inheritance, with many potential susceptibility genes and genomic regions under investigation. Although empiric risks exist for relatives to develop schizophrenia, no genetic test is currently available. Genetic counselling is an option for individuals with a family history of schizophrenia. About 1-2% of individuals with schizophrenia have a subtle chromosome abnormality called 22q11 deletion syndrome. Individuals affected with schizophrenia who have a history of congenital anomalies or speech and learning difficulties, should be offered referral for genetics evaluation for 22q11 deletion syndrome. Genetic counselling and testing in these situations may facilitate more specific management for affected individuals and reproductive planning decisions for families.

Bottom line: Genetic testing is not currently available for isolated schizophrenia. Genetic counselling is available for individuals and their families with a family history of schizophrenia. Genetic testing is appropriate for the rare “syndromic” version associated with other health problems.

The Disease¹,²
- Schizophrenia affects about 1% of the population; males and females are equally affected.
- Onset is typically in the early 20’s in males and late 20s in females.
- Early symptoms: social withdrawal, loss of previous interests, unusual thinking/behaviour, deterioration of hygiene/grooming, depression, irritability, anxiety and sleep disturbances.
- Late symptoms: hallucinations, delusions and disorganized behaviour, decrease in emotional range, poverty of speech, loss of interest and lack of drive.
- Cognitive symptoms: deficits in attention and executive functions like organization & abstract thinking.
- Treatment includes anti-psychotics such as haloperidol, risperidone, olanzapine and supportive therapy.

The Genes²,³
- There is a strong influence of heredity on schizophrenia.
- First-degree relatives (children, parents or siblings) of an affected individual have about a 10-fold increase in risk of developing schizophrenia or schizophrenia spectrum disorders (schizotypal personality disorder, paranoid personality disorder, schizoaffective disorder).
- Genetic studies suggest multiple genes and/or genomic regions, each making a small contribution to the risk of schizophrenia. The accumulation of susceptibility genes plus other factors (environmental, developmental) lead to disease.
- No single gene is known to contribute a major risk for schizophrenia. Many potential susceptibility genes have been identified. Recently chromosome micro-rearrangements, and copy number variants have been associated with an increased risk to develop schizophrenia. More studies are needed to determine how these findings contribute to an individual’s risk to develop schizophrenia.

<table>
<thead>
<tr>
<th>Affected family member ²,³</th>
<th>Estimated empirical risk for schizophrenia</th>
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</thead>
<tbody>
<tr>
<td>Population</td>
<td>1%</td>
</tr>
<tr>
<td>Sibling</td>
<td>7 - 10%</td>
</tr>
<tr>
<td>Dizygotic twin</td>
<td>10 - 17%</td>
</tr>
<tr>
<td>Monozygotic twin</td>
<td>40 – 50%</td>
</tr>
<tr>
<td>One parent</td>
<td>7 – 16%</td>
</tr>
<tr>
<td>Both parents</td>
<td>≥50%</td>
</tr>
<tr>
<td>One sibling &amp; one parent</td>
<td>15 – 17%</td>
</tr>
<tr>
<td>Second degree relative</td>
<td>2 – 6%</td>
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</tbody>
</table>
Genetic syndrome associated with schizophrenia: 22q11 deletion syndrome

- If an individual with schizophrenia has other health problems (such as a history of congenital anomalies, learning or speech difficulties), consider an evaluation for 22q11 deletion syndrome (also known as velocardiofacial syndrome or DiGeorge syndrome).
- Only 1-2% of individuals with schizophrenia are estimated to have 22q11 deletion syndrome.
- 22q11 deletion syndrome has variable features including a subtle yet characteristic facial appearance, birth defects (heart, palate), endocrine disorders (hypocalcaemia, hypothyroidism), speech (hypernasal) and learning difficulties.
- Approximately 25% of individuals with 22q11 deletion syndrome develop schizophrenia and about half have other psychiatric illnesses including: ADD, autism spectrum disorders, general anxiety and mood disorders.
- Individuals suspected of having 22q11 deletion syndrome should be referred to a genetics clinic. Genetic testing will detect ~95% of cases.
- Identification of the 22q11 deletion facilitates more specific management. Many individuals with this syndrome have unrecognized health problems; for example, seizures may not be recognized as a symptom of hypocalcemia, recurrent infections may be caused by immune deficiency. Families with an affected individual may also want genetic testing or counselling for family planning purposes.

✔ Consequences of having a susceptibility gene

- The consequences of susceptibility genes and genomic regions are unknown. It is likely that each has a small additive effect contributing to an increased risk of schizophrenia.
- Genetic risk plus other risk factors (i.e. environmental exposures) lead to a threshold, after which an individual will develop schizophrenia.

✔ Testing

- Genetic testing is not available or routinely recommended for schizophrenia.
- Testing for the susceptibility genes for schizophrenia has no clinical utility until it is determined how these genes modify an individual’s risk of developing schizophrenia.

✔ Benefits of genetic counseling

- Although there is no genetic testing for idiopathic schizophrenia, there are benefits of genetic counselling for those with a complex family history of mental health disorders, i.e. multiple affected relatives, more than one psychiatric diagnosis, several generations affected. These benefits include:
  - Providing empiric recurrence risks to family members and helping them adjust to their own risk
  - Educating family members about psychiatric illness
  - Family planning
  - Identification of the rare syndromic cause of schizophrenia

✔ Pitfalls - Watch out for…

- Be wary of direct-to-consumer marketing of genetic tests for psychiatric illness. The clinical utility of these tests has not been established.
- Stigma of psychiatric illness. Individuals may be unwilling to discuss a family history of psychiatric illness.
- Limitations of the available empirical data on recurrence risks to family members, i.e. there are few data on the risk for psychiatric illness where multiple family members are affected.
Web Resources: The Schizophrenia Society of Canada: http://www.schizophrenia.ca/

References:

“Gene Messenger” is for educational purposes only and should not be used as a substitute for clinical judgement. The “GenetiKit” team aims to aid the practicing clinician by providing informed opinions regarding genetic services that have been developed in a rigorous and evidence-based manner. Physicians must use their own clinical judgment in addition to published articles and the information presented herein. The members of the GenetiKit research team assume no responsibility or liability resulting from the use of information contained on “Gene Messenger.”

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