Evidence-based genetic counselling implications for Huntington disease intermediate allele predictive test results


Intermediate alleles (IAs) for Huntington disease (HD) contain 27–35 CAG repeats, a range that falls just below the disease threshold of 36 repeats. While there is no firm evidence that IAs confer the HD phenotype, they are prone to germline CAG repeat instability, particularly repeat expansion when paternally transmitted. Consequently, offspring may inherit a new mutation and develop the disease later in life. Over the last 5 years there has been a renewed interest in IAs. This article provides an overview of the latest research on IAs, including their clinical implications, frequency, haplotype, and likelihood of CAG repeat expansion, as well as patient understanding and current genetic counselling practices. The implications of this growing evidence base for clinical practice are also highlighted. These evidence-based genetic counselling implications may help ensure individuals with an IA predictive test result receive appropriate support, education, and counselling.

Conflict of interest

The authors have no conflicts of interest to declare.

Huntington disease (HD) is an incurable, autosomal dominant, neurodegenerative disease. Symptoms typically occur in the third or fourth decade of life and include profound involuntary movements, cognitive decline, and personality and mood disturbances (1). The genetic mutation is an expanded CAG trinucleotide repeat in the huntingtin (HTT) gene (2). Patients affected have ≥36 CAG repeats, although reduced penetrance is observed between 36–39 CAG resulting in a later age of onset and slower disease progression (3–5). HD was the first adult-onset disease for which direct-mutation predictive testing was offered and international predictive testing guidelines were published to outline best clinical practice (3). Due to the psychological and social complexities of predictive testing, only 5–25% of at-risk individuals pursue the test (6–8).

Shortly after the characterization of the genetic mutation, a distinct category of HD genes, termed intermediate alleles (IAs), were identified (9). IAs have 27–35 CAG repeats, a range that falls just below the threshold required for the disease (10). While there is no firm evidence that IAs confer the HD phenotype, they are prone to germline CAG repeat instability, particularly repeat expansion, when paternally transmitted. Consequently, offspring are at-risk of developing the disease later in life due to a new mutation. IAs are identified in two different clinical contexts – while commonly identified in families in which a new mutation has occurred, they are also coincidentally discovered on the unaffected side of families that have a long-standing history (11).

Over the last 5 years there has been a renewed interest in IAs. Notably, the international predictive testing guidelines have been updated and now acknowledge the possibility of IA predictive test results (PTRs) (3, 12). This article provides an overview of the latest research on IAs, including the clinical implications,
frequency, haplotype, and likelihood of CAG repeat expansion, as well as patient understanding and current genetic counselling practices. We use this evidence to highlight implications for genetic counselling practice, which will help ensure that individuals with an IA receive appropriate support, education, and counselling.

Clinical implications

For the individual

There is a general consensus that IAs have no clinical implications for the individual and this view is supported by the most recent predictive testing guidelines (12). However, questions about whether, and in what circumstance, persons with an IA might manifest HD have arisen. Over the last 5 years, there have been a number of case reports that documented genetic, clinical, and neuropathological findings in the presence of IA that are suggestive of HD (13–17). Notably, the symptom presentation in these cases varies widely and not all known HD phenocopies or HD-like disorders were excluded. Consequently, some of these reports have been met with scepticism and alternate explanations have been suggested (18). One possible explanation, given the high frequency of individuals in the general population with no association to HD that have an IAs, is the chance occurrence of an IA in the presence of an HD phenocopy or HD-like disorder (18–21). However, the likelihood of ascertaining an IA in persons with an HD phenocopy or HD-like disorder within the context of a family with a proven pathological mutation may be questionable.

Since the publication of these cases reports more formal studies on the clinical implications of IAs have been conducted, offering a more rigorous examination of this issue (22, 23). Data from the Prospective Huntington At-Risk Observational Study (PHAROS), a large longitudinal cohort of individuals at-risk for HD, was used to compare the clinical features of persons with an IA to individuals with either control or HD alleles (22). Individuals with an IA did not differ from the controls on their motor and cognitive assessments. However, they exhibited some behavioral features, including suicidal thoughts and apathy, which resembled persons with HD alleles. Consequently, the authors suggested that IAs may confer an abnormal behavioral phenotype. Another study found significant differences in baseline motor scores between individuals with a control and intermediate genotype in the Cooperative Huntington’s Observational Research Trial (COHORT) (23). While these two studies did not produce consistent findings, they suggest that IAs could produce a mild or endo-phenotype and highlight the possibility of genetic modifiers that influence the penetrance of these alleles (24). However, it is important to note that none of these case reports or studies provide evidence of a direct cause and effect relationship between the IA and the observed phenotype, underscoring the need for further study on the clinical implications of IAs for the individual.

For offspring

The clinical implication of IAs is primarily for offspring and/or future generations of the family who may inherit an expanded allele in the HD range. The likelihood of CAG repeat expansion into the disease-associated range is highly influenced by the sex of the transmitting parent and CAG size (10). Consequently, the risk of a new mutation varies along a continuum of increasing magnitude (theoretical, low, moderate, and high risk) depending on these two factors.

The risk of a maternal new mutation is largely theoretical. The vast majority of documented new mutations for HD have occurred in paternal transmission (9, 11). There is only a single case report of a maternal IA with 33 CAG repeats expanding into a pathological allele with 48 CAG repeats (25). Haplotype analysis indicated that this maternal IA was on a rare HD-associated haplotype. Therefore, while the allele would be expected to undergo repeat expansion at some point, most likely following paternal transmission, this case raises the possibility that new HD mutations may not be exclusive to the paternal germline. It is possible that unknown cis or trans genetic or environmental modifiers played a role in the occurrence of this maternal new mutation.

While maternal new mutations are extremely rare, CAG repeat expansion within the maternal germline has been documented. One study found that 20% of maternal IA familial transmissions demonstrated repeat instability (26). Of these unstable transmissions, approximately 41% were repeat expansions, although not into the disease-associated range. Notably, this study was limited by a small number of maternal transmissions examined at each IA CAG size. Therefore, the impact of CAG size on repeat instability in the maternal germline is not entirely clear and more research with larger sample sizes are needed. While the risk that maternal transmission of an IA will produce a new mutation cannot be eliminated, especially for IAs at the upper limits of the intermediate size range, it is unlikely and remains largely a theoretical risk. Consequently, the clinical implications of maternal IAs are more relevant to future generations of the family, particularly when the IA is transmitted through the male germline. Nonetheless, more research is required to establish empirical risk estimates for maternal repeat expansion, examine the impact of CAG size and unknown cis or trans genetic and environmental factors, and inform genetic counselling practices.

Paternal transmissions of IAs are associated with the greatest empirical risk of new mutations. Data generated from both familial transmission and sperm analyses showed that alleles at every CAG size in the intermediate range can expand into the HD range when passed through the male germline (26, 27). The large sample size offered by sperm analysis, both in terms of the number of IAs and sperm examined, has allowed for a more accurate quantification of the risk of CAG repeat expansion during paternal transmission (27). The data generated demonstrates that the frequency of repeat expansion ≥36 CAG dramatically increases over the
Genetic counselling implications for IAs

Table 1. Risk of new mutations for offspring of males with a low-, moderate-, or high-risk intermediate alleles

<table>
<thead>
<tr>
<th>Risk category</th>
<th>CAG size</th>
<th>HD range (≥36 CAG)</th>
<th>Reduced penetrance range (36–39 CAG)</th>
<th>Full penetrance range (≥40 CAG)</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>27</td>
<td>0.05</td>
<td>0.05</td>
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<td></td>
<td>28</td>
<td>0.05</td>
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<td></td>
<td>29</td>
<td>0.05</td>
<td>0.05</td>
<td>0.00</td>
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<tr>
<td>Moderate</td>
<td>30</td>
<td>0.15</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>0.25</td>
<td>0.15</td>
<td>0.10</td>
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<tr>
<td></td>
<td>32</td>
<td>0.25</td>
<td>0.00</td>
<td>0.25</td>
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<td></td>
<td>33</td>
<td>0.45</td>
<td>0.15</td>
<td>0.35</td>
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<tr>
<td>High</td>
<td>34</td>
<td>1.20</td>
<td>1.05</td>
<td>0.15</td>
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<tr>
<td></td>
<td>35</td>
<td>10.50</td>
<td>10.15</td>
<td>0.35</td>
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HD, Huntington disease.

intermediate size range. Consequently, while there are clinical implications for all offspring of males with an IA, the significance of this risk is highly dependent on CAG size. Therefore, paternal IA transmission is associated with low, moderate, and high risks for new mutations based on CAG size.

Paternal IAs with 27–29 CAG repeats are associated with the lowest risk for offspring to inherit an expanded HD allele. When accounting for the transmission of one of two paternal alleles, offspring have a 0.05% risk of inheriting a new mutation (Table 1) (27). These new mutation are most likely to fall in the reduced penetrance range and consequently, offspring would experience a later age of disease onset, if they develop clinical features at all during their lifetime (5). For example, if an offspring inherited an expanded allele with 36 CAG, only 29% would have a clinical phenotype at age 85 (28). Full penetrance HD expansions are not observed for low risk IAs, thus symptomatic cases of HD are mostly likely to arise in future generations of the family. Paternal alleles with 30–33 CAG are associated with a moderate risk for offspring to inherit a new mutation, ranging from approximately 0.15–0.45% (Table 1) (27). While the potential for a new mutation with full penetrance begins around 30 CAG repeats, males with a moderate risk IA have a relatively equal risk of transmitting an expanded allele in either the reduced or full penetrance range. Paternal alleles with 34–35 CAG are associated with the highest risk for offspring to inherit a disease-causing allele, approximately 1.20–10.50% (Table 1) (27). Importantly, offspring of males with a high risk IA have the greatest risk of developing the classical HD phenotype due to a full penetrance new mutation. Males with a 34–35 CAG also have the highest risk of transmitting an expanded allele in the reduced penetrance range.

Evidence-based genetic counselling implications

The knowledge on IAs gained over the last 5 years has broadened our understanding of this distinctive PTR and has important implications for genetic counselling practice.

Pre-test counselling

Individuals undergoing predictive testing for HD would benefit from pre-test counselling that includes information on IA-PTRs. The frequency of IAs amongst individuals in the general population supports pre-test counselling on IAs (19–21). These studies found approximately 6.0% of individuals who have no association with HD have an IA, suggesting that 1 in 17 persons undergoing predictive testing may receive an IA-PTR. The high likelihood of identifying an IA warrants education and preparation on all four possible PTRs, including normal, intermediate, reduced, and full penetrance results during pre-test counselling (Table 2). While it has been suggested that pre-test counselling on IAs may not be appropriate during the complex process of predictive testing decision-making (29), individuals who received this result indicated that they wished they knew in advance that IA-PTRs were a possibility (30). Results from the interview study also indicated that preparation for an IA-PTR in advance may minimize feelings of shock and anxiety and assist in long-term understanding of the complex clinical implications, which is particularly important given that over half of the individuals interviewed had either poor or uncertain knowledge (30).

Discrepancies in pre-test counselling were found based on the individuals’ family history (30). Individuals from new mutation families received the most pre-test information on IAs, whereas individuals with a long-standing family history received minimal knowledge. This counselling practice may reflect the belief that IAs are more likely to be identified in new mutation families and consequently, there is a greater need to educate and prepare clients for this possibility. However, recent studies indicate that IAs are actually more often identified on the non-HD side of families with a long-standing history of the disease than in new mutation families. The majority of participants in the
sperm (87%, \( n = 27/31 \)) and interview (86%, \( n = 25/29 \)) studies had a general population IAs inherited from their unaffected parent (27, 30). A similar finding was observed in the University of British Columbia Huntington Disease Biobank where the number of general population IAs (86%, \( n = 116/135 \)) exceeded IAs that led to new mutations (14%, \( n = 19/135 \)) (21). The Human Genetics Society of Australasia also estimated that at least two third of the time, IAs are inherited from the non-affected side of an HD family (31). While no specific data was provided to support this claim, it reflects what was observed in the latest research. These findings suggest that pre-test counselling should be standardized and all individuals, irrespective of their family history, should receive some education and preparation on the possibility of an IA-PTR in pre-test counselling (Table 2).

Comprehensive pre-test counselling should highlight the possibility of receiving an IA-PTR and describe the clinical implications for the individual, their children, and extended family members. In fact, the recent predictive testing guidelines now outline this as best clinical practice (12). The concept of CAG repeat instability, including factors that are associated with an increased risk of repeat expansion, could also be discussed and the relationship between IAs and new mutations explained. The possibility of unexpectedly inheriting an IA should also be emphasized given that many individuals have never heard of IAs, especially if they grew up with the disease in their family (30). Pre-test counselling could also prepare individuals for a result that has clinical uncertainty as many interview participants expressed an expectation that predictive testing would provide definitive information with clear clinical implications (30). Individuals may also benefit from a discussion that explores their desire to know a PTR with clinical uncertainty, particularly those individuals who have pursued testing to relieve uncertainty (32).

Risk assessment for CAG repeat expansion

CAG size and sex of the transmitting parent are two factors that should be considered during clinical risk assessment of an IA-PTR (Table 2). At present, the risk of new mutations for maternal transmission is primarily a theoretical risk; therefore, females who receive an IA-PTR can be reassured that the risk of their offspring receiving an expanded IA in the disease range is unlikely. Conversely, males who received an IA-PTR should be provided CAG-size specific risk estimates for their offspring to inherit an expanded allele in the HD range (Table 1). The magnitude of repeat expansion is also important to consider during paternal risk assessment given that the majority of new mutations observed in the sperm analysis were within the reduced penetrance HD range (27). Consequently, while there is a risk that offspring may receive an allele in the HD range, they may never display clinical manifestations or may have onset later in life. The risk for offspring to inherit an expanded allele with \( \geq 36 \) CAG should be considered in the context of hope that HD research will realize an effective therapy years prior to the offspring’s symptom onset.

Interview data from medical genetic service providers indicated that the clinical context of the IA (i.e. whether the allele was ascertained in a new mutation family or on the non-HD side of a family with a long-standing history) is often used during risk assessment for CAG repeat expansion into the HD range (30). Service providers report being more reassuring about the risk of a new mutation when the IA is inherited from the

Table 2. Evidence-based genetic counselling implications for intermediate allele predictive test results

<table>
<thead>
<tr>
<th>Pre-test counselling:</th>
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<tr>
<td>• Include information and preparation on all four possible predictive test results (i.e. normal, intermediate, reduced, and full penetrance) for all individuals.</td>
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<tr>
<td>• Standardized counselling on intermediate alleles for all individuals, irrespective of whether they have a long-standing or new mutation family history.</td>
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<tr>
<th>Risk assessment:</th>
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<tr>
<td>• CAG size and sex of the transmitting parent should be considered when assessing the risk of a new mutation.</td>
</tr>
<tr>
<td>• The clinical context of the intermediate allele should not be used in risk assessment.</td>
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<tr>
<td>• Paternal CAG-size specific risk estimates for offspring to inherit a new mutation should be provided.</td>
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<th>Post-test counselling:</th>
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<tr>
<td>• Comprehensive counselling on the clinical implications of an intermediate allele for the individual, their offspring, and future generations of their family.</td>
</tr>
<tr>
<td>• Provision of psychosocial support and guidance on intermediate allele result disclosure.</td>
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<tr>
<td>• Follow-up counselling.</td>
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<th>Prenatal counselling and testing:</th>
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<tbody>
<tr>
<td>• Counselling offered to all individuals with an intermediate allele.</td>
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<td>• Testing offered only to males with a high-risk intermediate allele.</td>
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<th>Genetic counselling and predictive testing for family members:</th>
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<tr>
<td>• Counselling available to offspring and family members of individuals with an intermediate allele.</td>
</tr>
<tr>
<td>• Testing available only to offspring of males with a high-risk intermediate allele.</td>
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</table>
Non-affected side of the family. However, recent data suggests that the clinical context should not be a factor used in risk assessment. While the familial transmission data did demonstrate a difference in instability between new mutation and general population IAs, it also showed that new mutation IAs had a significantly higher CAG size (26). Given that the sperm analysis produced strong evidence on the considerable impact of CAG size on the frequency of repeat expansion, the disparity in rates of instability between these two categories is likely a reflection of their differing CAG size. Further, IAs ascertained from the general population were found to have a high likelihood (60%) of being on a HD-associated haplotype (21, 33). Thus, despite no known association with HD, these general population IAs are expected to undergo repeat expansion events over time, particularly when transmitted through the male germline. On the basis of this data, the risk of repeat expansion should not be minimized when a general population IA is ascertained on the non-HD side of a family (Table 2).

While there is now data available that helps quantify the risk of IA CAG repeat expansion leading to a new mutation, individuals should be cautioned that this is a growing area of research. The quantified CAG-size specific risk estimates are relative risks of expansion that do not account for unknown genetic or environmental factors that may influence the frequency and magnitude of instability, nor do they account for the potential impact of CAG size on conception rates of sperm (27). Therefore, while these numerical risk estimates can be provided as a general assessment of repeat expansion, there may be additional factors that may modify the risk of a new mutation and differential rates of instability may exist for various ethnic populations. The relative nature of these risk figures should be highlighted during counselling; especially considering individuals may interpret these risks as having the same certainty as the 50% risk associated with a mutation-positive-PTR.

Post-test genetic counselling

Individuals who are found to have an IA-PTR should be provided comprehensive post-test counselling on the clinical implications for themselves, their offspring, and future generations of their family (Table 2). The magnitude of risk, based on the sex of the individual and CAG size, should also be clearly outlined. The concept of CAG repeat instability and its association with the clinical implications may also be reviewed. Individuals, especially those who were expecting definitive information, may struggle with feelings of confusion, uncertainty, or guilt regarding their IA-PTR (30). Therefore, these individuals may require further psychosocial support as they try to accept an unexpected result and grasp the unusual clinical implications (Table 2). Individuals who have made plans to disclose their PTR to family members may also require additional post-test support as some individuals indicated that they struggled with this communication process, particularly the challenge of informing family members of a result that is not well known and has uncertain and complex implications (30).

All individuals would benefit from being provided with written material describing the genetic and clinical aspects of their IA-PTR during post-test counselling. Information and educational resources available on IAs within the HD community are often vague and can conflict with our current scientific understanding; therefore, these written materials would support individuals’ long-term understanding and assist in family education. All individuals who receive an IA-PTR may also be invited to contact the clinic for additional education or support at any time in the future. As scientific knowledge on IAs is expected to grow, individuals could also be encouraged to stay in contact with the clinic and periodically inquire about new discoveries.

Given that the most significant risk of new mutations is associated with paternal transmissions of IAs with 34–35 CAG repeats (27), it is essential that these males have accurate understanding of the clinical implications. Many males have been found to have poor understanding and some were not even aware of their misunderstanding (30). Therefore, males, particularly those with high-risk IAs, may benefit from additional follow-up counselling after result disclosure (Table 2). This follow-up counselling will not only provide the opportunity for them to ask additional questions or request further support but also offers the chance for service providers to assess whether the men have incorrect knowledge and review the relevant information. Additional post-test counselling and education will likely improve their overall understanding of this complex PTR, which is particularly important for males who hold well-established beliefs that may act as a barrier to their understanding (30). Follow-up counselling could occur over the telephone after the individual has had sufficient time to reflect upon and absorb the new information.

Prenatal counselling and testing

While prenatal counselling could be offered to all individuals who receive an IA-PTR, this counselling is of particular importance for males with 34–35 CAG repeats (Table 2). During prenatal counselling the clinical implications for offspring, the concept of CAG repeat instability, and the risk of a new mutation based on the individual’s CAG size and sex, could be reviewed. Many individuals with an IA, including females, indicated that they would request prenatal counselling to clarify the clinical implications and magnitude of risk prior to starting a family (30). While prenatal counselling is of particular importance for males with a high-risk IA, it may also be relevant to females and males with smaller sized IAs. Many of these individuals had poor or uncertain understanding and indicated that they would refrain from having children because they believed there was a ‘significant’ risk associated with their IA (30). Prenatal counselling offers the opportunity to ensure individuals...
have accurate understanding upon which to base their reproductive decision-making. While prenatal counselling could be available to all individuals who receive an IA-PTR, prenatal testing should only be offered to couples who have a high risk of CAG repeat expansion into the HD range based on their sex and CAG size (Table 2). In other words, the availability of prenatal testing should be based upon a balance between the risk of a new mutation and pregnancy complications associated with the prenatal testing procedure, including chorionic villus sampling and amniocentesis. Males with 34–35 CAG repeats have the highest risk of producing a new mutation and thus could be eligible for prenatal testing (Table 1) (27). The risk of a new mutation associated with females and males with ≤33 CAG may not justify prenatal testing.

Couples eligible for prenatal testing should be engaged in a thorough discussion of the pros and cons of such testing and be encouraged to carefully weigh the likelihood of identifying an expanded allele in the HD range against the potential pregnancy complications due to the testing procedures. Despite the inherent risks associated with prenatal testing, many individuals who received an IA-PTR considered prenatal testing a feasible option (30). Many male participants indicated they would only pursue a family with the assistance of such testing. Couples should also be involved in a conversation about their rationale for pursuing prenatal testing and should only pursue testing if they would terminate the pregnancy if the foetus was found to have an expanded allele in the HD range. Pregnancy termination on the basis that the foetus has an IA is not warranted.

The use of pre-implantation genetic diagnosis (PGD) may provide another reproductive option for couples who have a considerable risk of a new mutation. Males with a 35 CAG are likely the most suitable candidates, especially given that their offspring have the highest risk of inheriting a full penetrance HD allele (27). Couples interested in pursuing PGD could be engaged in a discussion that weighs the physical and psychological challenges and high monetary cost of PGD, against the likelihood of repeat expansion into the disease range. If this procedure is financially feasible, it may provide an acceptable alternative for couples wishing to circumvent the possibility of pregnancy termination associated with traditional prenatal testing.

While the uptake of prenatal testing in the traditional context, when one parent has an allele in the disease-associated range, has generally been low (34, 35), this testing scenario is associated with a risk of identifying an IA. On the basis of the high frequency of IAs in the general population (19–21), all cases of prenatal testing have a possibility of identifying an IA that was inherited from the non-HD side of the family. In fact, this situation occurred in the Netherlands when a couple, with one parent having an expanded HD allele with 43 CAG repeats, applied for prenatal diagnosis and the foetus was found to have an IA with 31 CAG repeats inherited from the unaffected parent (29). Consequently, all couples pursuing prenatal testing for HD may benefit from a discussion on the possibility of unexpected results that may have uncertain clinical implications. A similar discussion could also be had with couples pursuing PGD due to the presence of a pathological mutation as this circumstance also has the possibility of identifying an IA from the non-affected parent.

Genetic counselling and testing for family members

The responsibility of disseminating genetic risk information within a family lies with the tested individual. Familial risk communication is of particular importance in families found to have a high-risk IAs with 34–35 CAG repeats. Given that IAs are not well known in the general HD community and are associated with atypical clinical implications, tested individuals may require support during this communication process. Offspring and family members may request genetic counselling in order to clarify the clinical implications of an IA for themselves (Table 2). Family counselling sessions could be utilized to reduce the number of counselling sessions required. While genetic counselling is warranted for offspring and family members, only offspring of males with 34–35 CAG should be eligible for predictive testing, once they reach the age of majority (Table 2). Given that medical resources are limited, there must be an appropriate balance between the risk of a new mutation associated with the IA and the number of individuals eligible for predictive testing in a family found to have an IA.

Individuals who experienced HD unexpectedly in their family were highly motivated to undergo predictive testing and did so almost immediately after learning of their at-risk status (30). The predictive testing experience in Australia suggests a similar trend, where individuals who had limited familial exposure received predictive testing less than 1 year after finding out their at-risk status (36). Medical genetic service providers should be aware that in the context of an IA, some persons may misjudge the impact and significance of predictive testing and their desire to quickly pursue predictive testing may simply reflect their limited knowledge and awareness of what it means to be at-risk. Consequently, these persons may benefit from delaying their genetic testing to allow them time to fully adjust to their new risk status and carefully consider their motivations and the ramifications of testing (29, 36).

Ethical challenges

With our growing knowledge on IAs, a multitude of ethical challenges have arisen. Panel discussions with scientists, clinicians, ethicists, and lay representatives will be needed to reach a consensus on these challenging issues.

Duty to recontact

The lower limits of the intermediate CAG size range have been redefined over the years as research has
shown which CAG sizes can expand and produce new mutations (11, 37, 38). Previous intermediate size ranges were 30–35 (38) and 29–35 repeats (11). Consequently, there are persons who have an IA but never received counselling on the clinical implications. During participant recruitment for the interview study and sperm analysis, there were numerous individuals who were not eligible to participate because they were never informed that their CAG size was in the intermediate range (27, 30). Such cases were also documented in the Netherlands, where individuals with IAs with less than 30 CAG were not informed when the lower limit of the intermediate size range was revised to include alleles with 27, 28, and 29 CAG (29). These cases call into question our duty to recontact tested individuals when new information modifies the clinical interpretation of their PTR. It is current standard of practice for clinical services, particularly in medical genetics, to place the responsibility of maintaining contact with the clinic on the patient or their primary care physician. This is justified by the large monetary and personnel costs required if all individuals undergoing genetic testing had to be contacted when new information became available, especially given the rapid pace of advancing knowledge in medical genetics. However, when changes to the clinical interpretation of genetic test results are not a common occurrence, as in HD, this standard of practice could be questioned. While it has been suggested that clinicians may have a duty to re-contact individuals who were never counselled about their IAs (29), the cost, burden, and potential for introducing psychosocial distress must be weighed against a risk of a new mutation, which is substantially less than 1%, given that these IAs are at the lower limits of the intermediate size range.

Prenatal testing

Prenatal testing in the context of an IA raises important ethical questions. While pregnancy termination is only warranted if the foetus is found to have inherited an expanded allele in the HD range, one challenge is in regards to the minimum CAG repeat length within the disease range that a couple may choose to terminate the pregnancy. Given that the majority of expansions into the disease-associated range observed in the sperm analysis were within the reduced penetrance range, some couples may feel it is acceptable to continue a pregnancy with 36–39 repeats (27). The late age of disease onset, combined with hope that progress in HD research will lead to a future therapy, may make this a suitable option. However, this circumstance could produce a mutation-positive-PTR for a child, which is contrary to the international best practice guidelines (3, 12). Couples who request prenatal testing in the context of a high-risk IA (i.e. paternal transmission of an IA with 34–35 CAG) should receive counselling on the harms associated with testing minors, including eliminating their child’s right to make this decision as an adult and the potential for differential treatment, if they choose to complete a pregnancy after the foetus is found to have an expanded allele in the HD range (39). Fortunately, to our knowledge, this ethical challenge has not yet been realized. There is only one documented case of prenatal testing in the context of an IA with 34 CAG repeats and the foetus inherited the parents’ normal alleles (29).

Ethical challenges regarding IAs may also arise for couples undergoing PGD in the traditional context, as this circumstance also presents the possibility of identifying an IA on the non-HD side of the family. In this situation, couples should be engaged in a discussion about their course of action should the embryos be found to carry an IA prior to beginning the procedure, particularly if no normal embryos are obtained. Couples should also consider the issue of discarding (or not) embryos with IAs, especially if normal embryos are available.

Future research

While greats strides have been made in our knowledge of IAs over the last 5 years, there remain many areas that require additional research.

IA phenotype

Research is urgently needed to clarify the clinical consequences of an IA for the individual and may include prospective observational studies that examine a large cohort of individuals with an IA for symptoms over time or retrospective case–control studies. These studies should meet the same standards and rigour required when making a novel gene-disease association and carefully exclude the possibility of a chance association between clinical findings and intermediate repeat lengths (19–21). Recommendations for diagnosing HD in the absence of ≥36 CAG have been outlined and include clinical manifestations and specific neuropathological findings consistent with HD; exclusion of all disorders with clinical overlap to HD; and the demonstration of co-segregation of the IA with disease phenotype in the family (18).

Phenotypic consequences of IAs or premutations in other trinucleotide disorders, including the spinocerebellar ataxia 2 (SCA2) and fragile X have been documented. Intermediate CAG repeat lengths in the ataxin-2 gene, responsible for SCA2, have been shown to be associated with the clinical phenotype of amyotrophic lateral sclerosis (40). Premutations in fragile have been associated with pre-mature ovarian failure in women and late onset fragile X tremor and ataxia syndrome in older men (41, 42). Given the numerous similarities amongst the trinucleotide disorders, particularly other polyglutamine disorders like the SCA2, future research may demonstrate that IAs for HD also impart clinical consequences. Understanding whether, and in what circumstance, IAs are associated with clinical features may also provide information on the factors that hasten the disease process in individuals that carry the HD mutation.
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Research is also needed to explore the underlying pathological mechanism of an IA phenotype. It is possible that intermediate repeat lengths fall at the end of the phenotypic spectrum, such that they may confer a very late onset of the disease or atypical symptoms (22). As an inverse relationship between CAG size and age of onset is well recognized, this correlation, which exists above the disease threshold of 36 CAG repeats, may also extend into the intermediate size range (43). The rare cases of disease features in the context of an IA may be due to genetic or environment modifiers that accelerate the disease process resulting in an earlier onset of symptoms (14). Clinical findings may also occur in unique instances were the pathogenicity of the IA is increased. Intermediate repeat lengths have been shown to cause biochemical disturbances, including energy and metabolic impairments (17, 44, 45). Consequently, some individuals may develop a subtle phenotype due to subclinical HTT toxicity (14, 45).

Somatic instability may also contribute to an accelerated disease process in some individuals with an IA. Somatic instability leading to large repeat expansions in the striatum and cerebral cortex of HD patients has been associated with earlier age of onset and more rapid disease progression (46). A single base excision repair enzyme called 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1) has been shown to be involved in progressive age-dependent somatic expansion in HD brains (47). Further, the neuronal population of the striatum was found to be particularly susceptible to a high rate of repeat expansion, which is thought to enhance the toxicity of the mutant HTT protein (48). Collectively, this data suggests that tissue-specific differences in CAG length could explain those individuals with an IA who display a clinical phenotype. More specifically, these individuals have a blood CAG size in the intermediate size range, the CAG repeat tract in their striatal neurons may be above the disease threshold.

Psychosocial impact

The psychosocial impact and unique predictive testing experience of individuals who receive an IA-PTR requires further examination. The psychological functioning of individuals who receive an IA-PTR needs to be quantitatively measured using outcome measures, such as depression and anxiety, and compared with individuals who receive mutation-positive or negative results. This research may point to risk factors for adverse psychological response and further inform genetic counselling practices. Importantly, level of distress should be evaluated in the context of the individual’s sex and family experience, as differences may exist between males and females and individuals who have grown up with the disease or experienced it unexpectedly. The impact of the person’s motivation for predictive testing, especially the desire to eliminate uncertainty should also be considered. We also need to thoroughly understand individuals’ risk perception regarding IA-PTRs and how it impacts their reproductive decision-making (30). The communication process within families about IAs is another area that requires study. More specifically, when and how are individuals disclosing the implication of an IA-PTR to their offspring and extended family members and how is this risk information being perceived within the family.

Conclusion

Over the last 5 years, there has been a substantial contribution to our knowledge on IAs for HD since they were first described 20 years ago. While this research has begun to fill the numerous gaps in our scientific knowledge, it is essential that we continue increasing our understanding with further study. Although efforts have been made to translate this new knowledge into clinical guidelines, the evidence-based genetic counselling implications outlined here provide additional guidance to medical genetics professionals, which will assist them in providing appropriate support, education, and counselling to individuals who receive an IA-PTR.

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