

BLOOD RELATIVES:

HOW WE ARE LEARNING MORE ... AND BANISHING MYTHS – AT A GLANCE



Up to **15%** - newborns globally with consanguineous parents

1.2m – size of British Pakistani community



13,000 – people in initial 2007-2011 BiB study

60% - couples of Pakistani heritage related by blood



3,000 – people in follow-up BiB study 2016-20

Revealed consanguinity rate had dropped to **43%**



1% - first cousin marriages in White British couples

99.99% - our genomes that are identical



24,000 – number of genes in humans

Between **20%** and **40%** - child deaths possibly due to genetic disorders associated with consanguinity



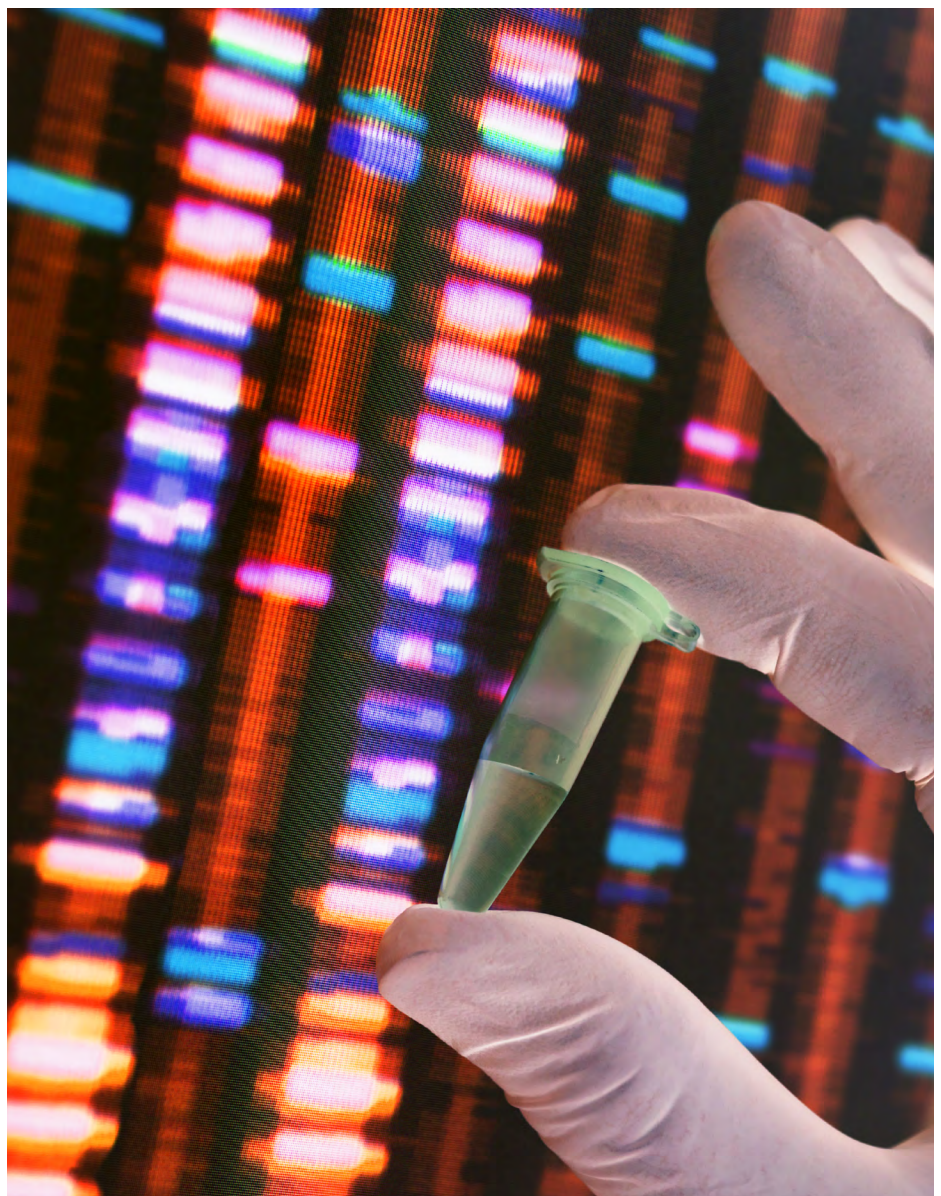
Just **3%** - increase in risk of congenital abnormalities in cousin marriages

400 – years of legal protection for cousin marriages in UK



EVIDENCE BRIEFING

GENES AND HEALTH: INHERITANCE AND RISK



GENETICS AND BORN IN BRADFORD

The **families in Born in Bradford (BiB)** have provided **crucial evidence** about how **consanguinity (sometimes referred to as cousin marriage)** impacts on health and wellbeing, and their **DNA samples** have led to **important drug discovery** and identification of **genes that predict diseases**.

Historically, genetic science has concentrated on White European populations, to the neglect of ethnic minority populations. **BiB has helped address this inequity**.

To contextualise this briefing, it is important to stress that British Pakistanis in Bradford follow a **slightly-different family and extended family organisation and pattern**. This is because a majority of Bradford Pakistanis **migrated from same place of origin** (Mirpur District of Independent Kashmir in Pakistan).

This historic geographical connection and subsequent settlement in same city i.e. Bradford **has influenced why there is a higher percentage of cousin marriages in Bradford-based**

British Pakistanis who represent BiB data, compared to British Pakistanis who migrated to UK from other parts of the country.

What is consanguinity?

Consanguineous marriage is defined as a union in which the male-female couple are **related as second cousins or closer**. The practice is socially embedded in many regions of the world, including **South Asia, North Africa** and the **Middle East**. It is estimated that globally around **10-15% of newborns** have consanguineous parents.¹

Consanguinity has a **long-standing tradition in the UK**, including the **Royal Family**, and in Victorian times was regarded as **romantic**.



Queen Victoria and Prince Albert depicted in 1846. They were first cousins.
Photo credit: via [Wikimedia Commons](#)

Some babies more at risk from genetic defects from first cousin marriages.
Photo credit: Flickr/Tella Chhe via Creative Commons



However, the prevalence **diminished rapidly during the 20th century** apart from specific ethnic minority groups, of which the **British Pakistani community** is the largest (~1.2 million).

How common is consanguinity in the UK?

Evidence from the Born in Bradford (BiB) study of ~13,500 families interviewed between 2007 and 2011 found that **60% of couples of Pakistani heritage** were related by blood (first cousin, second cousin or other blood relative), with **37% first cousin marriages** compared to less than **1% in White British couples**.

Pakistani parents who were UK-born were **less likely** to be in consanguineous relationships (**40% vs 60%**) and if **both parents** were born in the UK this **fell to 30%**.²

A follow-up cohort (Born in Bradford's Better Start) of ~3000 Bradford families recruited between 2016 and 2020 found that the consanguinity rate had **reduced from 60% to 43%** of British Pakistani couples (UK- and Pakistani-born).

This suggests that **greater awareness** about the risks of consanguinity from earlier BiB evidence, and **changing levels of education and acculturation** may be **influencing traditional marriage patterns**.

Why does consanguinity occur?

The practice of consanguinity has developed for **social and economic reasons**. Families know each other and so **social support** is likely to be **greater and more protective**.

Economically, **wealth is kept within the family group** and this can translate to health and educational benefits. Transnational marriages, for example, between partners in the UK and Pakistan, **strengthen links to cultural homelands** and **facilitate economic migration**.

Epidemiological evidence from BiB found that despite consanguineous couples being **poorer** and **less educated** they were **economically more secure**, had **more stable relationships** and **smoked less**.³

What are the genetic consequences of consanguinity?

All humans are related to some extent having descended from a small number of adults that moved out of Africa 60,000-80,000 years ago. Our genomes are **99.9% identical**, with the remaining 0.1% providing the **differences that make us unique**.

In parents who are biological relatives there is an **increased risk** that, although healthy, they both carry an **identical**

copy of a mutation causing a disorder with an autosomal recessive mode of inheritance.

In each pregnancy there will be a **25% chance** that this mutation is **co-inherited by their offspring**, resulting in the expression of the disorder. There also is a **wider risk** of an **adverse impact** on biological fitness through generational effects (so-called **inbreeding depression**).

Born in Bradford provides the **most definitive UK evidence** of risk of congenital anomalies.

After allowing for risk factors such as age, obesity and smoking, the risk of congenital anomalies **was doubled (3% to 6%)** in first cousin marriages and explained **30% of genetic disorders**.

However the risk to the child they give birth to **also doubled in White British women** over the age of 34 years.

At this point, it is important to mention that just like a cousin marriage is a **cultural practice** in Asian/British Pakistanis heritage, resulting in increasing risk factors for congenital anomalies, so too is choosing to give birth at or after the age 34 in White British women/couples.

This is largely a result of **choosing lifestyles embedded in liberal values** such as preferring jobs, careers, bodily fitness and individualism over giving birth before the age 34. This has been reported as the **highest cause** in BiB babies born with birth defects (19%) according to BiB data.

Education to degree level was a strong protective factor, **halving the risk of congenital anomalies irrespective of ethnic origin**.⁴

A recent study from Saudi Arabia found a **similar 3% residual risk** of autosomal recessive conditions in consanguineous couples.⁵

The risk in second cousins was **almost the same as for first cousins (5.8%)** indicating a background of generational endogamy: the practice of marrying within tribal or socio-occupational groups which may **increase genetic disorders** due to founder effects.

Detailed **genotyping** of the British Pakistanis in BiB also identified distinct **genetic differences** in **biraderi (clans)** due to long-established endogamy that may have begun **over 2,000 years ago** and increased at various times in history.

The risk of having a child with a recessive disorder **was increased in unrelated parents** who were from the same *biraderi*, but **substantially lower** than for related parents.⁷

Reviews of child deaths in UK Local Authorities (**Redbridge, Birmingham, Bradford**) have demonstrated that **20-40% of child deaths** may be due to genetic disorders associated with **consanguinity and chromosomal conditions**. These deaths can **contribute significantly** to the **higher-than-national average infant mortality rates** in these districts.

Evidence of the wider impact of generational impact comes from a recent study of **119 cohorts** that investigated the association between runs of **homozygosity** (a marker of genetic inbreeding) and **health and behaviours**. Deleterious effects were found in **32 out of 100** traits



studied, including **fertility, vision, hearing, grip strength, educational attainment, waist-hip ratio**, but there also were **beneficial reductions** in risk-taking behaviours, such as **alcohol, smoking** and **multiple sexual partners**.⁸

Perspectives from British Pakistanis about consanguinity and genetic risk

Qualitative research identified a **lack of awareness** about genetic risk but a **clear willingness** to understand and engage about this risk. Parents were **deeply concerned** about the health of their children.⁹

The focus on “cousin marriage” has the potential to **create stigma and alienation** between communities. It should be emphasized that the observed increase in the absolute risk of congenital anomalies is small (3%) and **equivalent in scale** to that experienced by older White British mothers.

Helping to develop new drugs to treat diseases

We have around **24,000 genes**, but don't understand what most of them do. **Knockout genes in mice** allow scientists to **investigate the effect** on health of removing single genes, but **mice are not humans**.

Humans can have naturally occurring knockout genes, and these are **much more common** in children of consanguineous couples. Gene sequencing in the BiB cohort has

identified over **1,100 naturally-occurring knockout genes** (homozygous loss of function variants) in **820 participants**.¹⁰ This research has already led to **promising developments** in drug discovery in severely disabling diseases such as **primary hyperoxaluria** and **psoriasis**.^{11,12}

Identification of genes that can help predict our risk of disease

Genetic risk scores can help people learn what their risk of developing certain diseases. BiB has been able to use genetic data to **develop prediction tools** (polygenic risk scores) for diseases such as **diabetes** and **heart disease** in South Asian populations.^{13,14}

Working with **international scientists**, BiB has helped identify genes that are important in the risk of severe illness from **COVID-19** that may lead to **new treatments for the illness** and well as help identify genes that are important for ageing.^{15,16}

IMPLICATIONS FOR POLICY AND PRACTICE

There have been attempts to **stigmatise** and **even ban** cousin marriage, but its widespread practice globally indicates that **more culturally sensitive approaches** are required.

Empirical evidence presented in this briefing paper indicates that **better education** and **acculturation** is likely to reduce the **overall rates of consanguinity** across future generations, especially with smaller family sizes restricting potential marriage partner choice. At the same time, there is also a clear need for **increased genetic literacy** and **awareness of risks for children and young people**.

Technological advances in genetic screening such as non-invasive cell-free DNA-based screening (fetal DNA in maternal blood) and **genome-wide analysis** (genotyping arrays or sequencing) on samples obtained through amniocentesis may support earlier identification of genetic disorders, although these are **often rare and specific disorders** may be restricted to small communities.

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