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Review article

# A perinatal approach to genetic disorders in Irish Travellers: A review

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ABSTRACT

Irish Travellers are an endogamous nomadic ethnic minority population mostly resident on the island of Ireland with smaller populations living in Europe & USA. As they practice consanguinity, rare and ultra-rare autosomal recessive conditions are observed which are infrequently seen in the general population. Awareness of the rare genetic disorders within an antenatal setting that recur within this population should facilitate quicker cost-effective diagnosis. These include disorders leading to recurrent miscarriage and multiple congenital anomalies. Prompt diagnosis and tailored management can affect prognosis and a multi-disciplinary team approach with the obstetrician, neonatologist and clinical geneticist should improve outcomes.



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## Introduction

Irish Travellers are a nomadic ethnic minority originating from Ireland with an estimated population of 40,000 on the island of Ireland, forming 1% of the Irish population and 0.2% of the population of the Northern Ireland poulation [1]. There are an estimated 5000 residing in the United Kingdom (London, East Anglia, Birmingham and Manchester regions) with smaller populations living in mainland Europe and North America (Texas and North Carolina) [2]. Irish Travellers have an overall health status which is more comparable to people living in underdeveloped countries than to those in developed Europe [3]. Although there has been a shift to settling of the group into housing, they remain an intensely private and socially self-contained group. Culturally, consanguineous marriages are common, which lends itself to a greater incidence of autosomal recessive genetic disorders. Within the Traveller population there is a *'clan'* based sub-structure, leading to a clustering of disorders within *'clans'* [2].

Traditionally, presentation to medical services can be inadequate as can the sharing of medical history, which can pose a challenge in identification of genetic syndromes [4]. Family history taking may not be informative as there is a reluctance to share diagnoses amongst the wider family. Privacy is a very important cultural concern and experience working with these families suggests that knowledge about the inherited disorders within the family is limited. This is a characteristic, which is relatively

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uncommon but seen in a number of endogamous populations including the Irish Travellers and Romani people.

The chance that a mother has experienced a previous stillbirth or miscarriage is significantly greater in the Irish Traveller population compared to the standard European population OR 4.07 (95% CI 2.37–7.01) and 2.1 (95% CI 1.69–2.52) respectively. This is also the case in relation to the peri-natal and infant mortality rates, which are four times that of the national average at 2.2 and 12.0 per 1000 live births respectively [1,[3]]. The incidence of a genetic syndrome within the Irish Traveller population is not known, due to incomplete census data and the fact that Irish Travellers do not routinely opt for post-mortem examination following a stillbirth and often do not disclose such information if available. To gauge a sense of the prevalence of genetic syndromes, one can assess audit data, which states that of those reported, nine percent of Traveller families claimed that they have had at least one child with a genetic syndrome and/or 12% with a 'disability' [3]. Assessing infant mortality deaths within the Traveller population between 2008/2009, where cause of death was ascertained, a diagnosed genetic syndrome (spinal muscular atrophy and metabolic disorders) or congenital structural anomaly was the cause in 72.7% (n = 8/11) cases from 2008 to 2009 [1].

It is important to be cognizant of the additional risk to Traveller pregnancies resulting from poor social circumstances. They often have large family sizes with an average of 5.4 children per family and at least 50% never having used contraception [1,3]. Lower socioeconomic status is primarily due to; (i) education - 28% of Travellers leave school by the age of 13-years; (ii) unemployment – Travellers are almost six times more likely to be unemployed compared to their non-Traveller counterparts; (iii) housing – although only 12% of Travellers now live in a caravan or mobile home, of those in settled accommodation, over half experience overcrowding and; (iv) health – the health gap between Travellers and non-Travellers rises steeply beyond 35-years associated with a shortened life-expectancy [5].

There is a paucity of evidence outlining the identified genetic Traveller disorders, however a recently published catalogue has collected 104 inherited disorders, primarily autosomal recessive in nature [2]. Many of the genetic conditions in Irish Travellers are predominantly monogenic with an autosomal recessive inheritance pattern & most are due to homozygous mutations. Knowledge of the known Traveller disorders facilitates rapid confirmation or exclusion of diagnoses as it allows targeted screening for the specific mutation. The aim of this review is to act as a guide and a resource for perinatal clinicians who encounter patients from the Irish Traveller population to facilitate early diagnosis and improved management of pregnancies with early referral to fetal maternal medicine sub-specialists and geneticists.

## Prenatal diagnosis

There are a number of rare genetic disorders amongst Travellers with identified mutations that present with congenital anomalies antenatally and may be detectable using fetal ultrasound. Ideally, prior to investigation, women from Traveller populations with a prior history of a child with a single gene disorder or where an anomaly has been detected on ultrasound should be referred to a tertiary fetal medicine centre. There, detailed fetal anatomical mid-trimester ultrasound assessment can be performed in an attempt to identify the fetal phenotype and prompt liaison with a clinical geneticist that has experience of this population should be instigated. While pre-conception screening for consanguinity would be an optimal approach, any pre-conceptual programme would interfere with choice of marriage partners and this is likely to be met with hostility. Pre-conceptual screening is a very sensitive subject and its introduction is more likely to succeed if the population in question request it rather than it be forced upon them from a state agency. This population are not requesting this service at this time. Currently, despite knowledge of consanguinity and the risk of having a child with an autosomal recessive syndrome, Irish Travellers will proceed with conception anyway.

The advantage of prenatal diagnosis of the disorders that recur in the Irish Traveller population include; (i) prior planning of location, mode and timing of delivery; (ii) development of a targeted neonatal management plan; (iii) identification of potentially life-limiting disorders with consideration to palliative care and termination where legally permissible; (iv) adequate pre and post-test counseling to facilitate the management of subsequent pregnancies e.g. pre-implantation diagnosis, recurrence risks and implications for the wider family; (v) obtaining fetal samples to facilitate DNA extraction and genetic diagnosis for future pregnancies; (vi) optimizing knowledge prior to embarking on fetal therapies and; (vii) the possibility of cascade carrier testing being offered to other at-risk relatives.

Traveller disorders, presenting primarily with one anatomical system with an anomaly on antenatal ultrasound are presented below [Fig. 1], as are multisystem disorders [Table 1]. Information is also provided on the occurrence of such genetic mutations

**Table 1**
Traveller syndromes presenting as a multisystem disorder on antenatal ultrasound (FGR = Fetal growth restriction; Observed occurrence: P = Private mutations, seen in one nuclear family; C = multiple affected individuals within one Clan; F = Founder mutations, seen in unrelated families).

| | FGR | Hydrops | Brain | Cranio/ Facial | Cardiac | Thorax | Uro-genital | Musculo-Skeletal | Observed occurence |
|---|---|---|---|---|---|---|---|---|---|
| Beaulieu-Boycott-Innes syndrome *THOC6* | | | x | | | | x | | P |
| Colobomatous microanopthalmia (MCOPCB) and Matthew Woods syndrome *STRA6* | x | | x | x | x | x | X | x | F |
| Deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOOR) syndrome *TBC1D24* | | | x | | x | | x | | P |
| Fanconi anaemia of complementation group A or J *FANCA* and *BRIP1* | x | | x | x | x | | X | x | F/P |
| Fraser syndrome *FREM2* | | | x | x | x | x | X | x | C |
| I-cell disease mucolipidosis II *GNPTAB* | x | x | | | x | | | x | F |
| Meckel syndrome *unknown* | | | x | x | x | x | X | x | P |
| NEK9 related lethal skeletal dysplasia[17] *NEK9* | | | | x | x | x | | x | F |
| Neu-Laxova syndrome *unknown* | x | | x | x | | x | | x | P |
| Van Maldergem Syndrome 1 *DCHS1* | | | x | x | | | x | x | P |
| Walker-Warburg syndrome *POMT1* | | | x | x | | | | | F |