HGSG Briefing Paper
Consanguineous Marriage and Inherited Disorders

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This paper was prepared for the Education, Engagement and Training Working Group of the Human Genomics Strategy Group (Department of Health). The Working Group is currently drafting a strategic framework for education, engagement and training in genomics and genetics. The framework will form part of the Human Genomics Strategy Group's First Report, to be published early in 2012.

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1 Background

1.1 Consanguineous means *being of the same blood* and consanguineous marriage is marriage between blood relatives, usually defined as marriage between people who are second cousins or closer. Globally at least 20% of the human population live in communities with a preference for consanguineous marriage, and at least 8.5% of children have consanguineous parents.

1.2 Migration and settlement of significant numbers of people from populations that favour cousin marriage has led to a multiethnic society with diverse marriage preferences that now co-exist. Although no longer customary in the majority White population, nevertheless, approximately 25% of cousin marriages in the UK are in this ethnic group. Cousin marriage is customary in varying degrees among people of Pakistani, Bangladeshi and Middle Eastern origin, and also among some groups of Indian origin, Irish travellers and some refugee groups. Those of Pakistani origin have the highest rate of cousin marriage (at least 55%).

1.3 Customary consanguineous marriage is associated with an increased prevalence of inherited recessive disorders. Of an estimated 2,300 children born annually with a severe recessive disorder in the UK at least 690 (30%) are from parents of Pakistani origin. They contribute 3.4% of births but have 30% of UK children with recessive disorders. About a third of the affected children die before five years of age. Most of the survivors suffer chronic disability, and are cared for by community or specialist paediatric services. A decline in infant mortality and improved health care has unveiled the contribution of severe recessive disorders to childhood mortality and morbidity.

1.4 Cousin marriage impacts almost exclusively on recessively inherited conditions and does not influence chromosomal abnormalities, sex-linked or dominantly inherited conditions. Many rare, but severe, recessive disorders are transmitted by healthy parents who carry one gene variant for the disorder. When, by chance, both parents carry the same variant, they have a 1 in 4 risk in each pregnancy of having a child affected by that disorder.

1.5 In populations where partner choice is largely random, recessive gene variants manifest unpredictably and are thinly scattered throughout the population. In contrast, in consanguineous communities recessive gene variants tend to cluster within extended family groups. Therefore, marrying a close blood relative increases the likelihood that a carrier will choose a partner who is also a carrier of the same variant. The result is an increased prevalence of infants with severe inherited disorders and an increase in the prevalence of serious disability.

1.6 On the other hand, the very clustering of variants within extended families provides the social infrastructure to facilitate a particularly effective integrated family and community approach to providing carrier testing and genetic counselling. The approach is based on WHO advice.

1.7 In 1994 and 1996, the World Health Organisation's Office for the Eastern Mediterranean Region (which covers North Africa and the Middle East including Pakistan) convened two meetings of experts in medical and social sciences to review

the place of genetics in medical services in the region. The participants agreed that consanguineous marriage is an integral part of cultural and social life in many areas, and that attempts to discourage it at the population level are inappropriate and undesirable, even though it is associated with an increased birth prevalence of children with recessive disorders. Instead they recommended a family-oriented approach that identifies extended families at increased risk and provides them with genetic counselling. They pointed out that this approach can be unusually effective in populations that favour consanguineous marriage, due to the clustering of recessives in extended families and the fact that an affected child signifies that family members may be carriers of the same recessive disorder. The strategy aims to inform and support families in greatest need, who can then become the source of capillary information to extended families and community.

1.8 The strategy to discourage consanguineous marriage as a health services solution has been tried in Iran and by the previous Birmingham Health Authority as part of a health promotion campaign. In both places it failed to have any significant impact on levels of disability but prompted negative community reaction and has been replaced by the family-oriented approach.

2 Current situation

2.1 DH and NHS Initiatives

2.1.1 The Department of Health does not provide general guidance to the public on cousin marriage, but it supports NHS initiatives among communities with a higher prevalence of cousin marriage on a number of issues. In particular the DH supports the need to work with communities to increase the understanding of genetic risk and raise awareness of the availability of genetics services that can provide advice and support for at risk families.

2.1.2 As of April 2008, the Local Government and Public Involvement in Health Act 2007, created the requirement for all Primary Care Trusts (PCTs) and local authorities to undertake Joint Strategic Needs Assessments. The objective of these assessments is to provide a strategy that builds stronger partnerships between communities, local government and the NHS, providing a firm foundation for commissioning that improves health and social provision and reduces inequalities.

2.1.3 As part of the complementary work to the Act, the DH published the *Implementation Plan for Reducing Health Inequalities in Infant Mortality: A Good Practice Guide.* The document provides details on how genetic screening and counselling services play an important part in this work. Specifically, it highlights the work of two DH-funded projects on how to provide appropriate genetic services and support to communities that practise cousin marriage.

2.1.4 The first project, *Community-Based Hospital-Linked Genetic Service for Consanguineous Asian Families affected by Autosomal Recessive Disorders*, carried out by Blackburn and Darwen Teaching Primary Care Trust and funded through the DH Genetics White Paper (2003), developed a culturally sensitive approach to delivering genetic information within the Pakistani origin community. A community-based genetic counsellor from a similar cultural background worked with at risk families in their own language to increase awareness of genetic issues and to improve access to specialist genetic services. This strategy has proved to be an effective way of working with the community and received continued funding by the local PCT. Similar services, based on this model, are being developed in other PCTs (Heart of Birmingham and Walsall tPCTs).

2.1.5 The Second Project *Exploring the Potential of Family Networks as a Resource for Genetic Testing and Counselling in a Community with a Preference for Cousin Marriage* undertook research in three cities with a high concentration of people of Pakistani origin. It examined the feasibility of the family-oriented approach to genetic testing and counselling. Findings showed that families of Pakistani origin were willing to share genetic information through family networks but were prevented from doing so due to lack of effective communication tools for professionals and families that would aid understanding of recessive inheritance and the availability of services. It recommended the development of (1) training for professionals that includes addressing the current rampant misinformation about cousin marriage and inherited disorders (2) communication tools and (3) community engagement programmes to increase public literacy in genetics.

2.1.6 During the lifetime of the project the Principal Investigator (Aamra Darr) worked closely with the Bradford and Airedale Infant Mortality Commission to examine strategies to deal with the findings of the Commission's report that identified increasing infant deaths and morbidity in the local consanguineous Pakistani origin population. In response, the project resulted in a number of activities that influenced practice during and after the project's lifetime:

2.1.6.1 A meeting was convened in July 2008 at the University of Bradford that included staff from Birmingham, Bradford and Kirklees Public Health and Infant Mortality Commissions (IMC). The meeting discussed epidemiological data on service indicators for consanguineous populations (see 2.1.6.3), previous health promotion approaches, communication tools, and emerging evidence in relation to consanguineous marriage and inherited disorders. It concluded with consensus about how to proceed at Public Health level and the beginnings of an action plan based on the family-oriented approach. On request, the epidemiological data and action plan have been forwarded to other PCTs (Walsall, Blackburn with Darwen, Leicester) creating an informal network between Public Health personnel and IMCs in the cities. Heart of Birmingham tPCT has embarked on a substantial programme to implement the family-centred approach. Similarly, Walsall has funded a community-based genetic counsellor to work specifically with consanguineous families. Bradford and Airedale tPCT has adopted a 3-pronged approach to increasing awareness of genetics involving working with (1) at-risk families (2) lay public (3) health and social care frontline staff.

2.1.6.2 Bradford PCT's willingness in 2008 to prioritise and fund training of professionals, prompted the setting up of a private enterprise (GCD: Genetics Communication Diversity) by Aamra Darr, to develop and deliver a one-day training course for a range of health professionals including GPs, Midwives, Health visitors, Children's Centre staff, Social Workers, Community Health Development Workers and Voluntary sector Advisors. The training has also been taken up by several other PCTs, local authority and voluntary organisations in Walsall, Kirklees, Leeds and Manchester. By January 2011 it will have been delivered to 560 professionals. GCD also produces communication tools for use by professionals and families. The strategy of responding to need through a private initiative has proved to be an efficient way of swiftly translating research into practice.

2.1.6.3 A prototype epidemiological database detailing consanguinity-related service indicators was developed in response to PCT demand by Professor Bernadette Modell, Director of the WHO Collaborating Centre for the Community Control of Inherited Disorders, University College London Centre for Health Informatics and Multiprofessional Education (CHIME) – also a co-applicant on the project. Examples of the centre's work on haemoglobin disorders can be found at www.chime.ucl.ac.uk/work-

areas/cab/. The prototype consanguinity database is currently being used by several PCTs for planning and commissioning purposes. Additional work is needed for the database to become a viable national resource, as it needs to be made available in the Web, in a form capable of incorporating new information as it becomes available, e.g. ethnicity data from the next census. A comparable national epidemiological database on haemoglobin disorders, commissioned by the National Sickle Cell and Thalassaemia Screening Programme for their PEGASUS educational programme, is available at http://www.pegasus.nhs.uk/.

2.1.6.4 In response to family need, and the manifest need for standardised information, a prototype instrument has been developed that has been tested and shown to have the capacity to (a) enable health professionals to accurately inform families at risk of rare recessive disorders of their specific familial risks, and direct them to support and preventative genetic services, (b) enable at-risk families to convey accurately the same information to their relatives who may also be at risk and (c) aid in empowering families to make informed choices and participate fully in the medically-supported management of their genetic risk. CHIME has developed the informatics blueprint to develop the instrument into an automated, bilingual genetic communication tool, to be used by health professionals and families, to increase family understanding of genetic inheritance. The tool would be web-based and capable of deployment throughout the NHS. The next stage (requiring funding) is to implement the blueprint, roll out the instrument and test it with a range of professionals.

2.2 *Other related projects*

2.2.1 A five year project funded by the Sir Jules Thorn Charitable Trust, currently in progress, aims to develop an international resource for autozygosity mapping and identification of recessive disease genes in consanguineous families. The project is based at the Leeds Institute of Molecular Medicine, St. James's University Hospital, University of Leeds.

3. Issues

3.1 Inherited disorders represent a growing health burden in terms of mortality, disability, and costs to the NHS, particularly in regions where consanguineous marriage is common. However, it is particularly complex to transmit genetic risk information across cultural and language barriers and health professionals struggle to accommodate diversity, given the lack of appropriate communication tools and training. Consequently many Pakistani-origin families remain unaware of the potential value of existing genetics services (genetic counselling, carrier testing) or of available options for reducing their genetic risk (choice of partner, restriction of family size, prenatal diagnosis). As a result, multiple births of affected children occur, avoidably, in many extended families. Since people who understand their genetic reproductive risk commonly take steps to reduce it , improved access to risk information is likely to lead to reduction in the number of affected infants born, and help to limit patient numbers and escalating treatment costs. As an example, treatment costs for thalassaemia (an inherited blood disorder) are of the order of £20,000 per patient per year.

3.2 Inadequate genetics-related service delivery to people of Pakistani origin, an ethnic group characterised by socio-economic disadvantage, is well documented. The presence, in many instances, of several children with the same recessive disorder in one family, can also be attributed to families' lack of access to services within disadvantaged communities.

3.3 In typical northern European populations where partners are largely chosen at random, genetic counselling and extended family studies are usually offered for dominant or X-linked disorders, because relatives have a high chance of being asymptomatic carriers, and may use this knowledge to reduce their personal and reproductive risks. Relatives of people with recessive disorders also have a high chance of being carriers, but extended family studies are rarely offered because (a) the risk that their partner will carry the same disorder is usually low, and (b) it is rarely possible to detect all DNA variants that can cause a given disorder. Hence cascade screening is less cost-effective for most recessive than for dominantly-inherited disorders. However, in communities where consanguineous marriage is common, families with recessive disorders move into a risk category comparable with that of families with dominant or X-linked disorders because (a) a carrier who marries within their extended family has a high (around 30%) risk that their partner is also a carrier and (b) carriers are highly likely to carry the DNA variant found in the presenting affected relative. Thus when a precise (usually DNA-based) diagnosis is possible for an affected person, carrier diagnosis, prenatal diagnosis and genetic counselling are usually all possible for the extended family.

It would seem logical then, to offer comparable genetic counselling services to consanguineous families at risk for recessive disorders. However there has been a paralysis in progressing towards solutions for consanguineous communities for a variety of reasons: (1) the development of community genetics infrastructures is in its infancy (2) there is limited understanding of genetic issues arising in diverse populations within public health, and among health professionals generally (3) the perceived large scale of the problem tends to intimidate (4) there is a need to develop novel community-based as well as specialist genetics services.

3.4 The incidence of mortality and morbidity related to recessive disorders is conspicuously concentrated in areas with a large population of Pakistani origin. At present, allocation of resources for genetic and community paediatric services is not adjusted for areas of high risk, leaving health professionals in such areas struggling to provide services for disproportionately large and growing numbers of children with chronic disabling disorders with inadequate resources.

3.5 A standardised national approach to the delivery and sharing of genetic information between professionals and families and within extended families is required. Currently this is dependant on the personal communication skills of professionals with access to scant materials (produced ad hoc) to aid the communication process. Accurate information is a major therapeutic intervention in genetics. A family's ability to make informed choices rests on the effective communication of complex genetic risk information by health professionals - information that needs to be passed on to other family members, who may also be at risk, and retained, for future use. A family's grasp of the inheritance pattern associated with a genetic disorder in their family is fundamental to, and a prerequisite for, understanding and making use of support and preventative services.

4 Recommendations

1. Development of a communications strategy to disseminate best practice, with the aim of developing a network of local multidisciplinary teams.

2. Development of integrated local strategies plus implementation and audit, across the Health service ranging from specialist clinical genetic services, hospital specialities (particularly paediatrics), to primary care, health and social care agencies, laboratory services and communities.

3. Adjustment of resource allocation on the basis of above two activities.

4. Workforce development – creation of community based genetic counsellor posts in key areas.

5. Development of communication tools.

6. Training of professionals.

7. Incorporation into professional education of genetics-related evidence on consanguineous marriage, dealing with diversity and equity in service delivery to a multiethnic population.

8. Community engagement to increase public literacy in genetics.