# Comparative Gene Map of Hypertriglyceridaemia

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**Abstract. Elevated triglyceride levels in the circulation are currently recognized as an independent risk factor for coronary artery disease. Hypertriglyceridaemia represents one of the attributes of metabolic syndrome and is present in the most common genetic dyslipidaemia, the familial combined hyperlipidaemia. The factual concentration of triglycerides is determined by a complex interaction of environmental and genetic components. Deeper understanding of the causative gene variants and the mode of their participation in the pathogenesis of hypertriglyceridaemia is required for devising efficient therapy of hypertriglyceridaemia. This is the first systematic review of linkage and candidate gene studies dealing with the dissection of genetic determinants of (hyper)triglyceridaemia in human and two major mammalian model species, mouse and rat. Based on the merged sets of data, a synthetic view of the genetic component of triglyceridaemia, the "hypertriglyceridaemia gene map", is presented.**

An elevated level of triglycerides (triacylglycerols, TG) in circulation is currently recognized as an independent risk factor for coronary artery disease (Hokanson and Austin, 1996; Jeppesen et al., 1998). Together with low concentrations of high density lipoprotein (HDL) cholesterol and small, cholesteryl ester-depleted low density lipoprotein (LDL) particles, hypertriglyceridaemia forms the "lipid triad" or atherogenic lipid phenotype (MIM 108725), a constituent attribute of metabolic syndrome, a prevalent complex condition comprising several metabolic and haemodynamic derangements. High concentrations of TG are also found in familial combined hyperlipidaemia (FCHL), the most frequent genetic dyslipidaemia. The triglyceridaemia itself is quite a complex phenotype, as it reflects the abundance of various classes of particles in circulation – mainly chylomicrons, very low-density lipoproteins (VLDL) and intermediate density lipoproteins (IDL), collectively called triglyceride-rich lipoproteins. It is becoming clear that though entangled within a network of mechanisms, there indeed is a strong genetic component affecting the factual triglyceridaemia. The heritability of this trait in human population is about 40%, as evidenced in several studies (Shearman et al., 2000; Newman et al., 2003), leaving a relatively important role also for the effects of environment and gene-environment interactions. A comprehensive study of such complex metabolic trait with a strong environmental component in general human population is an arduous process with a number of limiting factors, including genetic heterogeneity, low penetrance, and often limited statistical power (Glazier et al., 2002). Several of the major obstacles can be partially overcome in studies dealing with relative population isolates. These usually represent the descent of a small founder group such as the Hutterites in South Dakota (Newman et al., 2003) or the Saguenay-Lac-St-Jean population of French Canadians in Quebec, Canada (Pausova et al., 2001, 2002). On the other hand, the advantage may as well become a liability, as the possible presence of a strong founder effect may hamper the relevance of the identified allelic variants for different ethnic groups and general population as such.

Though some progress has been made and several studies identified major genes potentially involved in determination of triglyceridaemia, as discussed below, our knowledge of its overall genetical architecture is far from satisfactory. As in the case of other complex diseases, defined animal models are proving to be invaluable in the deciphering of pathways, genes, gene-gene and gene-environment interactions involved in pathogenesis of hypertriglyceridaemia (Cowley, 2003). The advent of integrative genomics brings along the possi-

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Abbreviations: Apo – apolipoprotein, BN – Brown Norway, BB/OK – Bio Breeding rat, *Cd36/Fat* – fatty acid translocase, DA – dark agouti, FCHL – familial combined hyperlipidaemia, HDL – high density lipoprotein, hHTG – hereditary hypertriglyceridaemic rat, HAS – human chromosome, IDL – intermediate density lipoprotein, LDL – low density lipoprotein, LOD – likelihood of odds, MMU – mouse chromosome, OLETF – Otsuka-Long-Evans-Tokushima fatty, PD – polydactylous rat, QTL – quantitative trait locus, RNO – rat chromosome, SHR – spontaneously hypertensive rat, SNP – single nucleotide polymorphism, TG – triglyceride, VLDL – very low density lipoprotein, WOKW – Wistar-Ottawa-Karlsburg rat.

bility to cross-annotate *in silico* sets of human, mouse and rat biological and genomic data in order to produce novel findings (Nobrega and Pennacchio, 2003; Twigger et al., 2004). The information gathered from the different strains is thus not redundant, for each of the strains represents a particular combination of alleles leading, with a specific pattern of sensitivity to external stimuli such as diet (Pausova et al., 2003) or stress (reviewed in Hamet and Tremblay, 2002) and temporal/ontogenetic factors (Hamet et al., 1998), to a unique manifestation of the studied trait, i.e. the dyslipidaemic profile including the elevated concentrations of triglycerides.

There are several ways to identify the genomic regions harbouring genes responsible for the quantitative trait variation. Two basic concepts – the candidate gene approach and the linkage analysis – are the most commonly used (often both sequentially within one study, i.e. identifying and testing positional candidate genes arising from a previous QTL analysis), each having different pros and cons. Moreover, several novel approaches have emerged lately aiming at more biologically appropriate, sophisticated mathematical models (Gagnon et al., 2003; Beaumont and Rannala, 2004). The detailed consideration of the peculiarities of different statistical approaches of the two broad concepts are beyond the scope of this review and have been reviewed recently (e.g. Borecki, 2003).

This review aims to add a systematic account of the genetic component of triglyceridaemia to the similar efforts already undertaken for complex traits such as obesity (Snyder et al., 2004), hypertension (Rapp, 2000) or LDL particle heterogeneity (Bosse et al., 2004b). In addition to a mere summing up of the known, the aspects otherwise "dissolved" in the multitude of published data may be elucidated.

## The association/candidate gene studies

The association studies represent a group of analyses where the association between a measured genetic variant (e.g. single nucleotide or other polymorphism) and a "disease" or phenotype is tested. The ultimate goal (as in the case of linkage studies) is the identification of a causal genetic variant with respect to the studied trait. Even if the exact variant in the previously ascertained locus is not measured directly, it will be in linkage disequilibrium with a marker that can be conveniently measured (Borecki, 2003). This is the reason why the association studies are mostly used for evaluation of candidate genes. In case of hypertriglyceridaemia, candidate genes arise from *a.* the current knowledge of TG metabolism and trafficking in the organism: apolipoproteins, lipases, several classes of nuclear receptors, etc. (functional candidates) *b.* information on the genomic locus harbouring gene(s) affecting TG levels (positional candidates). More than 60 genes associated with TG up to date are summarized in Table 1. Only positive associations are shown, effort has been made to include the chronologically first work showing the association. Most of the entries in Table 1 represent findings primarily from human studies, but genes with variants influencing TG first ascertained in mice (e.g. angiopoietin-like 3, ANGPTL3) or rats (e.g. fatty acid translocase CD36) are also included.

## The linkage studies

The linkage studies aim to identify genomic region(s) harbouring genetic variants, which are causally related to the analysed trait (disease). The advantages inherent in this "discovery-driven" method may be that it is basically hypothesis-free and can point to novel loci/genes with an effect on the trait that would not have been considered at all under the "hypothesis-driven" candidate gene approach. However, one of the major hindrances of the linkage analysis lies in the determination of the statistical relevance of the results (Fallin and Pulver, 2003). The summary of the major linkage studies in three species, human, mouse and rat follows.

## Human

More than a dozen genome-wide linkage studies assessing triglyceridaemia as a trait have been performed so far in the human subjects. A number of loci with a suggested major effect on TG levels have been identified, as summarized in Table 2. Several of the studies produced results seemingly converging to human chromosomes 7, 11 and 15.

Recently, using a variance component linkage analysis, Sonnenberg et al. (2004) found a QTL affecting both plasma TG (LOD 3.7) and LDL-cholesterol variation at chromosome 7q35-q36. These observations confirm the results of two earlier studies as they point to the same genomic location: first, in a cohort of Mexican Americans, Duggirala et al. (2000) identified a locus harbouring susceptibility genes for hypertriglyceridaemia; second, in the 332 largest families from Framingham Heart Study, the highest multipoint variance component LOD scores of 1.8 and 2.5 were ascertained for triglyceridaemia and triglyceride/HDL ratio, respectively (Shearman et al., 2000). By reanalysing the original Framingham data, Lin (2003) confirmed the linkage of HSA 7 and 20 regions and identified an extra QTL located on chromosome 6 that appeared to influence the co-variation of HDL-C and TG in the Framingham population. Arya et al. (2002) found evidence for linkage (LOD = 3.2) of the factor involving TG and HDL (as derived from the principal component factor analysis) to a genetic location on chromosome 7, however in a region distinct from those reported above.

Austin et al. (2003) have provided evidence for the linkage of TG to two locations on chromosome 15 (LOD scores of 2.56 and 2.44) in a set of 26 American kindreds with familial hypertriglyceridaemia, confirming previous findings in 27 Mexican American families (LOD 3.88) from San Antonio Family Diabetes Study

*Table 1. Alphabetically sorted list of genes shown to have variants associated with variation in triglyceride levels. *...based on comparative mapping only; mt…mitochondrial genome.*

| Gene symbol | Gene Name | Human | Rat | Mouse | Reference |
|---|---|---|---|---|---|
| **ABCA1** | ATP-binding cassette transporter 1 | 9q31.1 | 5q24 | 4 (23.1 cM) | Clee et al., 2001 |
| **ABCC6** | ATP-binding cassette, subfamily C, member 6 | 16p13.1 | 1q22 | 7 | Wang et al., 2001 |
| **ABCC8** | ATP-binding cassette, subfamily C, member 8 | 11p15.1 | 1q22 | 7 (41.0 cM) | Meirhaeghe et al., 2001 |
| **ACE** | Angiotensin converting enzyme | 17q23.3 | 10q32.1 | 11 (65.0 cM) | Katsuya et al., 1995 |
| **ACP1** | Acid phosphatase | 2p25 | 6q16 | 12 (A2) | Bottini et al., 2002 |
| **ADRB2** | Adrenergic beta-2- receptor | 5q32-q33 | 18q12.1 | 18 (34.0 cM) | Yamada et al., 1999 |
| **ADRB3** | Adrenergic beta-3- receptor | 8p12-p11.2 | 16q12.3 | 8 (10.0 cM ) | Kim-Motoyama et al, 1997 |
| **ALMS1** | Alstrom syndrome 1 | 2p13 | 1q41 | 6 (D1) | Weinstein et al., 1969 |
| **ANGPTL3** | Angiopoietin-like 3 | 1p32 | n.a. | 4 (C6) | Koishi et al., 2002 |
| **APOA1** | Apolipoprotein A-I | 11q23.3 | 8q23-q24 | 9 (27.0 cM ) | Utermann et al., 1982 |
| **APOA2** | Apolipoprotein A-II | 1q23 | 13q24 | 1 (92.6 cM) | Ferns et al., 1986 |
| **APOA4** | Apolipoprotein A-IV | 11q23 | 8q22 | 9 (27.0 cM ) | Menzel et al., 1988 |
| **APOA5** | Apolipoprotein A-V | 11q23 | 8q23 | 9 (A5.3) | Pennacchio et al., 2001 |
| **APOB** | Apolipoprotein B | 2p24.1 | 6q14 | 12 (A1.1) | Law et al., 1986 |
| **APOC3** | Apolipoprotein C-III | 11q23.3 | 8q23-q24 | 9 (27.0 cM) | Henderson et al., 1987 |
| **APOC4** | Apolipoprotein C-IV | 19q13.2 | 1q21* | 7 (4.0 cM) | Kamboh et al., 2000 |
| **APOE** | Apolipoprotein E | 19q13.2 | 1q21 | 7 (4.0 cM) | Utermann et al., 1979 |
| **APOH** | Apolipoprotein H | 17q24 | 10q32.1* | 11 (63.0 cM) | Cassader et al., 1994 |
| **ASP** | Acylation stimulating protein | 19p13.3-p13.2 | 9q11* | 17 (34.3 cM) | Murray et al., 1999 |
| **CD36** | Fatty acid translocase CD36 | 7q11.2 | 4q11 | 5 (2 cM) | Aitman et al., 1999 |
| **CREB1** | cAMP response element binding protein 1 | 2q34 | 9q32 | 1 (31.0 cM) | Herzig et al., 2003 |
| **CYP27A1** | Sterol 27-hydroxylase | 2q35 | 9q33 | 1 (43.1 cM) | Repa et al., 2000 |
| **CYP7A1** | Cholesterol 7alpha-hydroxylase | 8q11.2 | 5q12 | 4 (A1) | Couture et al., 1999 |
| **DGAT1** | Diglycerol O-acyltransferase 1 | 8q24.3 | 7q34 | 15 (46.9 cM) | Smith et al., 2000 |
| **DGAT2** | Diglycerol O-acyltransferase 2 | 11q13.3 | 1q32 | 7 (E1) | Stone et al., 2004 |
| **EPHX2** | Soluble epoxide hydrolase | 8p21 | 15p12 | 14 (32.5 cM) | Sato et al., 2004 |
| **FABP2** | Fatty acid binding protein 2 | 4q27 | 2q42 | 3 (55.0 cM) | Hegele et al., 1996 |
| **FATP1** | Fatty acid transport protein 1 | 19p13.12 | 16p14 | 8 (B3.3) | Meirhaeghe et al., 2000 |
| **FATP4** | Fatty acid transport protein 4 | 9q34.13 | 3p12* | 2 | Gertow et al., 2004 |
| **F-VII** | Factor VII | 13q34 | 16q12.5 | 8 (7.0 cM) | Humphries et al., 1994 |
| **G6PT** | Glucose-6-phosphatase | 17q21 | 10q32.1 | 11 | Smit et al., 1993 |
| **mtGPAT** | Mitochondrial glycerol-3-phosphate acyltransferase | 10q25.3 | 1q55 | 19 (52.0 cM) | Hammond et al., 2002 |
| **GYS1** | Muscle glycogen synthase | 19q13.3 | 1q22* | 7 (23.0 cM) | Orho-Melander et al., 1999 |
| **GYS1** | Muscle glycogen synthase | 19q13.3 | 1q22* | 7 (23.0 cM) | Orho-Melander et al., 1999 |
| **HNF4** | Hepatocyte nuclear factor 4 | 20q12-q13.1 | 3q42-43 | 2 (94.0 cM) | Shih et al., 2000 |
| **HSD11B1** | 11-beta hydroxysteroid dehydrogenase, type 1 | 1q32 | 13q27 | 1 (H6) | Masuzaki et al., 2001 |
| **IRS1** | Insulin resistance substrate 1 | 2q36 | 9q34 | 1 (C5) | Abe et al., 1998 |
| **LCAT** | Lecitin:cholesterol acyltransferase | 16q22.1 | 19q12 | 8 (53.0 cM) | Norum and Gjone, 1967 |
| **LDLR** | Low density lipoprotein receptor | 19p13.3 | 8q13 | 9 (5.0 cM) | Nishina et al., 1992 |
| **LEP** | Leptin | 7q31.3 | 4q22 | 6 (10.5 cM) | Nishina et al., 1994 |
| **LIPC** | Hepatic lipase | 15q21.3 | 8q24 | 9 (39.0 cM) | Breckenridge et al., 1982 |
| **LIPE** | Hormone sensitive lipase | 19q13.2 | 1q21 | 7 (5.5 cM) | Lavebratt et al., 2002 |
| **LMNA** | Lamin A/C | 1q21.2 | 2q31-q34 | 3 (42.6 cM) | Schimdt et al., 2001 |
| **Lp(a)** | Lipoprotein a | 6q27 | n.a. | n.a. | Dahlen and Berg, 1976 |
| **LPDL** | lpd lipase | 3p11* | 11p11-p12* | 16 (45cM) | Wen et al., 2003 |
| **LPL** | Lipoprotein lipase | 8p21.3 | 8 33.0 cM | 16p14 | Chamberlain et al., 1989 |
| **mt5178 A/C** | Mitochondrial DNA 5178 adenine/cytosine polymorphism | mt | mt | mt | Kokaze et al., 2001 |
| **MAT1A** | Methionine adenosyltransferase 1A | 10q22 | 16p14 | 14 (B) | Martinez-Chantar et al., 2002 |
| **MTP** | Mitochondrial triglyceride transfer protein | 4q23 | 2q44 | 3 (66.2 cM) | Austin et al., 1998 |
| **NPY** | Neuropeptide Y | 7p15.1 | 4q24 | 6 (26.0 cM) | Karvonen et al., 2000 |
| **PON** | Paraoxonase | 7q21.3 | 4q13 | 6 (1.0 cM) | Saha et al., 1991 |
| **PPARA** | Peroxisome proliferator-activated receptor alpha | 22q13.31 | 7q34 | 15 (48.8 cM) | Nielsen et al., 2003 |
| **PPARG** | Peroxisome proliferator-activated receptor gamma | 3p25 | 4q42 | 6 (52.7 cM) | Hasstedt et al., 2001 |
| **PPARGC1** | PPAR gamma, co-activator 1 | 4p15.1 | 14q11 | 5 (C1) | Agarwal and Garg, 2002 |
| **PTG** | Protein targeting to glycogen | 10q23-q24 | 4q42* | 19 (C2) | Crosson et al., 2003 |
| **RP1** | Retinitis pigmentosa 1 | 8q11.2 | 5q12* | 1 (6.5 cM) | Fujita et al., 2003 |
| **RXRG** | Retinoid X receptor gamma | 1q23 | 13q24 | 1 (88.1 cM) | Wang et al., 2002 |
| **SCARB1** | Scavenger receptor class B, member 1 | 12q24.31 | 12q15-q16 | 5 (68.0 cM) | Tai et al., 2003 |
| **SLC22A5** | Solute carrier family 22 , member 5 | 5q31 | 10q22 | 11 (28.0 cM) | Zhu et al., 2000 |
| **SLC6A4** | Serotonin transporter gene | 17q11.2 | 10q26 | 11 (42.0 cM) | Comings et al., 1999 |
| **SREBF1** | Sterol regulatory element-binding transcription factor 1 | 17p11.2 | 10q22 | 8 (33.0 cM) | Shimomura et al., 1998 |
| **TNFB** | Tumour necrosis factor beta | 6p21.3 | 20p12 | 17 (19.06 cM) | Vendrell et al., 1995 |
| **TXNIP** | Thioredoxin-interacting protein | 1q21.2 | 2q34 | 3 (47.1 cM) | Bodnar et al., 2002 |
| **UCP2** | Uncoupling protein-2 | 11q13 | 1q32 | 7 (50 cM) | Wang et al., 2004 |
| **USF1** | Upstream transcription factor 1 | 1q22-23 | 13q24 | 1 (93.3 cM) | Pajukanta et al., 2004 |
| **VLDLR** | Very low density lipoprotein receptor | 9p24 | 1q51 | 19 20.0 cM | Yagyu et al., 2002 |

*Table 2. Chronologically sorted list of the major linkage studies assessing triglyceridaemia in human subjects. Syntenic regions in rat and mouse correspond to the loci with highest linkage in human studies. *... too large for identification of unique syntenic regions.*

| | | | | | | | Genomic location | |
|---|---|---|---|---|---|---|---|---|
| **Authors** | **Year** | **Study design** | **N** | **LOD** | **Human** | **Flanking markers** | **Rat** | **Mouse** |
| Bosse et al. | 2004a | 534 sibpairs | 1068 | 2.32 | 2p14 | D2S441 | 14q22 | 11 (A.2) |
| | | | | 2.11 | 11p13 | D11S1392 | 3q32-q34 | 2 (57.0 cM) |
| | | | | 1.93 | 11q24.1 | D11S4464 | 8q22 | 9 (A5.1) |
| Sonnenberg et al. | 2004 | 507 families | 2209 | 3.70 | 7q35-36 | D7S3058 | 4q11 | 5 (12.0cM) |
| Naoumova et al | 2003 | 128 FCHL families | | 2.70 | 11p14.1-q12.1 | | * | * |
| | | | | 1.43 | 6q16.1-q16.3 | | 10q32 | 11 (69.0 cM) |
| Austin et al. | 2003 | 26 FHTG kindreds | 140 | 2.56 | 15q14 | D15S659-D15S643 | 8q24 | 9 (72.6Mb) |
| | | | | 2.44 | 15q21-q22 | GATA1S1F03-D15S655 | 1q31 | 7 (D3) |
| Newman et al. | 2003 | 1 pedigree (Hutterites) | 485 | 3.54 | 2q14 | D2S410-D2S1328 | 13q11 | 1 (123.1Mb) |
| Elbein and Hasstedt | 2002 | 42 families | 610 | 3.16 | 19q13.1 | D19S178-APOC2 | 1q12 | 7 (5cM) |
| Broeckel et al. | 2002 | 513 families | 1406 | 1.90 | 9q21 | D9S1122 | 1q41 | 19 (9cM) |
| Arya et al. | 2002 | 27 pedigrees (Mexican-American) | 261 | 3.20 | 7q21.3-7q31.1 | D7S479-D7S471 | 4q13 | 6 (A1) |
| Reed et al. | 2001 | 75 families | | 3.02 | 12q23-q24.1 | D12SPAH | 7q12-q13 | 10 (48.0 cM) |
| Klos et al. | 2001 | 232 pedigrees | 1484 | 1.64 | 13 | (86 cM) | n.a. | n.a. |
| Coon et al. | 2001 | 622 sibpairs (African-American) | 1244 | 2.77 | 20p12 | (28.6cM) | 3q36 | 2 (80.0 cM) |
| | | 649 sibpairs (Caucasian) | 1298 | 1.91 | 15q11-q13 | (28.8cM) | 1q22 | 7 (27cM) |
| Duggirala et al. | 2001 | 27 extended families (Mexican American) | 310 | 1.30 | 6q27 | D6S264 | 1q11 | 17 (A1) |
| Shearman et al. | 2000 | 332 families | 1702 | 1.80 | 7q32.3-qter | D7S2195-D7S3058 | 4q11 | 5 (A3) |
| | | | | 1.50 | 16q11.2-q21 | D16S3396-D16S2624 | 19p11 | 8 (D) |
| | | | | 1.30 | 20p12-p11.2 | D20S851-D20S470 | 3q36-q42 | 2 (76.7-81.4 cM) |
| Imperatore et al. | 2000 | 188 families | 547 | 1.70 | 3p14 | D3S2406 | 4q34 | 6 (101.9 cM) |
| Duggirala et al. | 2000 | 27 extended families (Mexican American) | 418 | 3.88 | 15q11.2-13.1 | GABRB3 - D15S165 | 1q22 | 7 (27cM) |
| | | | | 2.05 | 7q11.2 | D7S506-D7S653 | 9q21 | 11 (A2) |
| | | | | 1.86 | 7q34-q36 | D7S1824-D7S688 | 4q24 | 6 (B2.3) |
| Pajukanta et al. | 1998 | 35 Finnish FCHL families | 201 | 3.2(Z) | 10q11.2 | D10S1220 | 16p16 | 14 (10.5 cM) |
| | | | | 2.25(Z) | 2q31 | D2S1391 | 9q22 | 1 (C1) |
| Duggirala et al. | 1996 | 27 extended families (Mexican American) | 440 | 1.30 | 6q27 | D6S264 | 1q11 | 17 (A1) |

(Duggirala et al., 2000). Coon et al. (2001) detected a modest linkage (LOD 1.91) in 649 white sibpairs in a previously reported region of chromosome 15, and in 622 African American sibpairs, the highest LOD score reached 2.77 on chromosome 20.

Pajukanta et al. (1998) analysed the determinants of FCHL in Finnish FCHL families, thus identifying loci on chromosomes 10 (Z-score 3.2), and 2 (Z-score 2.25) potentially affecting TG levels. The genomewide scan of 75 obese families revealed a significant linkage of plasma TG concentration to chromosome 12 (D12SPAH) with a LOD of 3.02 (Reed et al., 2001). Elbein and Hasstedt (2002) report the chromosome 19q13.2 region close to the APOC-II/APOE/APOC-I/APOC-IV cluster to be linked with TG in a set of 42 diabetic multiplex families. Weaker linkages were shown for loci on chromosomes 2, 3 (Imperatore et al., 2000) and 13 (Klos et al., 2001). Newman et al. (2003) found major loci influencing serum triglyceride levels on chromosomes 2q14 and 9p21 localized by homozygosity-by-descent mapping in a large (1623 members) Hutterite pedigree.

## Rat

Rat has served as a model of choice for human physiology since the 19th century, as reviewed in Jacob and Kwitek (2002). Combination of its traditional role in research with the rapidly increasing availability of genomic resources, namely the finished draft sequence of the rat genome (Rat Genome Sequencing Project Consortium, 2004) and establishment of comprehensive model sets like the panels of recombinant inbred (Pravenec et al., 1989, 1995; Křen et al., 1996) or consomic rat strains (Stoll et al., 2001; Cowley et al., 2004) allows investigators to proceed from anecdotal observations to systems biology-based research of complex traits. Up to date, the studies in rat indicated significant linkage of triglyceride levels to a handful of genomic locations, which are summarized in Table 3. Two of them, localized on the rat chromosomes 4 and 8, were each ascertained in three independent studies, thus providing strong evidence for the presence of major genes affecting triglyceride levels.

### *Rat chromosome 4: Cd36/Fat*

This region of the rat genome is connected with a single case of success story, where the identification of

a QTL for dyslipidaemia and insulin resistance led, through a sequence including the microarray expression profiling, congenic strain derivation and transgenesis, to identification of the mutant allele of a single gene encoding the fatty acid translocase *Cd36*/*Fat* in the spontaneously hypertensive rat strain SHR/OlaIpcv (Aitman et al., 1997, 1999; Pravenec et al., 2001a). The whole process and its biological connotations have been reviewed recently (Pravenec et al., 2000; Pravenec and Kurtz, 2002). The transgenic insert has been mapped in the SHR-transgenic sublines (Liška et al., 2002) and it was shown that the Cd36 protein functions as an immunogenic domain of the RT8 alloantigen (Mlejnek et al., 2003). The genetic analysis of the whole metabolic syndrome in SHR was reviewed recently (Pravenec et al., 2004). It should be noted that in spite of a major impact of *Cd36/Fat* on metabolic disturbances in strains harbouring its mutated variant (Pravenec et al., 2001a, 2003; Šeda et al., 2002a), it is most likely not the single causative factor and other genes either present in its genomic neighbourhood or functionally interacting may be important as well. This arises from the observations in *a.* insulin resistant and dyslipidaemic SHR substrains carrying the unaffected allele of Cd36/Fat (Gotoda et al., 1999; Collison et al., 2000) and *b.* comprehensive analyses of metabolic derangements in SHR/OlaIpcv (Pravenec et al., 2001b, 2002) and derived congenic strains carrying the incriminated segment of chromosome 4 (Pravenec et al., 1999, 2004; Šeda et al., 2002a, 2003a, b). On the other hand, there are more lines of evidence for the metabolic relevance of the region in question: Kovacs et al. (1998, 2000) reported the Il-6/D4Mit9 (D4Mit2) region to be significantly linked to TG levels in BB/OK x (SHR/Mol x BB/OK) backcross and WOKW x DA F2 populations. Moreover, other attributes of the metabolic syndrome were shown to be linked to the *Cd36/Fat*-containing region, including mean arterial blood pressure in the set of HXB and BXH recombinant inbred rat strains (Pravenec et al, 1995), retroperitoneal fat weight in Otsuka-Long-Evans-Tokushima fatty (OLETF) rat (Ogino et al., 2000), and HDL-2 phospholipids (Bottger et al., 1996). Lately, we have made an interesting observation concerning the *Cd36/Fat*-containing region (Šeda et al., 2003b). We compared the linkage of the chromosome 4 between two F2 crosses – PD/Cub (polydactylous rat strain) x BN/Cub (Brown Norway) vs. PD/Cub x BN.SHR(*Il6-Cd36*) congenic strain. The BN.SHR4 carries a ca 10 cM region of chromosome 4 of the SHR origin on the Brown Norway genetic background (Šeda et al., 2002a). It was only in the genetic milieu combining *Cd36/Fat* alleles of PD/Cub

*Table 3. List of linkage studies assessing triglyceridemia in rat and mouse models. The syntenic regions of human and mice/rat genomes are shown for the peak linkage loci in the referred studies. F2 - intercross, second filial generation; BC - backcross; RI - recombinant inbred strain set; m - male; f - female; RNO - rat chromosome; MMU - mouse chromosome. *...P = 4.87.10$^{-6}$*

| RAT STRAINS | Study design | N | LOD | Genomic location Rat | Mouse | Human | Authors |
|---|---|---|---|---|---|---|---|
| HTG x LEW | F2 | 266 | 4.4 | D2Rat210 | 15 (A2) | 5p15.2-p15.1 | Ueno et al., 2004 |
| | | | 3.3 | D13Rat34 | 1 (H4) | 1q42-q44 | |
| | | | 3.1 | D2Rat61 | 3 (61.6 cM) | 4q23-q25 | |
| PD/Cub x BN.SHR4/Cub | F2 | 94 m | 3.26 | Il6-D4Bro1 | 6 (A3) | 7q31-32 | Šeda et al., 2003b |
| hHTG x BN | F2 | 189 m | 6.5 | D4Mit5-D4Mit17 | 6 (B2) | 7p15.1 | Klimeš et al., 2003 |
| | | | 4.2 | D8Rat164-D8Wox3 | 9 (A5) | 11q23 | |
| | | | 4 | D8Rat35-D8Mgh1 | 9 (B) | 15q22-q24 | |
| (Wild x SHR) x SHR | BC | 72 | 2.3 | D6Mit9 | 12 (A1) | 2p24.3 | Kloting et al., 2001a |
| | | | 3.6 | D17Mgh2 | 13 (A5) | 9q22.3 | |
| (OLETF x F344) x OLETF | BC | 115 m | * | D1Rat90 | 19 (D3) | 10q26 | Yamasaki, 2000 |
| WOKW x DA | F2 | 150 m | 4.7 | Il6-D4Mit2 | 6 (A3) | 7q31-32 | Kovacs et al., 2000 |
| (OLETF × BN) × OLETF | BC | 239 m | 4.71 | D8Mit2 | 9 (A5) | 11q23 | Okuno et al., 1999 |
| | | | 9.27 | D1Rat90 | 19 (D3) | 10q26 | |
| (BB/OK x SHR/Mol) x BB/OK | BC | 102 m | 3.3 | Il-6 - D4Mit9 | 6 (A3) | 7q31-32 | Kovacs and Kloting, 1998 |
| | | | 1.9 | D1Mit14 | 19 (D3) | 10q25 | |
| **MOUSE STRAINS** | | | | **Mouse** | **Rat** | **Human** | |
| SMXA | RI | | 2.5 (m) | D4Mit2 | 5q21 | 6q16.2 | Anunciado et al., 2000 |
| | | | 2.6 (f) | D11Rik146 | 10q32 | 17q25.1 | |
| SM/J x A/J | F2 | 321 | 2.6 | D4Mit17 | 5q24 | 9q33 | Anunciado et al., 2003 |
| | | | 3.4 | D8Mit18 | 16q12 | 8p23 | |
| | | | 2.3 | D9Mit19 (f) | 8q32 | 3p21 | |
| | | | 2.8 | D11Mit14 | 10q31 | 17q21.2 | |
| | | | 2.5 | D12Mit36 | 6q24 | 14q24.1 | |
| | | | 2.4 | D19Mit14 | 1q51 | 9q13-q21 | |
| C57BL/6J x KK-Ay/a | F2 | 190 | 5 | D9Mit163 | 8q24 | 15q22.3-q23 | Suto et al., 1999 |
| KK x RR | F2 | 145 f | 4.7 | D8Mit205 | 16p11 | 4q31 | Suto and Sekikawa, 2003 |
| (BALB/c x KK/Ta) x KK/Ta | BC | 208 m | 4.8 | D8Mit242-D8Mit166 | 19q12 | 16q24 | Shike et al., 2001 |
| | | | 3.2 | D4Mit336 | 5q36 | 1p34 | |

and SHR origin (i.e. in the PD/Cub x BN.SHR-Il-6-Cd36 cross) that the chromosome 4q11 region was linked to the triglyceride (and glucose) levels. Surprisingly, the SHR/SHR homozygotes for the markers around Cd36/Fat showed lower values when compared with SHR/PD heterozygotes or PD/PD homozygotes. Klimeš et al. (2003) showed that another region of rat chromosome 4 (D4Wox8-D4Mgh17, i.e. segment clearly distinct from the previously discussed one) harbours genes affecting triglyceride levels in the F2 cross of HTG x BN rats, the HTG alleles apparently predisposing for higher triglyceride concentrations.

### *Rat chromosome 8: ApoAI-CIII-AIV-AV cluster*

The region of rat chromosome 8q23 was shown to play an important role in the control of triglyceridaemia (and some other metabolic and hemodynamic variables) in a number of rat models of dyslipidaemia and insulin resistance. Klimeš et al. (2003) found multiple regions of the rat chromosome 8 to be affecting TG concentrations in the hHTG (hereditary hypertriglyceridaemic rat; Vrána et al., 2003) x BN F2 population. While the region D8Rat164-D8Wox3 was unique for this cross, the other seems to be overlapping with those previously reported in PD/Cub (Křen et al., 1995) and OLETF (Okuno et al., 1999) rats, i.e. encompassing the apolipoprotein gene cluster (*ApoA-I/C-III/A-IV/A-V*). When transferred onto the genetic background of normolipidaemic and normotensive BN/Cub (in the congenic BN-*Lx* strain), it induces deterioration of lipid and carbohydrate metabolism (Křen et al., 1995; Šeda et al., 2002a). Surprisingly, this segment of PD/Cub origin worsens the dyslipidaemia also on the SHR genetic background, though it reduces the blood pressure, as evidenced in the SHR-*Lx* congenic strains (Křen et al., 1997; Křenová et al., 2000; Šedová et al., 2000b). Interestingly, Klimeš et al. (2003) did not observe any effect of the chromosome 8 (and 4) loci on blood pressure in the hHTG x BN F2 cross, contrasting with the findings in SHR x BN crosses.

This locus can serve as an explicit example of the power of comparative genomics. Several lines of evidence showed that the syntenic loci of human chromosome 11q22-23 (e.g. Wojciechowski et al., 1991; Dallinga-Thie et al., 1997, Table 1), mouse chromosome 9 and rat chromosome 8 carry genes affecting various facets of dyslipidaemia, mainly the triglyceride levels. This, combined with the fact that the mentioned apolipoprotein cluster resides in the critical locus, led to the launch of an elegant study based on comparative sequencing of the mouse and human syntenic regions (Pennachio et al., 2001). This endeavour resulted in identification of a novel member of the apolipoprotein cluster, the ApoA-V. In parallel, ApoA-V was identified in rat liver and a comparison with human sequence was made (van der Vliet et al., 2001). Further studies in all three species showed the crucial importance of the newly discovered gene in regulation of triglyceride metabolism (recently reviewed in Šeda and Šedová, 2003).

Apart from rat chromosomes 4 and 8, several other genomic regions were linked to TG levels. On chromosome 1, the marker D1Mit14 was reported to be suggestively linked to triglyceridaemia by Kovacs and Kloting (1998) in (SHRxBB/OK)xBB/OK backcross (LOD 1.9) In a work by Ueno et al. (2004), a suggestive linkage for plasma triglycerides was localized only in the male population on chromosome 1 (between D1Rat64 and D1Rat71, LOD 2.7). This observation was consistent with the results of Kovacs et al. (2000) on the dissection of loci for plasma lipids and blood pressure in hypertensive hypertriglyceridaemic Wistar-Ottawa-Karlsburg rats with the $RT1^u$ haplotype.

Single observations of TG linkage were made for rat chromosomes (RNO) 2, RNO 5 (Ueno et al., 2004), RNO 6 and RNO 17 (Kloting et al., 2001a). A very recent work by Ueno and colleagues (2004) led to realization of a strong similarity between phenotypical manifestation and synteny of identified quantitative trait loci on RNO 1 and 13 to those in human FCHL Dutch and Finnish populations, respectively. The Prague hypertriglyceridaemic rat was thus proposed as a very promising model of FCHL.

## Mouse

In comparison to rat, there are relatively few linkage studies in mice addressing specifically the genetic determinants of triglyceride levels. A query in the Mouse Genome Database (http://www.informatics.jax.org/) revealed four triglyceride QTLs, *Triglq1* and *Triglq2*, identified on chromosomes 4 and 11, respectively, by Anunciado and colleagues (2000) in SMXA recombinant inbred strains and Trigq1 and Trigq2 located on chromosomes 9 and 8, respectively (Suto et al., 2003). More recently, the same group reported six suggestive and significant QTLs for triglyceridaemia in 10-month old SM/J x A/J F2 intercross mice on chromosomes 4, 8, 9, 11, 12, and 19, confirming the *Triglq2* (HSA 17q23-24, RNO10q32.3). The highest LOD score of 3.4 was reported for the marker D8Mit18 (Anuciado et al., 2003), co-localizing with the QTL found in KK x RR F2 mice (D8Mit205, LOD = 4.7) by Suto and Sekikawa (2003).

## A short note: pharmacogenetics of triglyceridaemia

As alluded to in the introductory paragraphs, there is a strong environmental component responsible for the modulation of TG levels at a particular setting of environment, lifestyle (diet, smoking) and medication. With the advent of pharmacogenomics and high-throughput methodologies for genetic testing, the documented interactions of the environmental components with the genetic background gradually come closer from sketchy

reports to a routine practice. There are two major patterns of pharmacogenetic interactions relevant for triglyceridaemia: *a.* there are certain "genotypes" that influence the efficacy of the hypolipidaemic drugs (Brisson et al., 2002 ); *b.* administration of several classes of drugs is empirically known to produce a rise in TG levels in subsets of treated individuals along with their major therapeutic action: retinoids; glucocorticoids, HIV protease inhibitors, amiodarone and others. The susceptibility to this hypertriglyceridaemic action is in great part a genetic one. Identification of the allelic variants and combinations that confer a risk of the potentially harmful side effects via pharmacogenetic interactions represents a stepping stone on the way to rational, individualized therapy. Such interaction was recently identified in the pioglitazone-treated SHR (Qi et al., 2002; with *Cd36/Fat* identified as the responsible gene) and in a comparison of the effect of rosiglitazone on the congenic pair of inbred strains, the Brown Norway (BN/Cub) and a congenic BN.SHR(Il6-Cd36) strain with a part of chromosome 4 introgressed from SHR. Interestingly, rosiglitazone induced a significant reduction in serum TG only in BN/Cub (Šeda et al., 2003a). Similar findings were reported for the lipid-raising side effects of retinoid administration in human (Rodondi et al., 2002) and rat model (Šedová et al., 2004) contexts. Despite partial successes, the systematic, large-scale identification of the allelic variants at the level of single nucleotide polymorphisms (SNPs) or haplotypes that produce clinically relevant side effects in response to usual therapeutic management of a given condition remains a considerable task for the near future.

## Synthetic view

An account of the genes and genomic regions proposed as participants of the genetic component of triglyceridaemia determination is given for human, rat and mouse. Figure 2 depicts an attempt to merge the

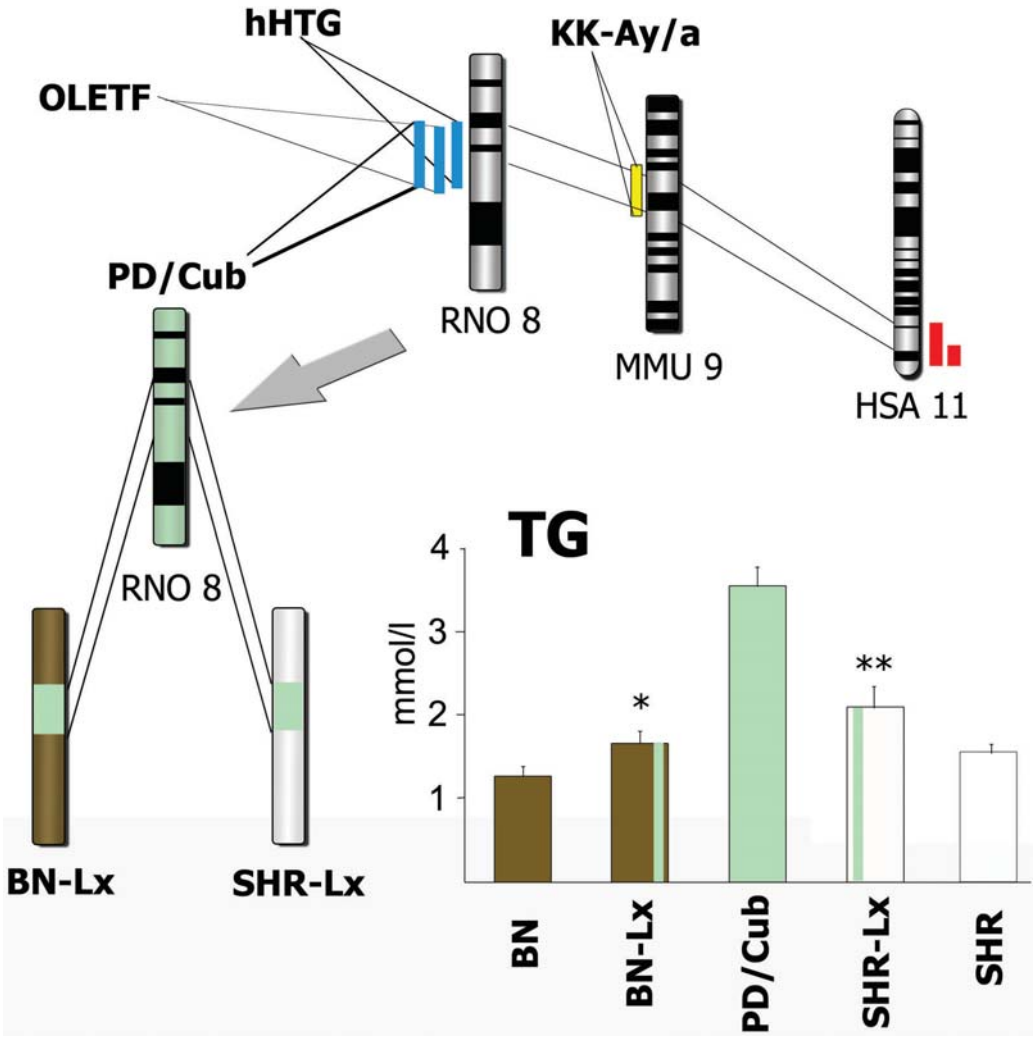
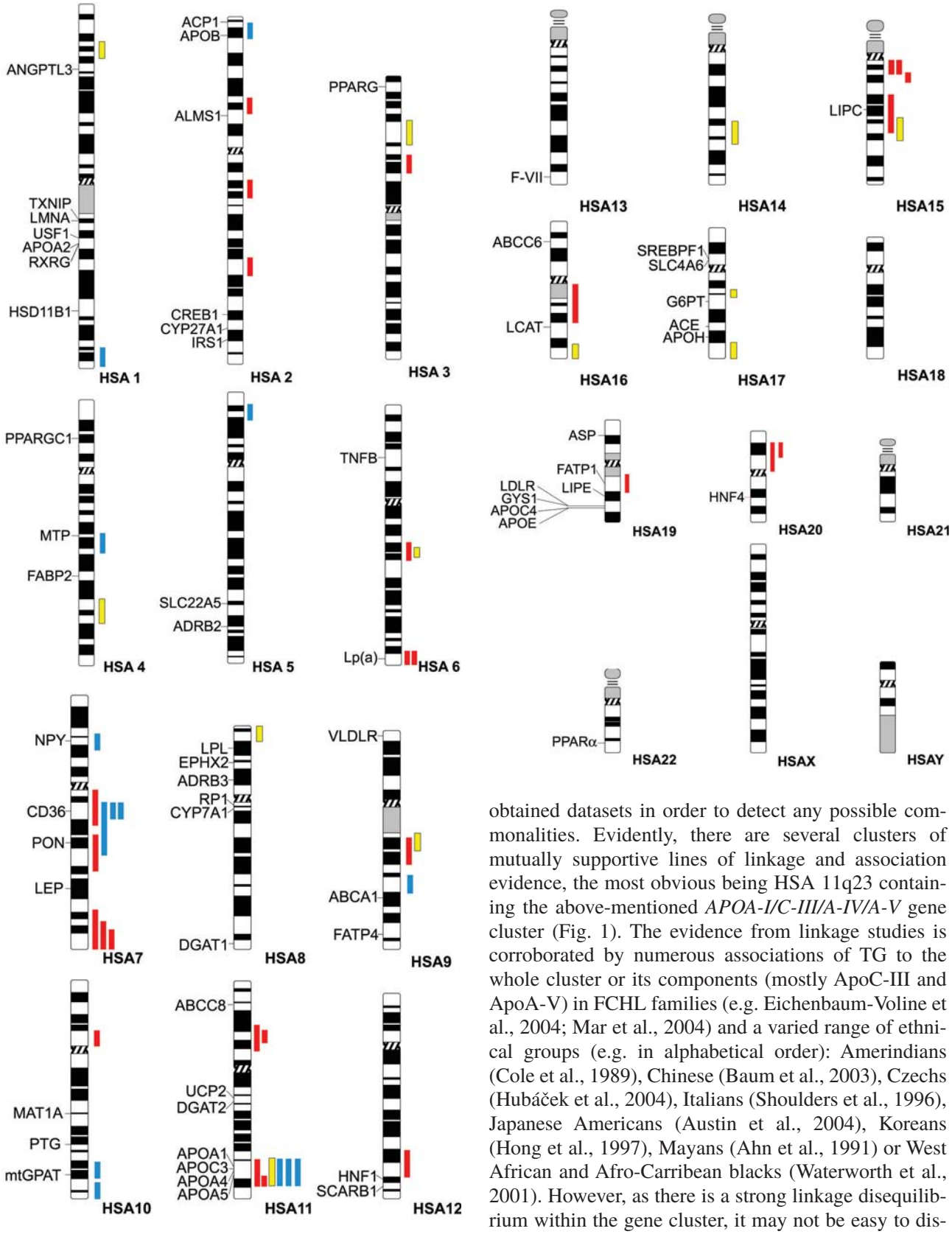



*Fig. 1.* Comparative mapping of triglyceridaemia to rat chromosome 8 and syntenic regions of mouse chromosome 9 and human chromosome 11. Vertical bands near the chromosomes show the span of linkage evidence for triglyceridaemia in rat (blue), mouse (yellow) and human (red) studies. Lower section: transfer of a differential segment of rat chromosome 8 of PD/Cub origin elicits increase of triglyceride (TG) levels in BN-*Lx* and SHR-*Lx* congenic strains, compared to their BN and SHR progenitors. Values are expressed as mean ± S.E.M. (N = 6–8 per group). Significance levels of Tukey's post-hoc test (ANOVA, factor STRAIN): *…$P < 0.05$, **…$P < 0.01$.




obtained datasets in order to detect any possible commonalities. Evidently, there are several clusters of mutually supportive lines of linkage and association evidence, the most obvious being HSA 11q23 containing the above-mentioned *APOA-I/C-III/A-IV/A-V* gene cluster (Fig. 1). The evidence from linkage studies is corroborated by numerous associations of TG to the whole cluster or its components (mostly ApoC-III and ApoA-V) in FCHL families (e.g. Eichenbaum-Voline et al., 2004; Mar et al., 2004) and a varied range of ethnical groups (e.g. in alphabetical order): Amerindians (Cole et al., 1989), Chinese (Baum et al., 2003), Czechs (Hubáček et al., 2004), Italians (Shoulders et al., 1996), Japanese Americans (Austin et al., 2004), Koreans (Hong et al., 1997), Mayans (Ahn et al., 1991) or West African and Afro-Carribean blacks (Waterworth et al., 2001). However, as there is a strong linkage disequilibrium within the gene cluster, it may not be easy to dis-

*Fig. 2.* The triglyceridaemia gene map. The map shows ideograms of human chromosomes with indication of candidate genes positively associated with triglyceridaemia (to the left from the chromosomes, for full names see Table 1) together with linkage of triglyceridaemia to genomic regions in rat (blue), mouse (yellow) and human (red) studies (to the right from the chromosomes). The names and positions of the genes appear as in the Gene (former LocusLink) module of the NCBI (http://www.ncbi.nlm.nih.gov).

sect the causal haplotypes conveying susceptibility to hypertriglyceridaemia, though these efforts are already well underway (Talmud et al., 2002).

In summary, we present a systematic review of linkage and association studies dealing with the dissection of genetic determinants of (hyper)triglyceridaemia in human and two major mammalian model species, mouse and rat. Based on the merged sets of data, a synthetic view of the genetic component of triglyceridaemia, the "hypertriglyceridaemia gene map", is presented.

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