# Familial defective apolipoprotein-B is rare in hypercholesterolaemic South African Afrikaners, coloureds and Indians

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The frequency of familial defective apolipoprotein B-100 (FDB) was assessed among hypercholesterolaemic Afrikaners, coloureds and Indians. Patients selected for screening did not carry any of the founder or common LDL-receptor mutations known to be associated with these groups. No FDB was detected and the mutation is therefore a rare cause of hypercholesterolaemia in these South African populations.

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Familial defective apolipoprotein B-100 (FDB) is characterised by the presence of LDL particles that carry apolipoprotein B-100 with the $arg_{3500}$-glu mutation; these have a markedly lower affinity for the LDL receptor and are cleared abnormally slowly from the circulation.[1] Heterozygotes for this disorder present with hypercholesterolaemia and clinical sequelae such as xanthomata with a frequency and severity similar to that found in heterozygotes with familial hypercholesterolaemia (FH), a disorder caused by LDL-receptor mutations.[2-4] Some individual cases, however, have been reported in which FDB heterozygotes[5] and one homozygote[6] had relatively moderate hypercholesterolaemia. The incidence of FDB is about 1/500 - 1/700 in North America and Europe.[3] Detailed haplotype analysis of mutant apo B alleles from many FDB individuals suggests that this is a founder-type mutation that occurred only once on an ancestral chromosome.[7] The frequency of such a mutation in different populations is likely to be governed by founder effects and random genetic drift and should vary greatly. Indeed this mutation has not been

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detected in Finns,[8] Japanese[9] or Israelis.[10] Consequently, in order to determine the impact of this mutation in South Africa, its frequency was determined in hypercholesterolaemic Afrikaners, coloureds and Indians with or without xanthomata.

## Methods

All patients were unrelated and attended lipid clinics in Cape Town, Durban and Johannesburg. Individuals were considered Afrikaner, coloured or Indian only if both parents belonged to that population group. The so-called coloured population of South Africa are of mixed racial descent and have genes of indigenous Africans and of European and Indonesian settlers. The Indian population is descended from Indian immigrants who arrived in South Africa between 1860 and 1911. Blood was taken after informed consent had been obtained, and with ethical approval by the appropriate institution.

DNA isolation from blood was carried out as described by Talmud *et al.*[11] FDB was screened for as described by Hansen *et al.*[12] and Tybjaerg-Hansen *et al.*[13] The FH Afrikaner-1, FH Afrikaner-3 and FH Cape Town-2 mutations were assayed as described previously.[14,15] The FH Afrikaner-2 mutation was detected by means of an amplification refractory mutation system (ARMS) polymerase chain reaction assay.[16] All Indian patients were screened for the FH Zambia mutation, as described by Rubinsztein *et al.*[17]

## Results and discussion

Hypercholesterolaemic South African Afrikaner, coloured and Indian patients were selected for screening for FDB after individuals who had any one of the common or founder LDL-receptor mutations known to be associated with these groups[14,15,17-19] had been eliminated (Table I). These individuals were classified as having either definite monogenic hypercholesterolaemia or type 2A hyperlipidaemia. Individuals were considered to have definite monogenic hypercholesterolaemia, i.e. either FH or FDB, if they had total cholesterol concentrations greater than 7,5 mmol/l or LDL-cholesterol concentrations greater than 5,2 mmol/l, together with xanthomata or thickened tendons in themselves or in a first-degree relative. Cholesterol concentrations above these limits are compatible with FH.[20] Three founder LDL-receptor mutations, FH Afrikaner-1, -2 and -3, account for approximately 90% of the FH in Afrikaners.[14,21] These three mutations and the FH Cape Town-2 mutation have been found in the coloured population (D. J. van der Westhuyzen and M. J. Kotze — unpublished data). Therefore, all patients with these mutations were eliminated from the study. The only mutation detected so far in more than one South African Indian family is FH-Zambia.[17] Similarly, all Indian patients with this mutation were not considered. None of the patients listed in Table I was found to have FDB. Therefore, all patients with definite monogenic hypercholesterolaemia are likely to have rare sporadic LDL-receptor mutations. FDB has been detected in two unrelated families in South Africa of mixed English and Afrikaner descent.[4,22] It was impossible to determine the geographical or genetic origin of the mutation in these two cases.

**Table I. Summary of South African lipid clinic patients screened for FDB***

| | Definite MH‡ | 'Type 2a'¶ |
|---|---|---|
| Afrikaners† | 20§ | 23 |
| Coloureds† | 8 | 8 |
| Indians† | 6 | 16 |

* All patients listed in this table were negative for FDB.
† All Afrikaner and coloured patients were screened for the FH Afrikaner-1, -2 and -3 founder mutations prior to analysis for FDB. Coloured patients were also screened for FH Cape Town-2. Indian patients were screened for the FH Zambia mutation. All patients positive for any of these LDL-receptor mutations were excluded from this analysis.
‡ Definite MH (monogenic hypercholesterolaemia) patients had total cholesterol > 7,5 mmol/l or LDL-cholesterol > 5,2 mmol/l together with xanthomata or thickened Achilles tendons in themselves or a first-degree relative.
¶ Type 2a patients had total cholesterol > 7,5 mmol/l or LDL-cholesterol > 5,2 mmol/l and triglycerides < 2,3 mmol/l without xanthomata in themselves or a first-degree relative.
§ Includes 13 patients screened by Graadt van Roggen *et al.*[14]

The frequencies of FDB and FH in North America and Europe are both about 1/500,[3,23] and the two diseases are clinically almost indistinguishable in terms of the presence of xanthomata.[2,3] In such populations, one would expect therefore to find equal numbers of FDB and FH alleles in hypercholesterolaemic individuals with xanthomata from which FH patients with common or founder LDL-receptor mutations were excluded. Since we detected no such patients with FDB, this disorder is probably not as common in Afrikaners, coloureds and Indians as sporadic FH. Also, because no FDB was detected in patients with type 2A hyperlipidaemia without xanthomata, it is likely that the frequency of FDB in these populations is less than 1/500. The possibility exists that FDB does occur with a higher frequency in these groups, but does not cause hypercholesterolaemia or xanthomatosis uniquely. We consider this possibility unlikely.

Since FDB is a founder-type mutation,[7] its frequency is likely to vary between different populations. To our knowledge, FDB has not been detected yet among Finns,[8] Japanese[9] or Israelis[10] and no studies have been reported for Indians or black Africans. It is possible that this mutation might have occurred after the events that gave rise to the different racial groups. The absence of FDB in the Afrikaners and coloureds could have arisen from a 'negative' founder-effect that diluted the frequency of this gene in the settlers relative to their parent European populations. We conclude that FDB is a rare cause of hypercholesterolaemia in these South African populations.

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