Founder effect in 20 Afrikaner kindreds with pseudoxanthoma elasticum

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Summary

The pedigrees of 20 families with pseudoxanthoma elasticum (PXE) were investigated. The analyses involved 13 generations up to and including the initial settlers, who arrived in the Cape before 1660. Four settler surnames predominate in these pedigrees. Because of the marriage patterns of the settlers' descendants it was necessary to classify the four surnames into two groups. It is suggested that these two groups are the founder groups of present-day PXE patients. Similar genealogical studies have been performed on kindreds with familial polyposis, familial heart block and familial hypercholesterolaemia, among other disorders. Due to geographical isolation, political developments and cultural factors in the Afrikaner, these investigations are feasible and often lead to the identification of founder origin.

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Pseudoxanthoma elasticum (PXE) is a hereditary disorder of elastin first described by Rigal[1] in 1881. On histological examination, the elastin fibres of sufferers are fragile, tend to fragment and undergo a process of calcification resulting in loss of tissue elasticity. The disorder, although rare, has been described in many different ethnic groups and populations; the estimated incidence in the populations of the USA is 1:100 000.[2] The clinical manifestations are usually evident from late childhood. The cutaneous lesions are progressive and result in a *peau d'orange* mottling of the flexural areas of the neck, axilla, antecubital fossa, popliteal area and groins. The skin usually becomes lax, thickened, and cosmetically unsightly. Angioid retinal streaks usually appear in the 2nd decade of life. These lesions weaken the vascular infrastructure and increase the risk of haemorrhage and neovascular changes. Gradual visual loss may occur, leading to severe handicap after the third decade of life. In addition, intimal degeneration of small- and medium-sized blood vessels contributes to loss of peripheral pulses, hypertension, intermittent claudication, coronary insufficiency and various stroke phenomena.

In a nation-wide survey of PXE in England and Wales, Pope[3-5] was able to differentiate clinically two autosomal recessive and two autosomal dominant forms of the disorder. A further autonomous entity in which profound ophthalmological sequelae occurred was later described in the Afrikaner population of South Africa by Viljoen *et al.*[6] From pedigree analyses of over 60 individuals it is apparent that this latter condition is autosomal recessive and the prevalence is remarkably high in this group. For cultural, religious and geographical reasons the Afrikaner is an isolate population. Accurate genealogical records are available from the time of the original Dutch settlement of the Cape in the 17th century. These factors provide ideal circumstances for the investigation of possible founder effect in a disorder such as PXE within the Afrikaner community. For these reasons a detailed genealogical study of 23 Afrikaner families in whom PXE is prevalent was undertaken. Our findings are documented here.

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Subjects and methods

Twenty-three pedigrees of families with PXE were studied of which 20 were derived from the records of the MRC Unit for Inherited Skeletal Disorders at the University of Cape Town and 3 from Tygerberg Hospital, Parowvallei, CP. After the identification of an affected individual (the proband) in each pedigree and working on the assumption that each proband was homozygous for the recessive gene, the lineage was sought from both the paternal and maternal branches of each kindred. In all 23 pedigrees the families denied having knowledge of previous generations affected with PXE, although siblings were affected in many instances. It was thus necessary to study each ancestral line starting from the parents of the proband and to work retrospectively through the generations.

The analyses were undertaken in two ways. In the first instance, every proband was visited and interviewed. Other relatives who were able to furnish further family details were then visited. Data relating to 3-5 previous generations was obtained in this manner.

Thereafter, intensive archival research was undertaken in the files of the Master of the Supreme Court, the State Archives and the Dutch Reformed Church Archives of the Cape and Transvaal provinces of South Africa. Through these sources, it was possible in some instances to gather data relating to 13 generations of each ancestral line. This was accomplished in 14 pedigrees, i.e. 28 parental ancestral lines.

In a further 6 pedigrees either the paternal or maternal line could not be researched. In some instances, failure was due to the location of family records in the Orange Free State, where the archive sources have not yet been researched (4 paternal lines). In another kindred, archival records were located in Namibia (1 maternal line) and, in a further family, the parental roots were overseas (1 paternal line). Thus 6 out of 12 possible ancestral lines in this group were studied. A total of 34 lines in 20 families were thus fully investigated.

Three pedigrees had to be discarded, primarily because the family data were logistically difficult to research.

Results

Archival searches were deemed to be complete once a link was made to previously researched family genealogies or to the De Villiers and Pama[7] record of genealogies of old South African families. These references allowed identification of the initial settlers/original ancestors in each of the 34 lines of the 20 probands under study. On compilation of a table of these individuals, 4 surnames predominated, namely M, B, V, and S (Figs 1-4). Each of these settlers had a number of children

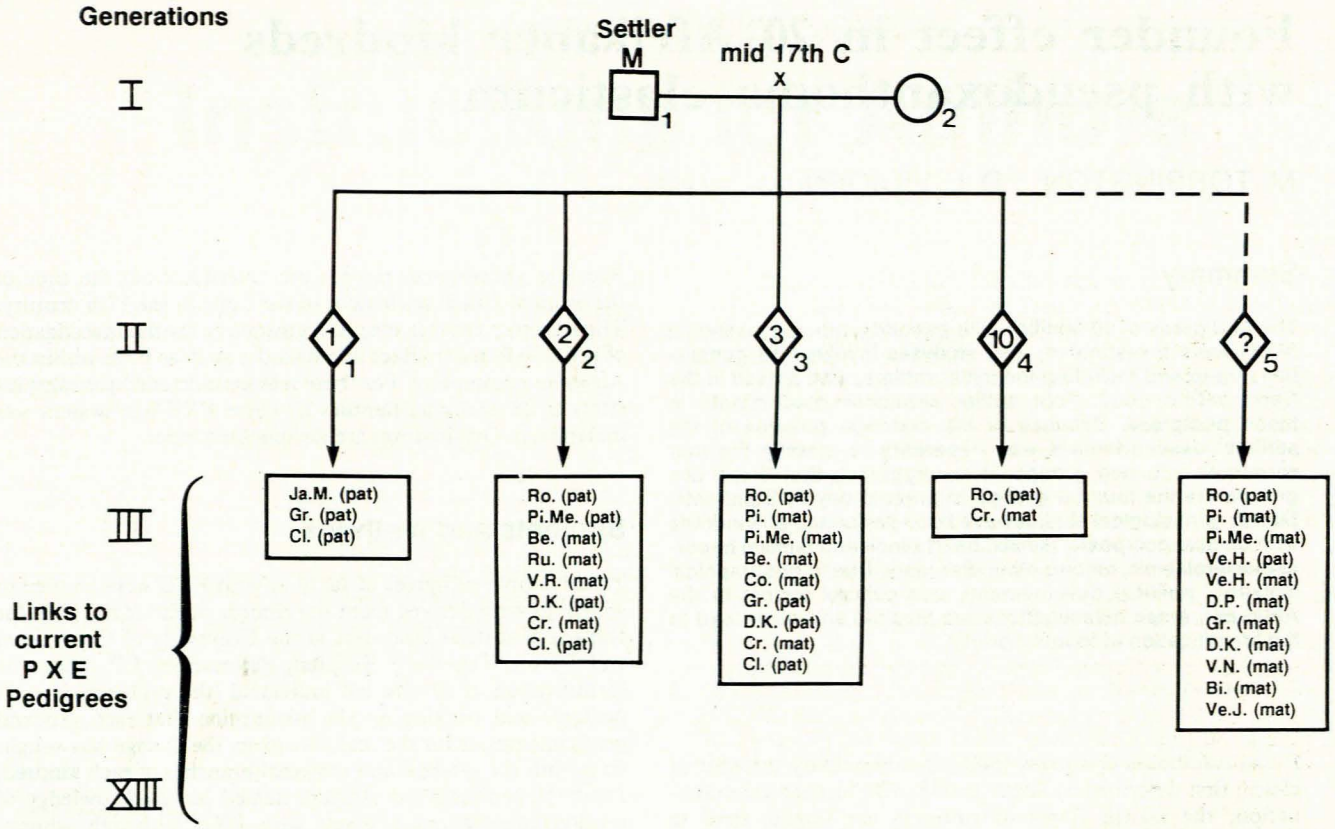


Fig. 1. Ancestral links to current PXE families (Settler M).

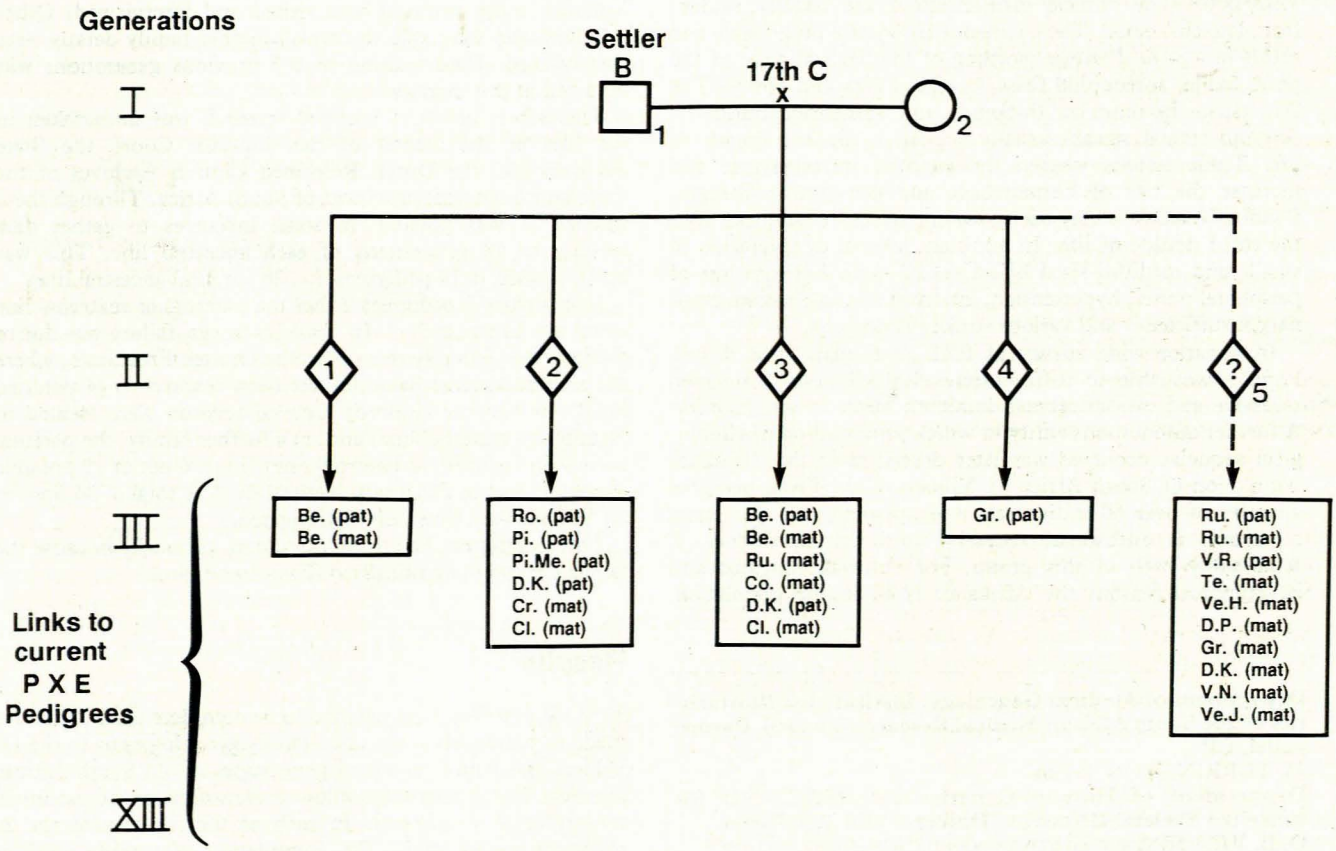


Fig. 2. Ancestral links to current PXE families (Settler B).

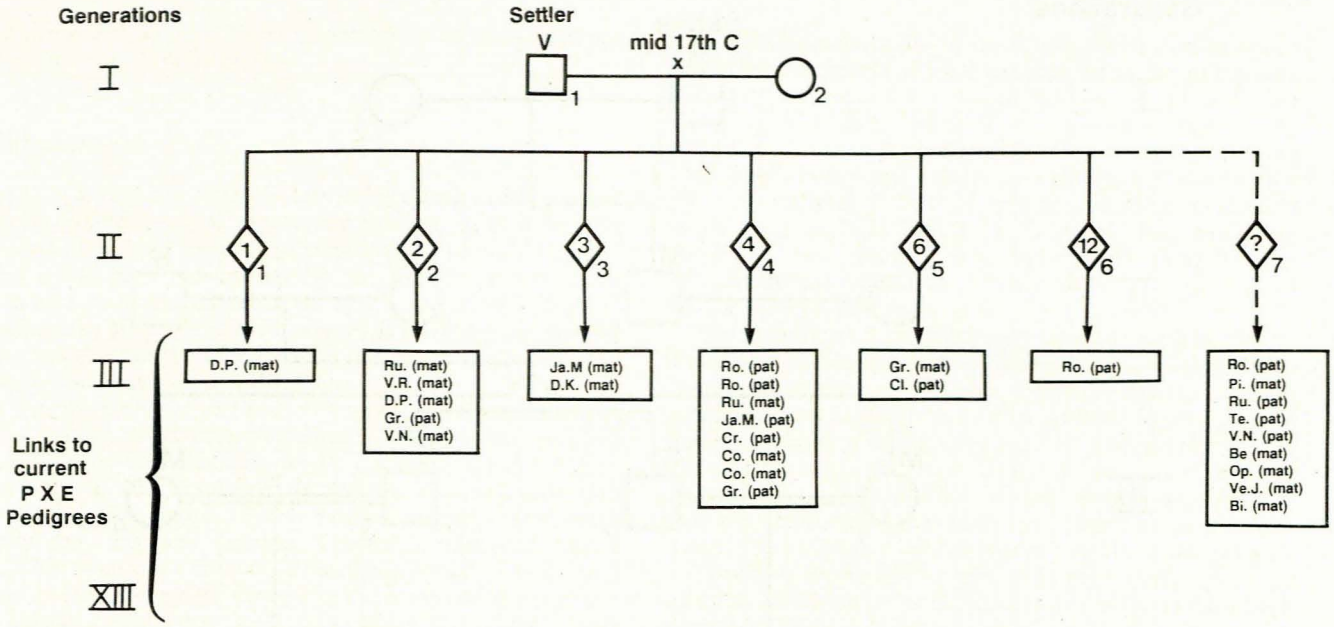


Fig. 3. Ancestral links to current PXE families (Settler V).

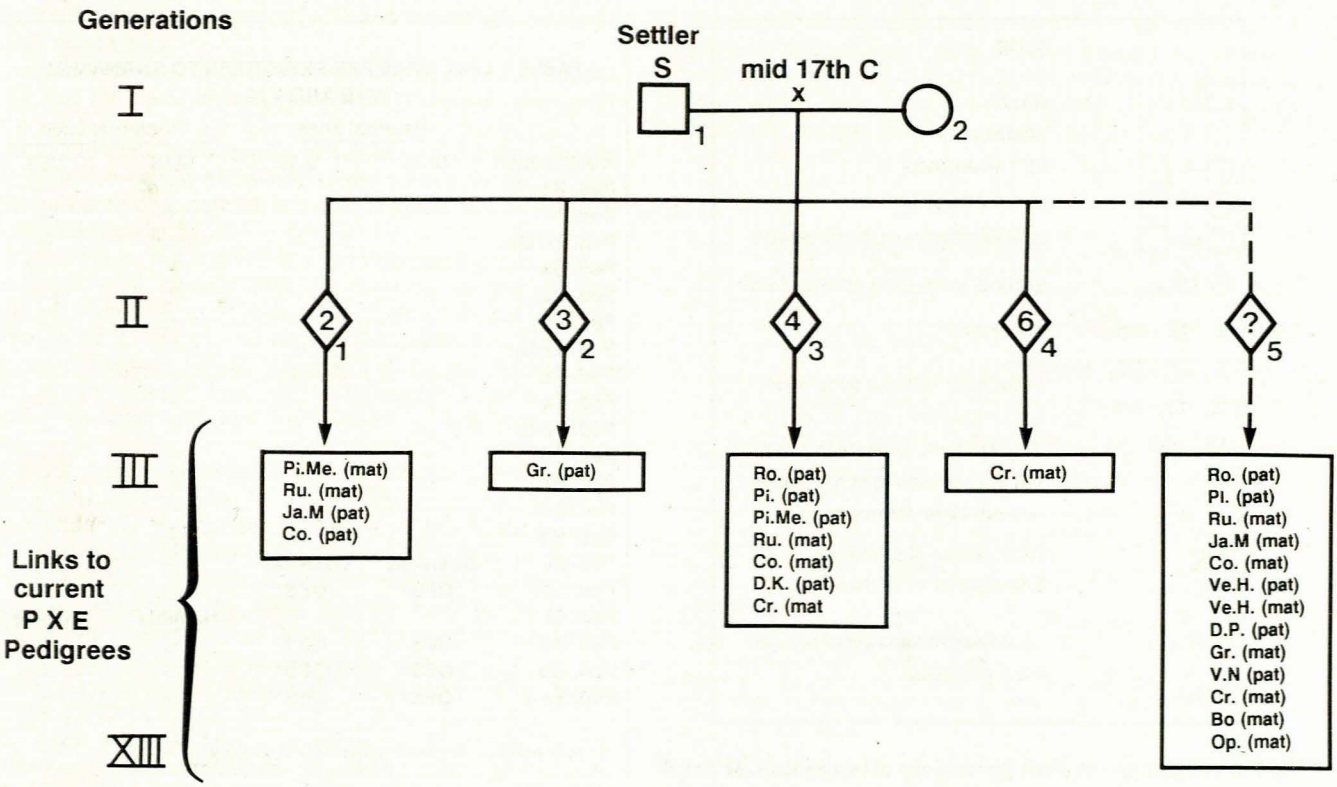
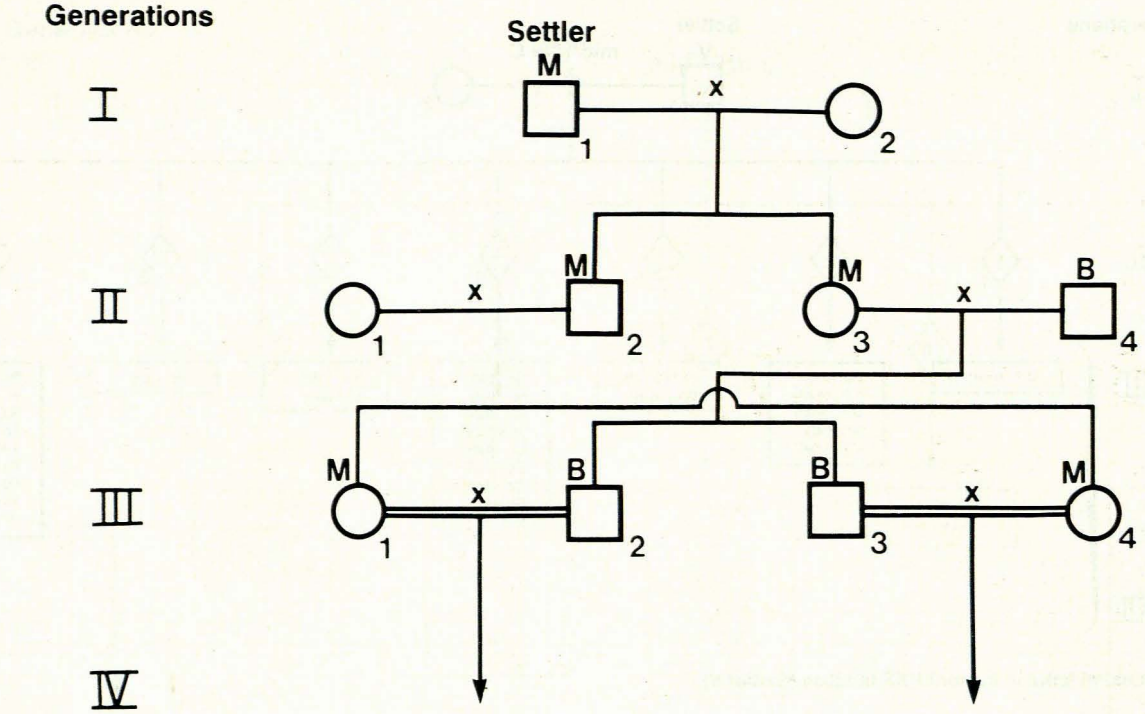


Fig. 4. Ancestral links to current PXE families (Settler S).

shown at gen II. The position of the child within the sibship has been given within the symbol. Thus in Fig. 1 II4 is the 10th child of settler M. Two current PXE pedigrees, namely Ro and Cr, have this child as their common ancestor, Ro through the paternal line and Cr through the maternal line. The 34 PXE ancestral lines (15 paternal lines and 19 maternal lines) were found to be linked to some of the children of each ancestor M, B, V and S.

Occasionally the retrospective tracing of a PXE proband lineage was linked to an individual with surname M, B, V, or S, but linkage could have occurred at any generation level. In these instances factors such as migration, wars and unrecorded births made the tracing of records linking the latter individual and the original ancestor impossible. This necessitated the grouping of such individuals into columns headed '5?' and '7?' in Figs 1 - 4. Although the link to the founder had not been established, it is certain that at this early stage of Afrikaner history the individuals listed in column '?' were from the



CODE

- MALE
- FEMALE
- 1 ST MARRIAGE
- 2ND MARRIAGE
- CONSANGUINEOUS MARRIAGE
- Second, tenth child of settler, etc.
- Generation
- Individuals within a generation
- This surname appears in pedigree but link to a child of the settler has not been determined.
- Pat — Paternal line of proband
- Mat — Maternal line of proband
- Ja.M, Gr, Cl., etc — Identification lettering of current P X E pedigrees

Fig. 5. Intermarriages in three generations of two settlers, M and B.

TABLE I. LINK OF 20 PXE PEDIGREES TO SURNAMES M/B AND V/S

	Paternal lines		Maternal lines	
Identification	M/B	V/S	M/B	V/S
Ped. Ro	4	4	4	–
Ped. Pi	4	4	4	+
Ped. Pi/Me	4	4	4	+
Ped. Be	4	–	4	–
Ped. Ru	4	+	4	+
Ped. V.R.	4	–	4	+
Ped. Ja M.	4	+	–	+
Ped. Co	–	+	+	+
Ped. Te	–	+	+	–
Ped. Ve H	+	+	+	–
Ped. D.P.	–	+	+	+
Ped. Gr	+	+	+	+
Ped. D.K.	+	+	–	+
Ped. V.N.	–	+	+	+
Ped. Bi	**Overseas***	**Overseas***	+	+
Ped. Cr	**OFS***	**OFS***	+	+
Ped. Cl	+	+	**Namibia***	**Namibia***
Ped. Bo	**OFS***	**OFS***	–	+
Ped. Op	**OFS***	**OFS***	–	+
Ped. Ve.J	**OFS***	**OFS***	+	+

+ = positive link; – = no link to ancestors; * = not traced.

original founder(s). Most pedigrees extended to 13 generations with the probands appearing at generations XI and XII, respectively.

The 4 identified surnames, however, did not appear as free independent family names because of recurrent consanguinity. For example, there were several instances of intermarriage between families M and B in the late 17th century (Fig. 5). At generation II, settler M's daughter II3 had married settler II4. Their children at generation III married first-degree cousins, III2 and III4 being 2 sisters marrying 2 brothers III2 and III3 respectively. Too complex to demonstrate, consanguineous marriages occurred frequently in each pedigree over several generations and were also observed between surnames V and S. These intermarriages obscured the identification of two independent founder members and made it necessary to group the four surnames into two sets, M/B and V/S (Table I). In the 15 PXE male ancestral lines studied and the 19 PXE female lines, the surnames M/B appeared 11 and 15 times, respectively (73% and 79%). The surnames V/S appeared 13 and 15 times, respectively (87% and 79%). Even taken individually, these 4 surnames were shown to link up as follows: surname M appeared in 33 of the possible 34 ancestral lines;

surname B in 25 of 34 lines; surname V in 28 of 34 lines; and surname S in 26 of 34 lines.

Discussion

PXE is a disorder with protean clinical manifestations and severe ophthalmological, cardiac and cosmetic implications. The disorder has been intensively investigated in South Africa[8-11] and it has been recognised that an autonomous, autosomal recessive form occurs relatively commonly in the Afrikaner community. At present no biochemical or molecular markers are available for the identification of heterozygous carriers or preclinical homozygous individuals.

Twenty Afrikaner probands were genealogically investigated. The history of Afrikaner settlement in the subcontinent of Africa lends understanding to the dissemination of the gene for PXE in this population. In the late 17th and early 18th centuries, the original Dutch settlers migrated northwards from the Cape and followed a nomadic existence until a suitable habitat was found. Great distances had to be covered due to the shortage of water, and the communities that were eventually established were geographically isolated. Other factors, such as cultural considerations, language differences and religious practices, further maintained the isolation of the Afrikaner. Consanguineous marriages were common and the frequency of rare homozygous affected individuals increased in this community.

In the 19th and 20th centuries, large urban communities arose and the social organisation of the Afrikaner community changed. Cross-cultural admixture occurred freely and randomly, and there were fewer consanguineous matings. Family size also decreased. All these factors tended to 'dilute' the abnormal gene pool established earlier through various selection forces and founder effect.

In this study, it was possible — by constructing genealogical pedigrees — to identify both the common ancestors in the kindreds with PXE and the original founder members of PXE in South Africa. Figs 1 - 4 illustrate the manner in which each ancestor (designated M, B, V and S) had specific children who were identified and from whose descendants the maternal and/or paternal branches were linked to individuals with PXE.

During this investigation it was not possible to separate the families M and B, and V and S. There are two possible explanations for this finding. Firstly, that two of the original four settlers fortuitously brought the PXE gene to South Africa. Secondly, a single individual heterozygous for PXE may have settled in the Cape and the high prevalence of consanguinity together with large family numbers may have increased the abnormal gene frequency rapidly.

The identification of M/B and V/S as the founder individuals in PXE adds to the growing list of genetic disorders that have been studied from a genealogical viewpoint in the Afrikaans-speaking community. Founder members have already been identified for familial polyposis of the colon[12] and familial heart block.[13] Familial hypercholesterolaemia in a religious isolate has been described in this group.[14] The current search for founder members of PXE has also led to the unexpected finding of an association between familial cancers and some PXE families. This finding forms part of a thesis to be submitted by one of the authors (D.L.V.) to the University of Cape Town in the near future. In addition, the other author (M.T.) has identified the PXE founder individuals as those in whose descendants familial pre-menopausal breast cancer has occurred. These findings have as yet to be published but substantiate the association between familial cancer and/or familial breast cancer and PXE.

The identification of families at risk for various genetic disorders will allow preventive programmes to be instituted in South Africa when appropriate molecular markers become available. These findings can also be extended to the European countries of origin of the Cape settlers. Recent collaborative research with geneticists in Belgium[15] has confirmed the presence of a form of PXE in that community, which is clinically indistinguishable from that described in the Afrikaners. This supports the hypothesis that the abnormal gene originated in the Low Countries of Europe. Indeed, the four ancestors identified in South Africa were emigrants from Oud-Beyerland, Lübeck, Maastricht and Ommen respectively.

At present, heterozygous carriers of PXE cannot be identified clinically or through the use of sophisticated biomolecular techniques. However, investigations are under way using elastin and collagen molecular probes, which may eventually allow elucidation of the defective gene. When the technology becomes available to identify either heterozygous carriers or homozygous affected individuals, then at-risk families identified in this study can be appropriately investigated and counselled.

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