INTERMEDIATE ALLELES

Huntington Society of Canada
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Learning that you or a family member carries an intermediate allele can raise questions about the future and lead to uncertainty and concern for the next generation. This factsheet is for individuals who have received a genetic test result showing an intermediate allele. It will cover what this means, what it does not mean, and the possible implications for children and family planning. Genetic counsellors, healthcare professionals, and caregivers may also find this resource helpful in guiding conversations and supporting those navigating the emotional and practical challenges of these results.

What causes Huntington disease (HD)?

- HD is caused by a change (mutation) in a gene.
- Everyone has the HD gene, but the number of CAG repeats in the gene decides if someone will get the disease.

What are the implications of the CAG repeat ranges?

- **Normal alleles: ≤ 26 CAG repeats.** These repeat lengths are stable when passed from parent to child, and will not result in HD.
- **Intermediate alleles (IAs): 27-35 CAG repeats.** These repeat lengths do not cause HD in the individual carrying them. However, they are unstable during transmission, especially from the father, meaning it is possible - but not guaranteed - that they will expand when passed to the next generation.
- **Reduced penetrance alleles: 36-39 CAG repeats.** Some carriers in this range will develop HD symptoms (often later in life), while others do not.
- **Full penetrance alleles: 40+ CAG repeats.** This range will result in HD at some point in the individual's lifetime, with earlier onset generally linked to higher repeat sizes.

What do IAs mean for families?

- A person with an IA will most likely not get HD.
- However, their children may be at risk.
- When the gene is passed from parent to child, the number of repeats can sometimes grow.

If the CAG repeat expands to 40 or more in the child, they will develop HD (full penetrance). Expansions to 36–39 repeats carry reduced penetrance: the child may develop symptoms (often later in life), but some individuals do not.

What causes CAG repeat expansion?

- Scientists are currently studying a number of molecules that may play a role in this process, with hopes of new therapeutic targets entering clinical trials soon.
- Expansion happens more often when the gene is passed from a father.
- CAG repeats can also expand when passed from a mother, but it is much less common and usually involves smaller changes than when passed from the father.
- The larger the repeat number, the more likely it is to expand.

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What are the chances of expansion?

- The chance depends on the **father's CAG repeat number:**
  - 27–30 repeats: very low risk (less than 0.1%).
  - 31–33 repeats: moderate risk (less than 0.5%).
  - 34–35 repeats: higher risk (1 to 10%).
- **Mothers with IAs:** much lower risk of passing on HD through expansion.

How common are IAs?

- About 1 in 17 people tested for HD have an IA.
- About 6 to 7% of the general population (even without HD in their family) have an IA.

How are IAs found?

IAs can show up in two ways:

- **No family history:** Sometimes HD appears for the first time in a family because an IA expanded when passed from a father to a child. This is called a new mutation.
- **Long family history:** Sometimes an IA is passed down from the parent without HD (the non-HD side of the family).

Why are IAs confusing?

- IAs make HD genetics harder to understand.
- Many people think only families with a history of HD are at-risk, but IAs show this is not always true.
- People who learn they have an IA often need extra support, education, or counselling.

Want more information?

If you have questions, you can contact your local medical genetics clinic or visit huntingtonsociety.ca. Scientists are still learning about IAs, so staying in touch for updates is helpful.

Factsheet developed by the HSC Family Services team. Reviewed by Tanya Greaser, BA, BSW, Registered Social Worker and Family Services Educator, and Dr. Alexander Maxan, PhD in Huntington disease research, Director of Research and Strategic Partnerships at the Huntington Society of Canada.

RESOURCES

Reach out to your local Resource Centre Director (RCD) of the Family Services Program at HSC for ongoing support and education at hdsupport.ca

If you are ready to receive individual or group support from the Huntington Society of Canada, you can self-refer here: http://contactme.cloud/form/huntingtonsociety

Informational fact sheets for family and friends impacted by HD are available to view, print and download at hdfactsheets.ca

Healthcare professionals and caregivers needing a more in depth understanding on caring for someone with HD can find guides at hdresources.ca

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