What is the role for preconception carrier screening in neurology?

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Key take home messages:

- One of the current hottest topics in clinical genetics is whether countries should implement population-wide preconception carrier screening.
- Preconception carrier screening identifies recessive diseases that individuals are carrying before those individuals have children.
- Preconception carrier screening implemented for specific populations with high carrier frequencies for certain diseases, has significantly reduced the incidence of the diseases in those populations.
- Current discussion centres on whether new genetic knowledge and technologies, especially next generation sequencing, can be used to make preconception carrier screening available to entire populations. This would allow anyone who wishes to undergo such screening to avoid having children with genetic diseases.

The sixty-year-old dogma calculated by Newton Morton[1] is that each of us is carrying 3-5 lethal recessive diseases. The trouble is that most of us don't know which 3-5 lethal recessive diseases we are carrying and we don't know which 3-5 lethal recessive diseases our partner is carrying. Therefore, when we shuffle the packs of our genes in our children, like Forrest Gump's box of chocolates, we don't know what we are going to get. We play when we have children, what I have called "genetic roulette."[2] If one of the 3-5 lethal recessive diseases that you are carrying matches one of the 3-5 lethal recessive diseases that your partner is carrying, then there is a one in four chance of a child with a lethal recessive disease. A large percentage of genetic diseases (usually stated as one third[3]) are neurological. These include spinal muscular atrophy, where the carrier frequency is 1:40 to 1:50[4,5] and the special case of Duchenne muscular dystrophy, where, because it is an X-linked recessive disease, only the mother needs to be a carrier for 1:4 of the children to be affected.

I have been involved in molecular diagnosis of Duchenne muscular dystrophy since 1987 and, in that nearly 30 years, I have lost count of the times where, after identifying a boy with Duchenne, we have shown that the mother, unknown to her, was a carrier. This story is repeated all over the world. Would the mothers of Duchenne boys, or the mothers and fathers of children with spinal muscular atrophy, or other severe neurogenetic diseases, like to know they are carriers before having children?

There has been a great deal of rhetoric about how the genomics revolution is going to change health and medicine, with the buzz catchphrase of "personalised medicine" hauled out at every opportunity. But, what might some of the practical implementations of genomic personalised medicine be? Preconception carrier screening might be one of them.

A well-known example of preconception carrier screening targeted at a population with high frequency of a recessive disease, is screening for carrier status for Tay-Sachs disease in the Ashkenazi population. This screening significantly reduced the incidence of Tay-Sachs disease in that group of people.[6] Reduction of the incidence of thalassaemia in Mediterranean countries is another success story of preconception carrier screening.[7] Screening for multiple recessive diseases in a geographically restricted population within the Netherlands,[8] is a use of targeted preconception carrier screening that might not readily spring to mind.

The US National Institutes of Health,[9] the American College of Medical Genetics (ACMG)[10] and the American College of Obstetrics and Gynaecology (ACOG)[11] recommended around the turn of the millennium that population screening for carrier status for cystic fibrosis should be made available. Individual experts in the field have also recommended implementation of preconception screening, stating for example that "carrier screening for various serious disorders should be available."[12] In 2011, the UK Human Genetics Commission concluded that there was no ethical impediment to preconception carrier screening being offered in a population-screening programme.[13] There appears therefore to be no ethical or policy reasons to block population-wide preconception carrier screening being implemented. Nevertheless, population-wide carrier screening programmes remain the exception rather than the rule.[14] Why might this be?

Most of the successful programmes have been implemented for population groups with high carrier frequencies of single founder mutations and therefore the programmes could be highly effective in reducing the incidence of disease using laboratory methods targeted to detect a small number of mutations. Programmes for whole multi-ethnic populations are not so simple to implement.

The best practice example of a population-wide pan-ethnic preconception carrier-screening programme appears to be that in Israel. A decade

or more ago, Israel initiated programmes for diseases prevalent in its Ashkenazi and non-Jewish populations, but also population-wide pan-ethnic carrier screening for recessive diseases, such as cystic fibrosis and spinal muscular atrophy, which are common in all ethnic groups.[15] The Israeli programme is now providing pre-conception carrier screening to more than 60,000 individuals a year[16] but still, significantly, is largely based on founder mutations.

Expanding programmes to entire populations, especially the outbred populations of most countries, introduces the technical challenge of having to screen genes for a far higher number of disease-causing mutations. An illustration of this is that carrier screening for Tay-Sachs disease in the Ashkenazi population requires analysis for only one variant and has a sensitivity of basically 100%, but screening for the 23 cystic fibrosis variants recommended by the ACMG or ACOG, has a sensitivity of only 80%.[17]

Next generation sequencing provides the possibility of screening large numbers of genes, including the entire exome, simultaneously. Bell et al in 2011[18] explored the possibility of carrier screening using next generation sequencing of a targeted panel of disease genes. Their panel consisted of 437 genes responsible for 448 severe recessive childhood diseases.[18] Interestingly, the average number of severe recessive diseases carried by the individuals they tested was 2.8: close to the dogma of 3-5. The Bell et al result[18] is based on only 437 genes and many more disease genes for severe recessive disorders have been identified since, including by my own Group.[19,20] Others have since further explored the use of next generation sequencing for preconception carrier screening.[21,22] However, whether we are ready to implement such screens has been questioned,[17] as has whether screening more and more genes is in fact better.[23]

Problems with next generation sequencing-based carrier screening include:

1) The large number of "variants of unknown significance" identified, how to interpret them and how to calculate the residual risk after screening.
2) Some of the mutations that cause common severe genetic diseases that should be screened for, such as spinal muscular atrophy and myotonic dystrophy, are not readily detected by next generation sequencing technologies. One would thus have to run multiple procedures for each individual to cover all the diseases that should be screened.

Another major issue is residual risk. The fact that the pathogenicity of many variants in the human genome remains unknown (i.e., of uncertain significance) means that when screening disease genes using next generation sequencing, it will not be possible to predict for many findings whether the variant will in fact cause disease in the next generation. It is recommended that only variants of known pathogenicity should be used in screening.[23] Preconception carrier screening cannot therefore guarantee a child free of genetic disease, including those diseases that are screened for.

Preconception carrier screening also cannot prevent genetic disease resulting from de novo mutation, which is a major cause of severe genetic disease.[24] The risk can only be reduced.

Another issue that needs to be considered in relation to prevention of genetic disease is that the long-term clinical effectiveness of many current therapies for genetic diseases is unknown, and it may take decades to determine the effectiveness of presently experimental therapies. The best treatment for genetic disorders may well be prevention.

Prior[17] suggests that we need to implement pilot studies to research preconception carrier screening, including which genes should be screened, population attitudes to screening and counselling requirements. Best practice preconception carrier screening programmes will vary in the different health systems around the world. This becomes especially obvious when it is considered that preconception carrier screening is an issue for both developed and developing countries.[25] Provision of preconception carrier screening by commercial entities, which is already happening in many countries,[23] might work better in countries with more private health systems than in those with more state-provided healthcare. Pilot programmes therefore need to be run in multiple countries.

Preconception carrier screening has the potential to significantly reduce the morbidity and mortality from genetic disease in all societies. It poses however major questions that each country has to grapple with. Answering those questions will require a greater spend on researching prevention of genetic disease.

Finally, you may like to ask yourself a few questions. If you were having children now or were planning to have children in the future, would you like to be able to do as much as you can to avoid passing a severe genetic disease to your children, including using preconception carrier screening? Or, do you think we should continue to play genetic roulette, as generation after generation has done up until now? Should we use the new genetic knowledge and tools we have to take control over the genetic legacy we leave our children, or should we not?

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