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# PARENTAL CONSANGUINITY AND FAMILIAL RECESSIVE-PATTERN DISORDERS IN TEHSIL TIMERGARA, KHYBER PAKHTUNKHWA, PAKISTAN: A PEDIGREE-BASED STUDY OF ELEVEN FAMILIES

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## Abstract

**Background**. Consanguineous marriages are common in Khyber Pakhtunkhwa (KP), Pakistan, but pedigree-level data on familial disorders from Dir Lower are scarce.

**Methods**. Between January and July 2023, families with visible heritable disorders were identified in seven localities of Tehsil Timergara. Family histories were obtained, and pedigrees were drawn using standard nomenclature. We summarised families, sibships and the consanguinity of the parents of affected individuals, and compared the proportion of affected sibships with consanguineous parents against published background rates using exact binomial tests.

**Results**. Eleven families (537 members; 3–6 generations) contained 44 affected individuals (23 male, 21 female): intellectual disability (n = 13; four families), deafness (n = 12; two families), baldness (n = 8; two families), anophthalmia (n = 5), albinism (n = 4) and polydactyly (n = 2). Ten families had at least one consanguineous parental union. Parents were consanguineous for 37 of 44 affected individuals (84.1%) and for 14 of 20 affected sibships (70.0%; 95% CI 48.1–85.5). This proportion exceeded the 46.2% reported for Dir Lower district (exact p = 0.042) but not the 55% reported for Timergara tehsil (p = 0.26). The polydactyly pedigree contained no consanguineous union and is more compatible with dominant inheritance with reduced penetrance.

**Conclusions**. Most pedigrees are consistent with autosomal recessive inheritance, but ascertainment through affected families, the absence of a comparison group, and the lack of clinical or molecular confirmation prevent causal inference. Because background consanguinity is high, population-based studies and molecular diagnosis are needed to quantify the contribution of consanguinity in this region.

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**Keywords**: consanguinity; autosomal recessive inheritance; pedigree analysis; congenital disorders; Khyber Pakhtunkhwa; Pakistan; intellectual disability; hearing loss.

## 1. INTRODUCTION

Consanguineous marriage, the union of two individuals who share at least one common ancestor, has been practised since the early history of modern humans, and it remains a social preference in large parts of North Africa, the Middle East and Central and South Asia. It has been estimated that roughly one in five people worldwide live in communities that favour unions between relatives [1,2]. Reasons for the preference include the security of a known spouse and in-laws, the consolidation of family property and ties, lower marriage costs and the ease of arranging marriages [3,4].

The genetic consequence of such unions is a higher probability that the offspring inherit identical copies of a rare deleterious allele from both parents. Children of first cousins have an expected inbreeding coefficient of 1/16 (0.0625), so on average one-eighth of their genes are shared by descent between the parents [3]. The reproductive and health consequences, including more stillbirths, infant mortality and recessive congenital disorders, have been studied for decades [5–7]. In a multi-ethnic UK birth cohort in which the Pakistani-heritage community made up a large proportion of consanguineous couples, the risk of congenital anomaly in the offspring of related parents was roughly double that in unrelated couples [8]. Genomic studies in Pakistan have also shown that parental consanguinity increases homozygosity for rare loss-of-function variants and exposes recessive phenotypes [9,10]. At the same time, the absolute risk increase for any one couple is modest, and customary consanguinity should be addressed through culturally sensitive counselling rather than prohibition [1,11].

Pakistan has one of the highest rates of consanguineous marriage in the world, and unions between first cousins are the most common type [12]. In KP, a survey of 1,192 rural couples in the Malakand district reported that about two-thirds of marriages were consanguineous, and that the rate had risen in the decade of conflict and displacement that followed 2001 [13,14]. A cross-sectional study of 1,250 individuals in the adjacent Dir Lower district found that 46.2% of unions were consanguineous, with higher rates in Timergara (55%) and other tehsils that received displaced families; consanguinity was also more frequent among literate and higher-income respondents [15,16]. In contrast, other districts of northwest Pakistan show evidence of a temporal decline [17]. Despite this high background rate, we are not aware of published family-based descriptions of heritable disorders from Tehsil Timergara.

Pedigree analysis remains the simplest way to document how a trait segregates in a family and whether parental relatedness is plausibly involved. In the present study, we assembled and analysed eleven pedigrees of families with six categories of heritable disorders (albinism, anophthalmia, baldness, deafness, intellectual disability and polydactyly) in Tehsil Timergara. We aimed to describe the families and affected individuals, to document the consanguinity of the parents of affected individuals, and to assess, with explicit attention to ascertainment, whether the pedigree patterns are consistent with autosomal recessive inheritance.

## 2. Materials and methods

### 2.1 Study area and design

The study was carried out in Tehsil Timergara, District Dir Lower, Khyber Pakhtunkhwa, Pakistan, between January and July 2023. Seven localities (Timergara city, Utala, Khungi, Katan, Dabar, Pengal and Hawa Derai) contributed families. This was a descriptive, family-based study: families with affected members were identified through hospitals, schools, clinics, and community visits and were visited at home.

### 2.2 Ascertainment and phenotype definition

Families were included if they had at least one member with a visible heritable disorder reported by the family. Both consanguineous and non-consanguineous parental unions were recorded in the pedigrees. Phenotypes were classified by the investigators as albinism, anophthalmia, baldness, deafness (recorded as 'deaf and mute' in the field), intellectual disability (recorded as 'mental retardation'), and polydactyly. No audiometry, ophthalmic

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examination, psychometric testing, dermatological assessment, or molecular testing was performed; phenotypes therefore rest on clinical observation and family report.

### 2.3 Pedigree construction

Informants were interviewed about the family history. Pedigrees were drawn following the recommendations for standardised human pedigree nomenclature [18–20]: squares denote males and circles denote females; filled symbols denote affected individuals; a diagonal line denotes a deceased individual; a single horizontal line joins partners and a double line joins partners who are related by blood; generations are numbered with Roman numerals and individuals within a generation with Arabic numerals from left to right. A number inside a symbol indicates that number of unaffected siblings of the same sex shown as a single symbol. Personal names were removed and replaced by pedigree codes. In this paper, the pedigrees were redrawn from the original family records with identical structure; for each pedigree, the number of persons represented was checked against the recorded family size (Table 2).

### 2.4 Ethical considerations

Participating families were informed about the purpose and procedures of the study and gave their consent before data were collected. Personal names were removed, no photographs of affected individuals were published, and no biological samples were collected.

### 2.5 Data analysis

Counts and percentages were calculated for villages, disorders, sex, and parental consanguinity. Percentages for disorders are given as the share of the 44 affected individuals and are not prevalence estimates, because the population denominator was not enumerated. Because affected siblings from the same parents are not independent, consanguinity of the parents of affected individuals was analysed at the level of the affected sibship (a set of full siblings, at least one of whom is affected). Consanguineous parents were those joined by a double line in the pedigree; the degree of relationship was not systematically recorded, and partners who married into a family were taken to be unrelated unless a double line was recorded. The proportion of affected sibships with consanguineous parents was compared with published background rates of consanguineous marriage for Dir Lower district and Timergara tehsil [15] using a two-sided exact binomial test; 95% confidence intervals were calculated by the Wilson method [21]. Segregation ratios were not estimated because families were ascertained through affected members, which inflates the observed proportion of affected siblings [22,23]. Analyses were performed in SPSS 26. Charts and pedigree diagrams were generated with OriginPro from the data given in Supplementary Tables S1 and S2.

## 3. Results

### 3.1 Overview of families and affected individuals

Eleven families from seven localities were included (Table 1; Table 2). Family size ranged from 28 to 75 members (total 537; median 51) across three to six generations, and the pedigrees contained 44 affected individuals, 23 male and 21 female. Six disorder categories were recorded (Fig. 1 and Fig. 2). Intellectual disability was the most frequent in terms of both families (four) and individuals (13; 29.5% of the 44 affected), followed by deafness (two families; 12 individuals; 27.3%), baldness (two families; eight individuals; 18.2%), anophthalmia (one family; five individuals; 11.4%), albinism (one family; four individuals; 9.1%) and polydactyly (one family; two individuals; 4.5%).

**Table 1. Distribution of affected families and individuals by locality and disorder in Tehsil Timergara (January–July 2023).**

| Locality | Disorder | Families (n) | Affected individuals (n) |
|---|---|---|---|
| Dabar | Baldness | 1 | 3 |
| Hawa Derai | Polydactyly | 1 | 2 |
| Katan | Intellectual disability | 1 | 4 |

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| | | | |
|---|---|---|---|
| Khungi | Albinism | 1 | 4 |
| Pengal | Intellectual disability | 1 | 3 |
| Timergara city | Anophthalmia | 1 | 5 |
| | Baldness | 1 | 5 |
| | Deafness | 1 | 9 |
| Utala | Deafness | 1 | 3 |
| | Intellectual disability | 2 | 6 |
| **Total** | **6 disorders** | **11** | **44** |

**Table 2. Characteristics of the eleven families.**

| ID | Disorder | Locality | Fig. | Members | Gen. | Affected (M/F) | Consang. unions | Affected sibships with consang. parents |
|---|---|---|---|---|---|---|---|---|
| F1 | Albinism | Khungi | 4A | 32 | 3 | 4 (2/2) | 2 | 1/1 |
| F2 | Anophthalmia | Timergara city | 4B | 28 | 4 | 5 (3/2) | 2 | 2/3 |
| F3 | Baldness | Dabar | 5A | 51 | 4 | 3 (2/1) | 1 | 1/1 |
| F4 | Baldness | Timergara city | 5B | 56 | 3 | 5 (2/3) | 1 | 1/1 |
| F5 | Deafness | Timergara city | 6A | 36 | 6 | 9 (2/7) | 2 | 2/3 |
| F6 | Deafness | Utala | 6B | 69 | 3 | 3 (3/0) | 1 | 1/1 |
| F7 | Intellectual disability | Katan | 7A | 30 | 3 | 4 (2/2) | 1 | 1/1 |
| F8 | Intellectual disability | Utala | 7B | 50 | 4 | 4 (2/2) | 4 | 2/3 |
| F9 | Intellectual disability | Pengal | 7C | 56 | 3 | 3 (3/0) | 1 | 1/2 |
| F10 | Intellectual disability | Utala | 7D | 54 | 3 | 2 (1/1) | 2 | 2/2 |
| F11 | Polydactyly | Hawa Derai | 8 | 75 | 3 | 2 (1/1) | 0 | 0/2 |
| **Total** | | | | **537** | **3–6** | **44 (23/21)** | **17** | **14/20** |

Gen., number of generations; Consang. unions, consanguineous partnerships (double lines) drawn in the pedigree. Locality 'Timergara city' = Timergara urban area.

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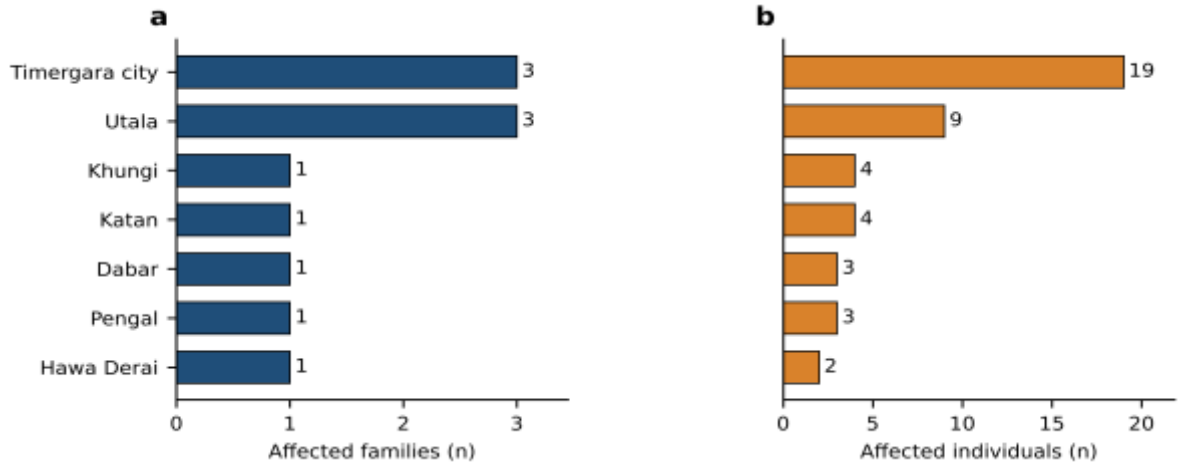



**Figure 1. Affected families (a) and affected individuals (b) by locality in Tehsil Timergara.**

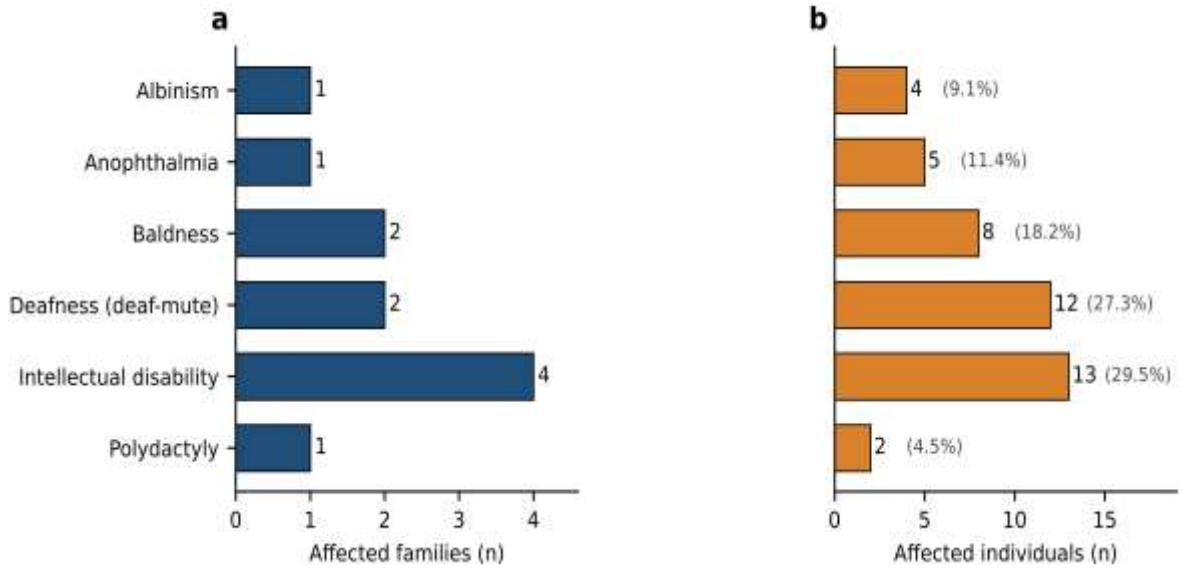



**Figure 2. Affected families (a) and affected individuals (b) by disorder; percentages in (b) are shares of the 44 affected individuals, not prevalence.**

### 3.2 Distribution by locality

Timergara city and Utala each contributed three families, and the other five localities one family each (Fig. 1a). Timergara city contributed the largest number of affected individuals (19; anophthalmia 5, baldness 5, deafness 9), followed by Utala (9; deafness 3, intellectual disability 6), Khungi (4), Katan (4), Dabar (3), Pengal (3) and Hawa Derai (2) (Fig. 1b). Because families were ascertained opportunistically, these counts describe where families were found and do not indicate locality-specific risk.

### 3.3 Sex distribution

Overall, 52.3% of affected individuals were male (23/44; exact $p = 0.88$ against 1:1). Within disorders the numbers are small: albinism 2 male and 2 female, anophthalmia 3 and 2, baldness 4 and 4, deafness 5 and 7, intellectual disability 8 and 5, polydactyly 1 and 1 (Fig. 3a). All three affected individuals in family F6 (deafness) and in family F9 (intellectual disability) were male, whereas seven of nine affected individuals in family F5 (deafness) were female.

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### 3.4 Parental consanguinity

Seventeen consanguineous partnerships (double lines) were drawn among 89 partnerships in the eleven pedigrees. Ten of the eleven families contained at least one consanguineous union among the parents of affected individuals; the exception was the polydactyly family (F11), in which no consanguineous union was recorded. Overall, 37 of 44 affected individuals (84.1%; 95% CI 70.6–92.1) had consanguineous parents (Fig. 3b), including all affected individuals with albinism (4/4), baldness (8/8), anophthalmia (4/5), deafness (10/12) and intellectual disability (11/13), but neither of the two with polydactyly.

The 44 affected individuals belonged to 20 sibships. Fourteen sibships (70.0%; 95% CI 48.1–85.5) had consanguineous parents (Table 3; Supplementary Table S2). This proportion was higher than the 46.2% reported for unions in Dir Lower district (exact two-sided p = 0.042) but not higher than the 55% reported for Timergara tehsil (p = 0.26) [15]. Neither comparison is adjusted for the generation or the period of marriage.

**Table 3. Consanguinity of the parents of affected individuals compared with background rates of consanguineous marriage.**

| Analysis unit | k/n | % (95% CI) | Background rate | Exact p |
|---|---|---|---|---|
| Affected sibships | 14/20 | 70.0 (48.1–85.5) | 55% (Timergara tehsil) | 0.26 |
| Affected sibships | 14/20 | 70.0 (48.1–85.5) | 46.2% (Dir Lower district) | 0.042 |
| Affected individuals* | 37/44 | 84.1 (70.6–92.1) | — | — |
| Families with ≥ 1 consanguineous parental union | 10/11 | 90.9 (62.3–98.4) | — | — |

CI, Wilson 95% confidence interval; p, two-sided exact binomial test. *Individuals within a sibship are not independent; no test is applied. Background rates from Ahmad et al. [15].

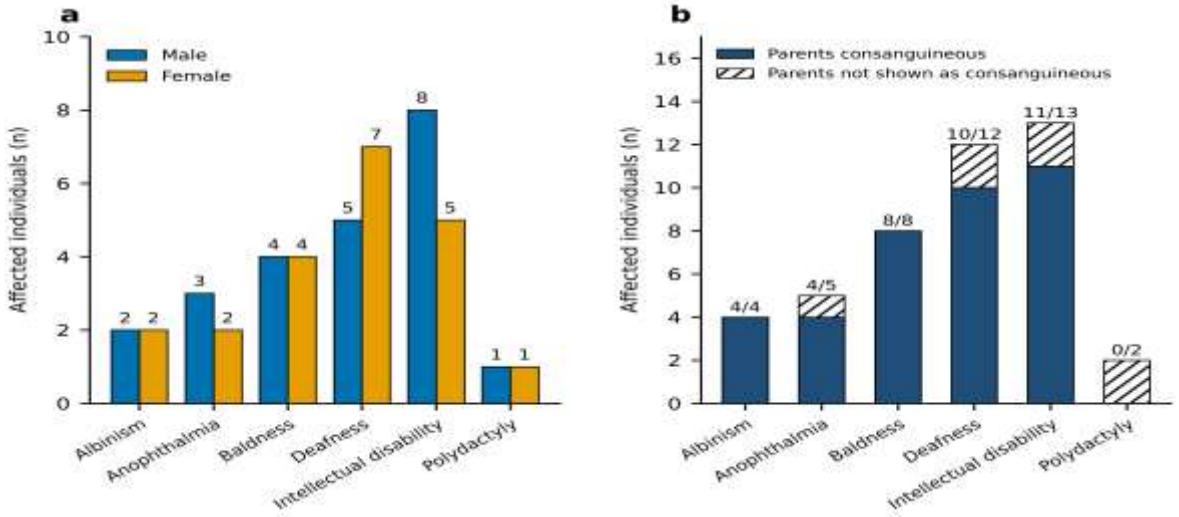



**Figure 3. (a) Sex of affected individuals by disorder. (b) Number of affected individuals whose parents are shown as consanguineous (solid) or not (hatched).**

### 3.5 Pedigrees by disorder

**Albinism (F1; Khungi).** The pedigree (Fig. 4A; 32 members, three generations) shows four affected siblings, two males and two females (III-2, III-3, III-5, III-6), among six full siblings whose parents (II-1 and II-2) are joined by a double line. A second consanguineous union in the family (II-5 and II-6) produced no affected child among five offspring. The pattern is that of a recessive trait expressed in a single sibship.

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**Anophthalmia (F2; Timergara city).** In this four-generation family of 28 members (Fig. 4B), five individuals are affected. Two independent first-cousin unions, III-2 × III-3 and III-6 × III-7, each produced two affected children (IV-1, IV-3 and IV-4, IV-5), and in both cases the husband and wife are first cousins through the shared grandparents I-1 and I-2. A fifth affected individual, III-1 (deceased), was born to unrelated parents (II-1 and II-2). Such a case would require the unrelated spouse II-1 to be a carrier, unrecognised relatedness, or a different cause.

**Baldness (F3, Dabar; F4, Timergara city).** In F3 (Fig. 5A; 51 members, four generations), three of eight siblings (two males, one female) are affected; their parents (II-3 and II-4) are consanguineous. In F4 (Fig. 5B; 56 members, three generations), five of nine siblings are affected (two males, three females), and the parents (I-1 and I-2) are consanguineous. The affected proportions in both sibships are above the Mendelian 25% expected for a recessive trait, as is usual when sibships are ascertained through affected members [22].

**Deafness (F5, Timergara city; F6, Utala).** F5 (Fig. 6A; 36 members, six generations) is the largest multigenerational pedigree, with nine affected individuals (seven female, two male) in three consecutive generations. Two affected sisters (IV-3, IV-4) were born to a non-consanguineous couple (III-1 × III-2). Their unaffected brother IV-2 later married a relative (IV-1) and three of their nine children (V-3 to V-5) are affected; one of those children's unaffected siblings (V-9) married a relative (V-10) and all four of their children are affected (VI-3 to VI-6). Repeated consanguinity in this branch produces a pedigree that resembles dominant transmission (pseudodominance) although the pattern is also compatible with autosomal recessive inheritance. In F6 (Fig. 6B; 69 members, three generations), three of eight siblings are affected, all males, born to a consanguineous couple (II-1 and II-2).

**Intellectual disability (F7–F10).** In F7 (Katan; Fig. 7A; 30 members), four of eight siblings are affected (two males, two females) and the parents are consanguineous. In F8 (Utala; Fig. 7B; 50 members, four generations), four individuals are affected in three separate sibships, two of which have consanguineous parents; the affected woman II-13 was born to a non-consanguineous couple. In F9 (Pengal; Fig. 7C; 56 members), three males are affected: two (III-6, III-7) belong to a sibship with consanguineous parents (II-5 and II-6), and one (III-13) to a sibship with parents not recorded as related. In F10 (Utala; Fig. 7D; 54 members), one woman (III-4) and one man (III-10, deceased) are affected, each from a separate consanguineous union.

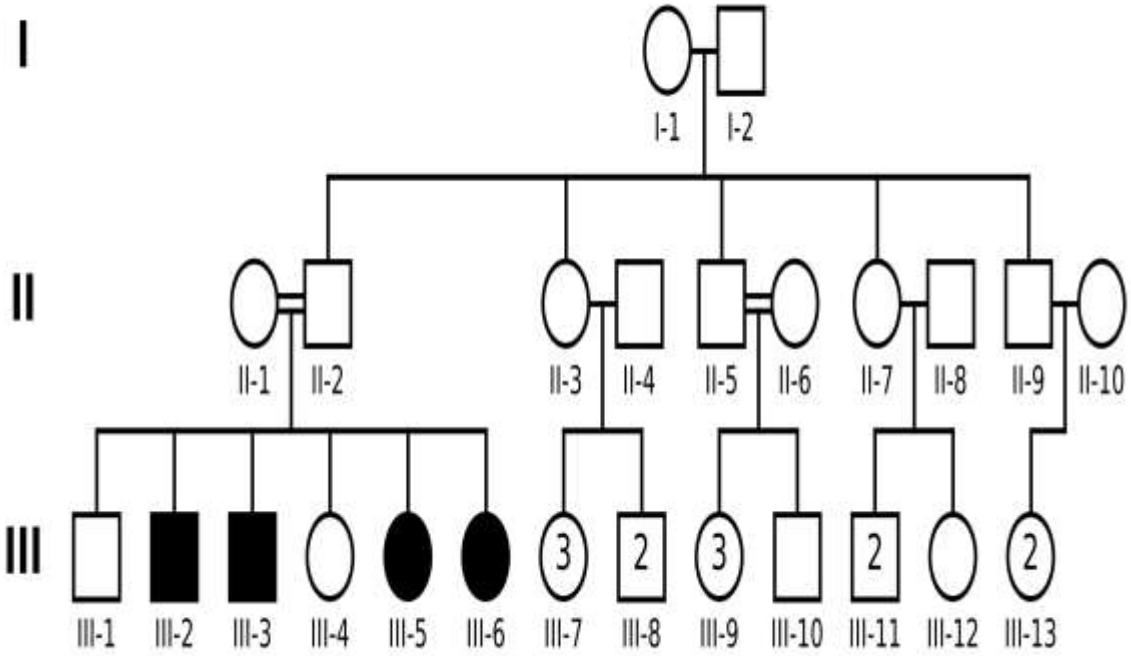
**Polydactyly (F11; Hawa Derai).** The pedigree (Fig. 8; 75 members, three generations) has two affected individuals, an aunt (II-9) and her nephew (III-3, the son of her unaffected brother II-2). No consanguineous union is recorded. This is compatible with autosomal dominant inheritance with reduced penetrance, the usual mode for non-syndromic polydactyly [24,25], and it should not be read as an example of recessive inheritance related to parental consanguinity.

### 3.6 Pedigree figures

Pedigrees are shown in Figures 4–8. Symbols follow the nomenclature described in the Methods; filled symbols are affected, a diagonal line indicates a deceased individual, a double line joins consanguineous partners, and a number inside a symbol is the number of unaffected individuals of that sex it represents.

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A. Albinism (family F1; Khungi)




B. Anophthalmia (family F2; Timergara city)

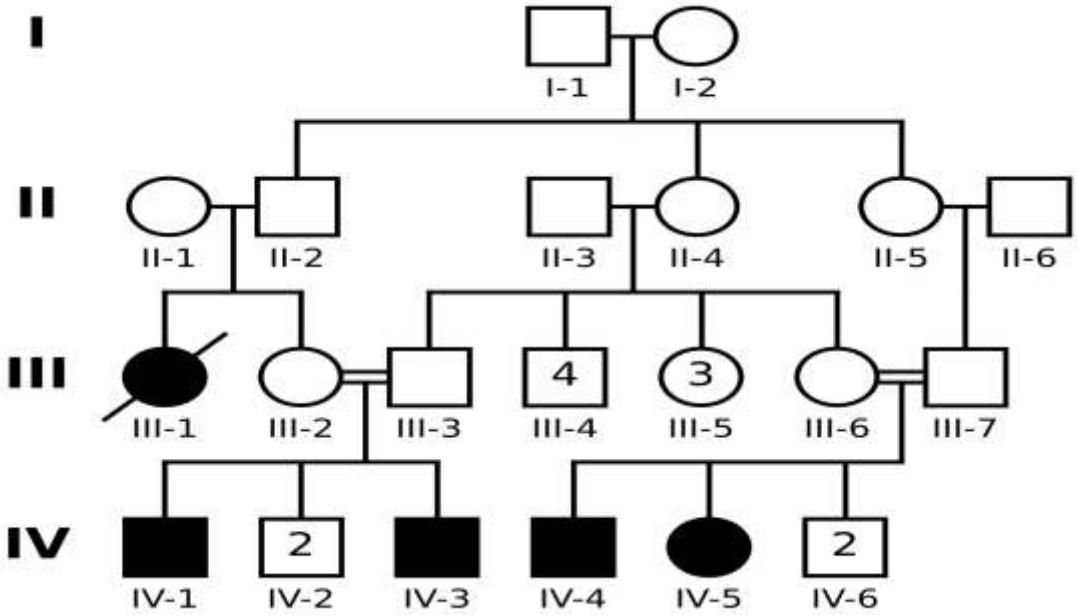
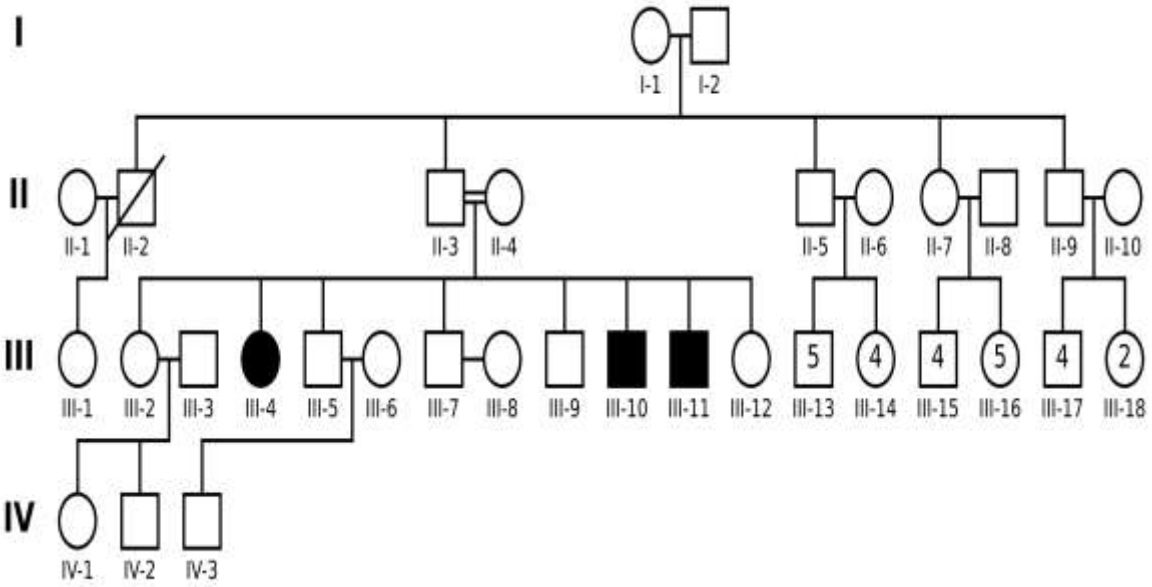



Figure 4. Pedigrees of albinism (A) and anophthalmia (B). IDs on the symbols are pedigree codes.

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A. Baldness (family F3; Dabar)




B. Baldness (family F4; Timergara city)

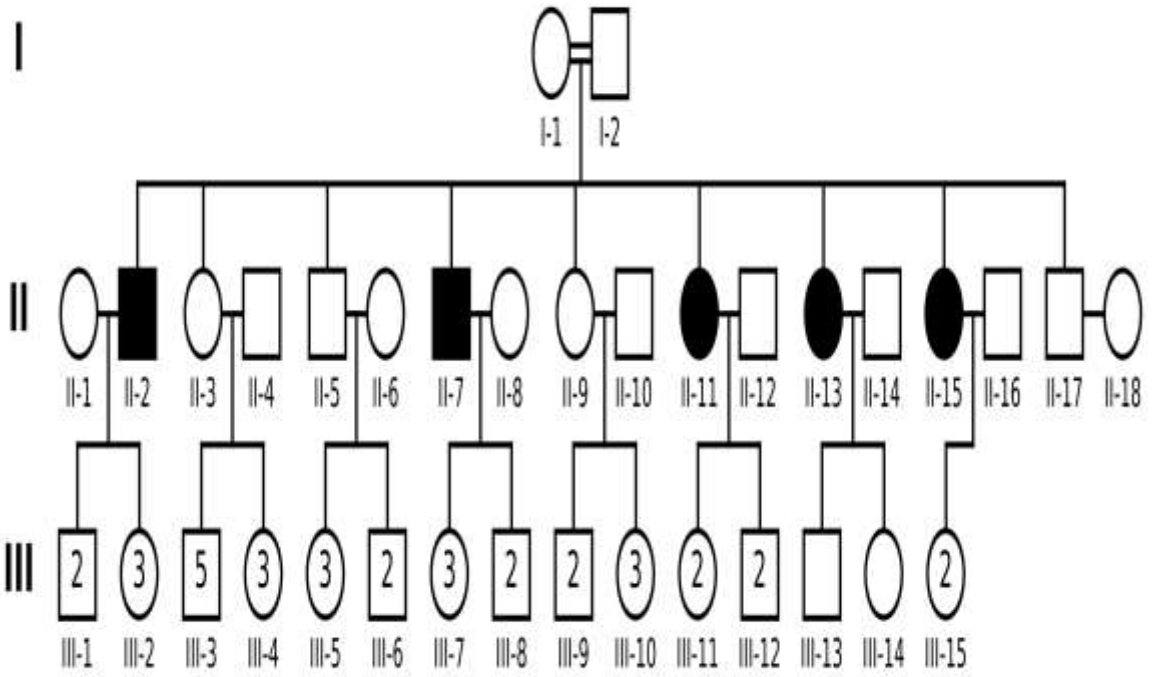
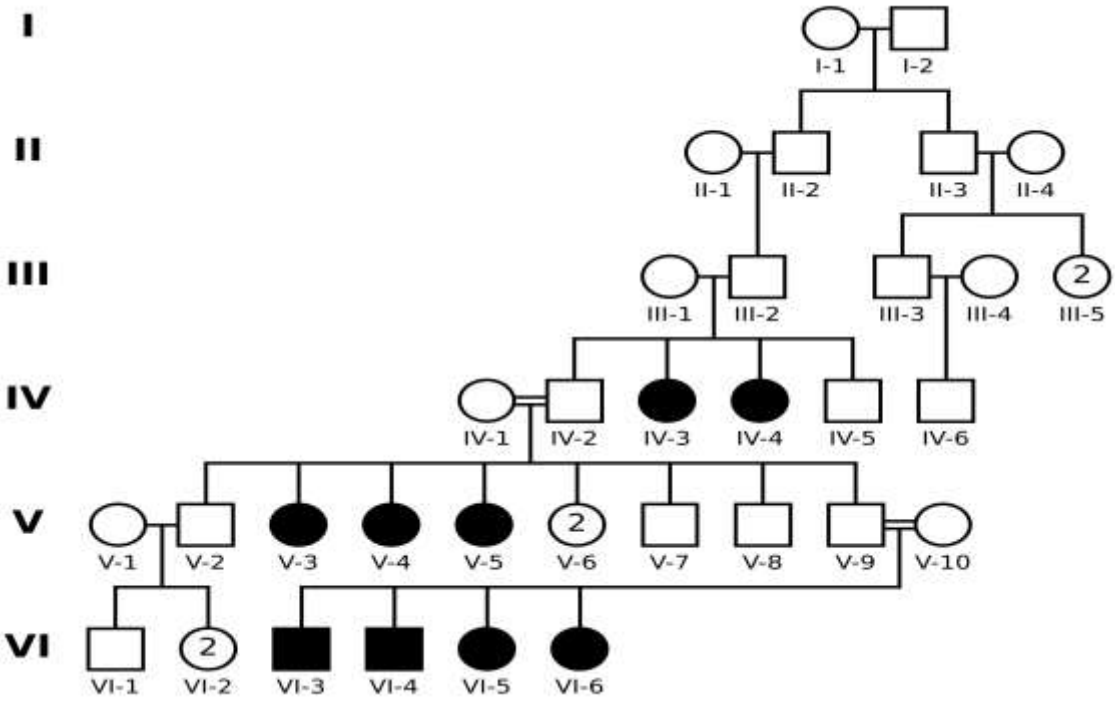



Figure 5. Pedigrees of two families with baldness (type unspecified).

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A. Deafness (family F5; Timergara city)




B. Deafness (family F6; Utala)

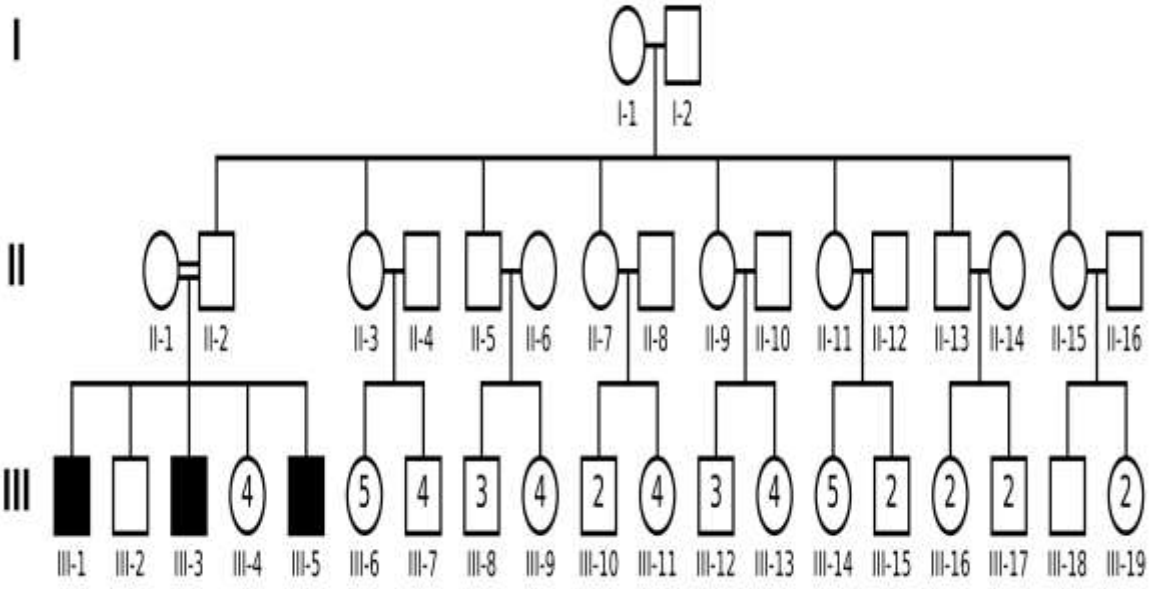
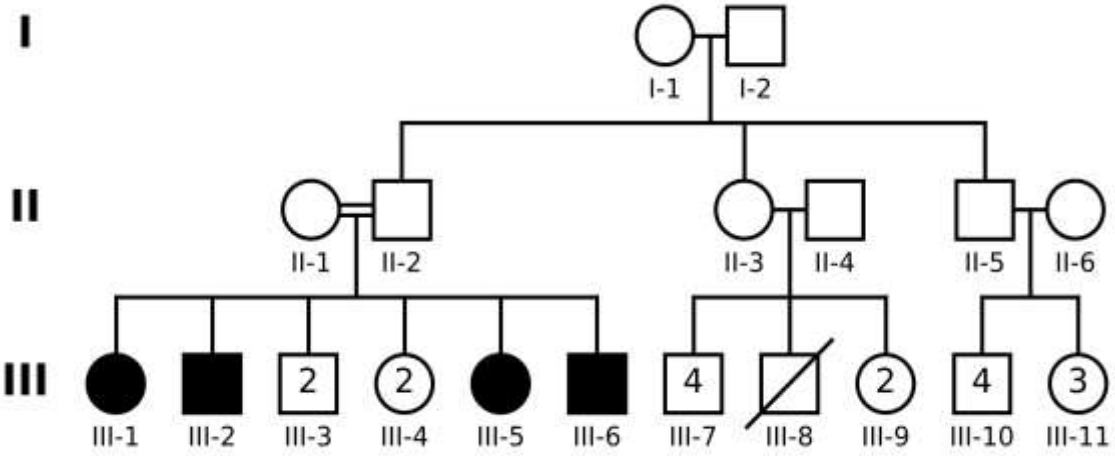


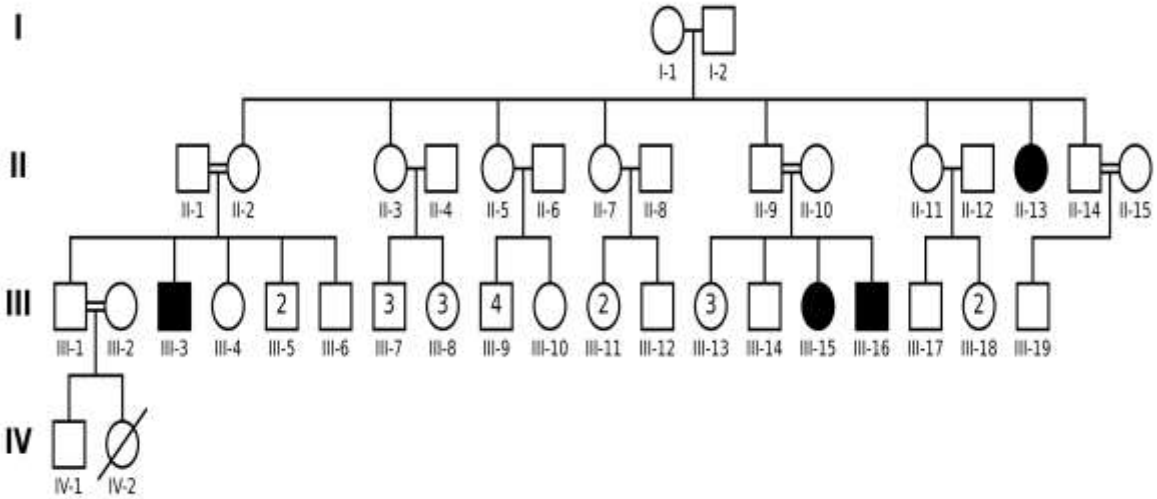

Figure 6. Pedigrees of two families with deafness (recorded in the field as 'deaf and mute').

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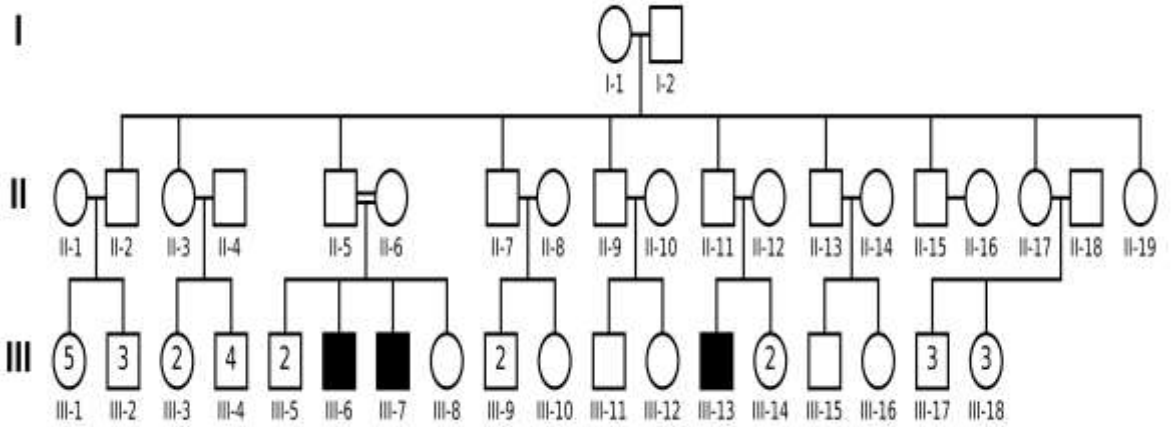
A. Intellectual disability (family F7; Katan)




B. Intellectual disability (family F8; Utala)




C. Intellectual disability (family F9; Pengal)




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**D. Intellectual disability (family F10; Utala)**

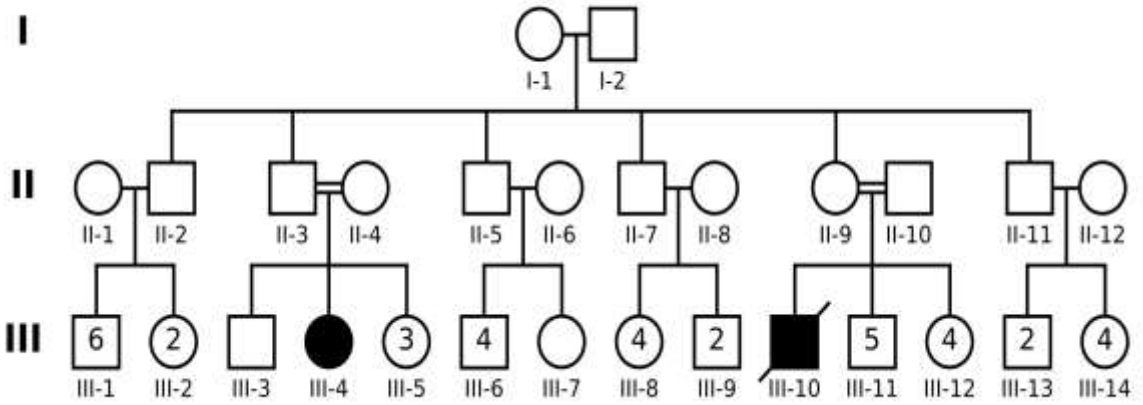



**Figure 7. Pedigrees of four families with intellectual disability (recorded in the field as 'mental retardation').**

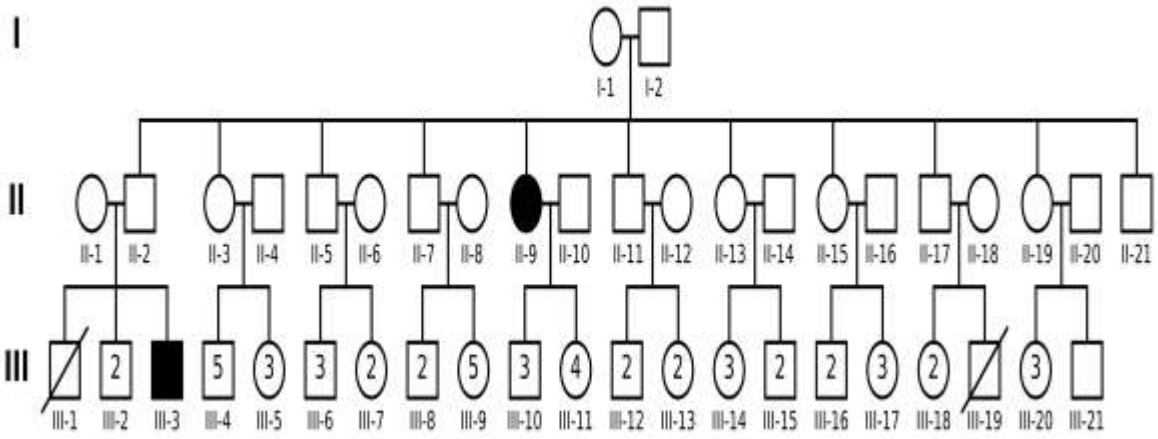



**Figure 8. Pedigree of the family with polydactyly (F11; Hawa Derai). No consanguineous union is recorded.**

## 4. Discussion

### 4.1 Principal findings

In eleven families from Tehsil Timergara, parental consanguinity was recorded for 84.1% of affected individuals and 70.0% of affected sibships, and in ten of eleven families at least one consanguineous parental union was present. Several pedigrees show features expected under autosomal recessive inheritance: multiple affected siblings of both sexes born to related, unaffected parents (F1, F3, F4, F7), recurrence in independent consanguineous unions within one extended family (F2, F10), and affected individuals in later generations after repeated consanguinity (F5).

The interpretation, however, depends on the background rate of consanguinity. Consanguineous marriage is the norm in this region: reported rates are 46.2% in Dir Lower district and 55% in Timergara tehsil [15], and about two-thirds in neighbouring Malakand [13]. A proportion of 70% among affected sibships (95% CI 48.1–85.5) is therefore only modestly above the background, and it differs nominally from the district rate ($p = 0.042$) but not from the tehsil rate ($p = 0.26$). With 20 sibships and two possible comparators, we regard this comparison as exploratory. The data are consistent with a contribution from consanguinity, but they cannot demonstrate it, and they cannot quantify excess risk, which requires a population-based design with unaffected comparison families, or a case-control comparison, or a cohort with enumerated denominators [6,8].

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### 4.2 Disorder-specific observations

**Albinism.** Oculocutaneous albinism has a worldwide prevalence of roughly 1 in 20,000 and is inherited as an autosomal recessive trait with several causative genes (including TYR, OCA2, TYRP1 and SLC45A2) [26,27]. Prevalence varies markedly between populations, for example between ethnic groups within South Africa [28]. Four affected siblings from a consanguineous couple (F1) fit this model, but the type of albinism cannot be assigned without ophthalmological and molecular assessment.

**Anophthalmia.** Anophthalmia and microphthalmia are genetically heterogeneous. SOX2 variants are the most frequent single cause overall, but biallelic ALDH1A3 variants are the leading cause of recessive disease in consanguineous families, including families of Pakistani origin [29–31]. The recurrence of anophthalmia in two independent first-cousin sibships of F2 is the most convincing recessive signal in our series. The affected woman III-1, born to apparently unrelated parents, shows why molecular testing is needed to determine whether one or two loci are involved.

**Baldness.** 'Baldness' is not a diagnosis. Congenital or early-onset hair loss in consanguineous families may be due to recessive variants in genes such as HR (atrichia with papular lesions), LIPH and LPAR6, which have been identified in Pakistani families [32–34], whereas alopecia areata is an autoimmune and multifactorial disorder and androgenetic alopecia is polygenic [35]. The sibships in F3 and F4 are compatible with recessive inheritance but could not be classified; trichoscopy and sequencing would be required, and our baldness data should be read as a description of familial hair loss of unspecified type.

**Deafness.** Hearing loss is among the most common congenital disorders; more than half of the childhood cases have a genetic cause, and most non-syndromic cases are autosomal recessive [36–38]. GJB2 (connexin 26) variants are a common cause in many populations [39], but the genetic profile differs between populations and cannot be inferred from pedigrees. The F5 pedigree, with nine affected individuals over three generations and two successive consanguineous unions, illustrates how repeated consanguinity creates pseudodominant patterns. The older field term 'deaf and mute' is no longer used, because deaf people are not mute and many use sign language.

**Intellectual disability.** Intellectual disability affects roughly 1% of the population [40], and autosomal recessive forms are a major cause in consanguineous populations, with hundreds of genes involved [41,42]. Exome sequencing in consanguineous Pakistani families has identified many novel candidate genes [43]. The four families of our series (F7–F10) share the common feature that most affected individuals came from consanguineous sibships, although F8 and F9 each also contain an affected individual from a sibship with no recorded consanguinity, which is expected in a genetically heterogeneous condition with substantial non-genetic causes.

**Polydactyly.** Non-syndromic polydactyly is mostly inherited as an autosomal dominant trait with variable expressivity and incomplete penetrance, and recessive forms are generally syndromic [24,25]. The affected aunt and nephew in F11 with an unaffected intervening parent point to reduced penetrance. This family illustrates that a heritable disorder can occur in a large family in which no consanguinity is recorded, and it was therefore not counted as evidence for the recessive hypothesis.

### 4.3 Implications for counselling and public health

The pedigrees describe families in which recessive disorders of high burden, such as severe intellectual disability and hearing loss, recur. Counselling for consanguineous couples is most effective when it is non-directive, respects the social role of cousin marriage, and provides information on the absolute risk, on carrier testing when the familial variant is known, and on early detection and rehabilitation [1,2,11]. Early hearing screening and developmental assessment would give the affected children in these families a chance for earlier intervention. Referral of the families in this study for diagnostic molecular testing could turn the

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pedigrees into a basis for cascade testing in the extended families.

## 5. Conclusions

In this pedigree-based study of eleven families from Tehsil Timergara, the parents of 84.1% of the 44 affected individuals and of 70.0% of affected sibships were consanguineous, and the pedigree patterns of ten of eleven families are consistent with autosomal recessive inheritance. Because families were ascertained through affected members, had no comparison group, and lacked clinical and molecular confirmation, and because background consanguinity in the region is already high, our data are consistent with but do not prove a causal contribution of consanguinity. They indicate a need for diagnostic genetic services, culturally sensitive counselling and population-based studies in Dir Lower.

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**Supplementary Material**

Supplementary Table S1 (family-level data) and Supplementary Table S2 (affected sibships: size, number affected, parental consanguinity) are provided in the accompanying workbook (OriginPro_data_workbook.xlsx).

| Village | Affected families | Affected individuals |
|---|---|---|
| Timergara city | 3 | 19 |
| Utala | 3 | 9 |
| Khungi | 1 | 4 |
| Katan | 1 | 4 |
| Dabar | 1 | 3 |
| Pengal | 1 | 3 |
| Hawa Derai | 1 | 2 |

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