

Capture Probe, Familial Chylomicronemia Syndrome Detection Kit Containing the Same, and Use Thereof**Technical Field**

The present application relates to the field of biomedical detection, and in particular to a capture probe, a familial chylomicronemia syndrome detection kit containing the same, and use thereof.

Background Art

Familial chylomicronemia syndrome (Familial chylomicronemia syndrome, FCS) is an autosomal recessive genetic disease, also referred to as primary hyperlipoproteinemia type I. FCS is characterized by severe fasting hypertriglyceridemia, secondary to the accumulation of triglyceride (TG)-rich lipoproteins, especially chylomicrons, and requires long-term restriction of the fat content in the diet. The clinical manifestations of FCS are most typically eruptive xanthomas, which are commonly seen on the buttocks, thighs, arms, back, and face, and may also involve the oral mucosa, and other symptoms include upper abdominal pain, which may be caused by tension of the liver and spleen capsules, hepatosplenomegaly, and pancreatitis. This disease is rare and lacks specificity, has potentially serious clinical consequences, and siblings of the patient have a 25% chance of having this disease.

At present, the diagnostic criteria for FCS are mainly derived from European clinical practice and are comprehensive diagnostic criteria, mainly relying on factors such as: triglyceride level, the patient's response to drugs for lowering triglyceride levels, and a medical history of frequent attacks of abdominal pain or pancreatitis. Routine laboratory and clinical examinations cannot precisely identify the cause of the disease, and changes in triglyceride levels are also observed in other diseases and are not changes entirely specific to FCS, and therefore, in clinical practice FCS is often missed in diagnosis. Overall, the current diagnostic methods cannot provide accurate and timely FCS diagnostic results, which is not conducive to timely treatment of FCS, and precise identification and localization of FCS still remain challenging.

Summary of the Invention

In view of this, one objective of one or more embodiments of the present application is to provide a capture probe, and the probe can be used for accurate detection of FCS-related gene mutations.

In one or more embodiments of the present application, a capture probe is provided, which comprises one or more probe set selected from probe set 1 to probe set 6;

probe set 1 comprises one or more probes selected from probes 1 to 26;

probe set 2 comprises one or more probes selected from probes 27 to 64;

probe set 3 comprises one or more probes selected from probes 65 to 112;

probe set 4 comprises one or more probes selected from probes 113 to 139;

probe set 5 comprises one or more probes selected from probes 140 to 382;

probe set 6 comprises one or more probes selected from probes 383 to 425;

the probes 1 to 425 are constructed for target gene fragments located between different start positions and end positions on the following chromosomes and are complementary to and paired with said target gene fragments:

Probe number	Chromosome	Start position	End position
Probe 1	chr11	116660063	116660183;
Probe 2	chr11	116660168	116660288;
Probe 3	chr11	116660273	116660393;
Probe 4	chr11	116660378	116660498;
Probe 5	chr11	116660483	116660603;
Probe 6	chr11	116660588	116660708;
Probe 7	chr11	116660693	116660813;
Probe 8	chr11	116660798	116660918;
Probe 9	chr11	116660903	116661023;

Probe 10	chr11	116661008	116661128;
Probe 11	chr11	116661113	116661233;
Probe 12	chr11	116661218	116661338;
Probe 13	chr11	116661323	116661443;
Probe 14	chr11	116661428	116661548;
Probe 15	chr11	116661533	116661653;
Probe 16	chr11	116661638	116661758;
Probe 17	chr11	116661743	116661863;
Probe 18	chr11	116662282	116662402;
Probe 19	chr11	116662387	116662507;
Probe 20	chr11	116662508	116662628;
Probe 21	chr11	116663076	116663196;
Probe 22	chr11	116663181	116663301;
Probe 23	chr11	116663286	116663406;
Probe 24	chr11	116663391	116663511;
Probe 25	chr11	116663496	116663616;
Probe 26	chr11	116663601	116663721;
Probe 27	chr12	50497271	50497391;
Probe 28	chr12	50497376	50497496;
Probe 29	chr12	50497481	50497601;
Probe 30	chr12	50497586	50497706;
Probe 31	chr12	50497691	50497811;
Probe 32	chr12	50497796	50497916;
Probe 33	chr12	50498337	50498457;
Probe 34	chr12	50498442	50498562;
Probe 35	chr12	50499311	50499431;
Probe 36	chr12	50499416	50499536;
Probe 37	chr12	50500051	50500171;
Probe 38	chr12	50500156	50500276;
Probe 39	chr12	50500568	50500688;
Probe 40	chr12	50500673	50500793;
Probe 41	chr12	50501330	50501450;
Probe 42	chr12	50501435	50501555;
Probe 43	chr12	50501540	50501660;
Probe 44	chr12	50501787	50501907;
Probe 45	chr12	50501892	50502012;
Probe 46	chr12	50503186	50503306;
Probe 47	chr12	50503291	50503411;
Probe 48	chr12	50503396	50503516;
Probe 49	chr12	50503501	50503621;
Probe 50	chr12	50503606	50503726;
Probe 51	chr12	50503711	50503831;
Probe 52	chr12	50503816	50503936;
Probe 53	chr12	50503921	50504041;
Probe 54	chr12	50504026	50504146;
Probe 55	chr12	50504131	50504251;
Probe 56	chr12	50504236	50504356;
Probe 57	chr12	50504341	50504461;
Probe 58	chr12	50504446	50504566;
Probe 59	chr12	50504551	50504671;
Probe 60	chr12	50504656	50504776;

Probe 61	chr12	50504761	50504881;
Probe 62	chr12	50504866	50504986;
Probe 63	chr12	50504971	50505091;
Probe 64	chr12	50505076	50505196;
Probe 65	chr16	903614	903734;
Probe 66	chr16	903719	903839;
Probe 67	chr16	903824	903944;
Probe 68	chr16	903929	904049;
Probe 69	chr16	904034	904154;
Probe 70	chr16	904139	904259;
Probe 71	chr16	904244	904364;
Probe 72	chr16	904349	904469;
Probe 73	chr16	904454	904574;
Probe 74	chr16	904559	904679;
Probe 75	chr16	904664	904784;
Probe 76	chr16	905087	905207;
Probe 77	chr16	905192	905312;
Probe 78	chr16	918924	919044;
Probe 79	chr16	919029	919149;
Probe 80	chr16	919863	919983;
Probe 81	chr16	919968	920088;
Probe 82	chr16	920709	920829;
Probe 83	chr16	920814	920934;
Probe 84	chr16	921141	921261;
Probe 85	chr16	921246	921366;
Probe 86	chr16	929550	929670;
Probe 87	chr16	929655	929775;
Probe 88	chr16	942987	943107;
Probe 89	chr16	960911	961031;
Probe 90	chr16	961016	961136;
Probe 91	chr16	981622	981742;
Probe 92	chr16	981727	981847;
Probe 93	chr16	983971	984091;
Probe 94	chr16	984076	984196;
Probe 95	chr16	984170	984290;
Probe 96	chr16	1004337	1004457;
Probe 97	chr16	1004442	1004562;
Probe 98	chr16	1004547	1004667;
Probe 99	chr16	1004652	1004772;
Probe 100	chr16	1020768	1020888;
Probe 101	chr16	1020873	1020993;
Probe 102	chr16	1020978	1021098;
Probe 103	chr16	1031125	1031245;
Probe 104	chr16	1031230	1031350;
Probe 105	chr16	1031335	1031455;
Probe 106	chr16	1031440	1031560;
Probe 107	chr16	1031545	1031665;
Probe 108	chr16	1031650	1031770;
Probe 109	chr16	1031755	1031875;
Probe 110	chr16	1031860	1031980;
Probe 111	chr16	1031965	1032085;

Probe 112	chr16	1032070	1032190;
Probe 113	chr19	45448788	45448908;
Probe 114	chr19	45448893	45449013;
Probe 115	chr19	45448998	45449118;
Probe 116	chr19	45449103	45449223;
Probe 117	chr19	45449208	45449328;
Probe 118	chr19	45449313	45449433;
Probe 119	chr19	45449418	45449538;
Probe 120	chr19	45449628	45449748;
Probe 121	chr19	45449733	45449853;
Probe 122	chr19	45450048	45450168;
Probe 123	chr19	45450363	45450483;
Probe 124	chr19	45450468	45450588;
Probe 125	chr19	45450573	45450693;
Probe 126	chr19	45450678	45450798;
Probe 127	chr19	45451518	45451638;
Probe 128	chr19	45451623	45451743;
Probe 129	chr19	45451728	45451848;
Probe 130	chr19	45451833	45451953;
Probe 131	chr19	45451938	45452058;
Probe 132	chr19	45452043	45452163;
Probe 133	chr19	45452148	45452268;
Probe 134	chr19	45452253	45452373;
Probe 135	chr19	45452358	45452478;
Probe 136	chr19	45452463	45452583;
Probe 137	chr19	45452568	45452688;
Probe 138	chr19	45452673	45452793;
Probe 139	chr19	45452778	45452898;
Probe 140	chr8	19796244	19796364;
Probe 141	chr8	19796349	19796469;
Probe 142	chr8	19796454	19796574;
Probe 143	chr8	19796559	19796679;
Probe 144	chr8	19796664	19796784;
Probe 145	chr8	19796769	19796889;
Probe 146	chr8	19796874	19796994;
Probe 147	chr8	19796979	19797099;
Probe 148	chr8	19797084	19797204;
Probe 149	chr8	19797189	19797309;
Probe 150	chr8	19797294	19797414;
Probe 151	chr8	19797399	19797519;
Probe 152	chr8	19797504	19797624;
Probe 153	chr8	19797609	19797729;
Probe 154	chr8	19797714	19797834;
Probe 155	chr8	19797819	19797939;
Probe 156	chr8	19797924	19798044;
Probe 157	chr8	19798029	19798149;
Probe 158	chr8	19798134	19798254;
Probe 159	chr8	19798239	19798359;
Probe 160	chr8	19798344	19798464;
Probe 161	chr8	19798449	19798569;
Probe 162	chr8	19798554	19798674;

Probe 163	chr8	19798659	19798779;
Probe 164	chr8	19798764	19798884;
Probe 165	chr8	19798869	19798989;
Probe 166	chr8	19798974	19799094;
Probe 167	chr8	19799079	19799199;
Probe 168	chr8	19799184	19799304;
Probe 169	chr8	19799289	19799409;
Probe 170	chr8	19799394	19799514;
Probe 171	chr8	19799499	19799619;
Probe 172	chr8	19799604	19799724;
Probe 173	chr8	19799709	19799829;
Probe 174	chr8	19799814	19799934;
Probe 175	chr8	19799919	19800039;
Probe 176	chr8	19800024	19800144;
Probe 177	chr8	19800129	19800249;
Probe 178	chr8	19800234	19800354;
Probe 179	chr8	19800339	19800459;
Probe 180	chr8	19800444	19800564;
Probe 181	chr8	19800549	19800669;
Probe 182	chr8	19800654	19800774;
Probe 183	chr8	19800759	19800879;
Probe 184	chr8	19800864	19800984;
Probe 185	chr8	19800969	19801089;
Probe 186	chr8	19801074	19801194;
Probe 187	chr8	19801179	19801299;
Probe 188	chr8	19801284	19801404;
Probe 189	chr8	19801704	19801824;
Probe 190	chr8	19801809	19801929;
Probe 191	chr8	19801914	19802034;
Probe 192	chr8	19802019	19802139;
Probe 193	chr8	19802124	19802244;
Probe 194	chr8	19802229	19802349;
Probe 195	chr8	19802334	19802454;
Probe 196	chr8	19802439	19802559;
Probe 197	chr8	19802544	19802664;
Probe 198	chr8	19802649	19802769;
Probe 199	chr8	19802754	19802874;
Probe 200	chr8	19802859	19802979;
Probe 201	chr8	19802964	19803084;
Probe 202	chr8	19803069	19803189;
Probe 203	chr8	19803174	19803294;
Probe 204	chr8	19803279	19803399;
Probe 205	chr8	19803384	19803504;
Probe 206	chr8	19803489	19803609;
Probe 207	chr8	19803594	19803714;
Probe 208	chr8	19803699	19803819;
Probe 209	chr8	19803804	19803924;
Probe 210	chr8	19803909	19804029;
Probe 211	chr8	19804014	19804134;
Probe 212	chr8	19804119	19804239;
Probe 213	chr8	19804224	19804344;

Probe 214	chr8	19804329	19804449;
Probe 215	chr8	19804434	19804554;
Probe 216	chr8	19804539	19804659;
Probe 217	chr8	19804644	19804764;
Probe 218	chr8	19805064	19805184;
Probe 219	chr8	19805169	19805289;
Probe 220	chr8	19805274	19805394;
Probe 221	chr8	19805379	19805499;
Probe 222	chr8	19805484	19805604;
Probe 223	chr8	19805589	19805709;
Probe 224	chr8	19805694	19805814;
Probe 225	chr8	19805799	19805919;
Probe 226	chr8	19805904	19806024;
Probe 227	chr8	19806009	19806129;
Probe 228	chr8	19806114	19806234;
Probe 229	chr8	19806219	19806339;
Probe 230	chr8	19806324	19806444;
Probe 231	chr8	19806429	19806549;
Probe 232	chr8	19806534	19806654;
Probe 233	chr8	19806639	19806759;
Probe 234	chr8	19806744	19806864;
Probe 235	chr8	19806849	19806969;
Probe 236	chr8	19807269	19807389;
Probe 237	chr8	19807374	19807494;
Probe 238	chr8	19807479	19807599;
Probe 239	chr8	19807584	19807704;
Probe 240	chr8	19807689	19807809;
Probe 241	chr8	19807794	19807914;
Probe 242	chr8	19807899	19808019;
Probe 243	chr8	19808319	19808439;
Probe 244	chr8	19808424	19808544;
Probe 245	chr8	19808529	19808649;
Probe 246	chr8	19808634	19808754;
Probe 247	chr8	19808739	19808859;
Probe 248	chr8	19808844	19808964;
Probe 249	chr8	19808949	19809069;
Probe 250	chr8	19809054	19809174;
Probe 251	chr8	19809159	19809279;
Probe 252	chr8	19809264	19809384;
Probe 253	chr8	19809369	19809489;
Probe 254	chr8	19809474	19809594;
Probe 255	chr8	19809579	19809699;
Probe 256	chr8	19809684	19809804;
Probe 257	chr8	19809789	19809909;
Probe 258	chr8	19809894	19810014;
Probe 259	chr8	19809999	19810119;
Probe 260	chr8	19810104	19810224;
Probe 261	chr8	19810209	19810329;
Probe 262	chr8	19810314	19810434;
Probe 263	chr8	19810419	19810539;
Probe 264	chr8	19810524	19810644;

Probe 265	chr8	19810629	19810749;
Probe 266	chr8	19810734	19810854;
Probe 267	chr8	19810839	19810959;
Probe 268	chr8	19810944	19811064;
Probe 269	chr8	19811049	19811169;
Probe 270	chr8	19811154	19811274;
Probe 271	chr8	19811259	19811379;
Probe 272	chr8	19811364	19811484;
Probe 273	chr8	19811469	19811589;
Probe 274	chr8	19811574	19811694;
Probe 275	chr8	19811679	19811799;
Probe 276	chr8	19811784	19811904;
Probe 277	chr8	19811889	19812009;
Probe 278	chr8	19811994	19812114;
Probe 279	chr8	19812099	19812219;
Probe 280	chr8	19812204	19812324;
Probe 281	chr8	19812309	19812429;
Probe 282	chr8	19812519	19812639;
Probe 283	chr8	19812624	19812744;
Probe 284	chr8	19812729	19812849;
Probe 285	chr8	19812834	19812954;
Probe 286	chr8	19812939	19813059;
Probe 287	chr8	19813044	19813164;
Probe 288	chr8	19813149	19813269;
Probe 289	chr8	19813254	19813374;
Probe 290	chr8	19813359	19813479;
Probe 291	chr8	19813464	19813584;
Probe 292	chr8	19813569	19813689;
Probe 293	chr8	19813674	19813794;
Probe 294	chr8	19813779	19813899;
Probe 295	chr8	19813884	19814004;
Probe 296	chr8	19814094	19814214;
Probe 297	chr8	19814199	19814319;
Probe 298	chr8	19814304	19814424;
Probe 299	chr8	19814619	19814739;
Probe 300	chr8	19814724	19814844;
Probe 301	chr8	19814829	19814949;
Probe 302	chr8	19814934	19815054;
Probe 303	chr8	19815039	19815159;
Probe 304	chr8	19815144	19815264;
Probe 305	chr8	19815249	19815369;
Probe 306	chr8	19815354	19815474;
Probe 307	chr8	19815459	19815579;
Probe 308	chr8	19815774	19815894;
Probe 309	chr8	19815879	19815999;
Probe 310	chr8	19815984	19816104;
Probe 311	chr8	19816194	19816314;
Probe 312	chr8	19816299	19816419;
Probe 313	chr8	19816404	19816524;
Probe 314	chr8	19816509	19816629;
Probe 315	chr8	19816614	19816734;

Probe 316	chr8	19816719	19816839;
Probe 317	chr8	19816824	19816944;
Probe 318	chr8	19816929	19817049;
Probe 319	chr8	19817034	19817154;
Probe 320	chr8	19817139	19817259;
Probe 321	chr8	19817559	19817679;
Probe 322	chr8	19817664	19817784;
Probe 323	chr8	19817769	19817889;
Probe 324	chr8	19817874	19817994;
Probe 325	chr8	19817979	19818099;
Probe 326	chr8	19818084	19818204;
Probe 327	chr8	19818189	19818309;
Probe 328	chr8	19818294	19818414;
Probe 329	chr8	19818399	19818519;
Probe 330	chr8	19818504	19818624;
Probe 331	chr8	19818609	19818729;
Probe 332	chr8	19818714	19818834;
Probe 333	chr8	19818819	19818939;
Probe 334	chr8	19818924	19819044;
Probe 335	chr8	19819029	19819149;
Probe 336	chr8	19819134	19819254;
Probe 337	chr8	19819239	19819359;
Probe 338	chr8	19819344	19819464;
Probe 339	chr8	19819449	19819569;
Probe 340	chr8	19819554	19819674;
Probe 341	chr8	19819659	19819779;
Probe 342	chr8	19819764	19819884;
Probe 343	chr8	19819869	19819989;
Probe 344	chr8	19819974	19820094;
Probe 345	chr8	19820079	19820199;
Probe 346	chr8	19820184	19820304;
Probe 347	chr8	19820289	19820409;
Probe 348	chr8	19820394	19820514;
Probe 349	chr8	19820499	19820619;
Probe 350	chr8	19820604	19820724;
Probe 351	chr8	19820919	19821039;
Probe 352	chr8	19821024	19821144;
Probe 353	chr8	19821129	19821249;
Probe 354	chr8	19821234	19821354;
Probe 355	chr8	19821339	19821459;
Probe 356	chr8	19821759	19821879;
Probe 357	chr8	19821864	19821984;
Probe 358	chr8	19821969	19822089;
Probe 359	chr8	19822284	19822404;
Probe 360	chr8	19822389	19822509;
Probe 361	chr8	19822494	19822614;
Probe 362	chr8	19822599	19822719;
Probe 363	chr8	19822704	19822824;
Probe 364	chr8	19822809	19822929;
Probe 365	chr8	19822914	19823034;
Probe 366	chr8	19823019	19823139;

Probe 367	chr8	19823124	19823244;
Probe 368	chr8	19823229	19823349;
Probe 369	chr8	19823334	19823454;
Probe 370	chr8	19823439	19823559;
Probe 371	chr8	19823544	19823664;
Probe 372	chr8	19823649	19823769;
Probe 373	chr8	19823754	19823874;
Probe 374	chr8	19823859	19823979;
Probe 375	chr8	19823964	19824084;
Probe 376	chr8	19824069	19824189;
Probe 377	chr8	19824174	19824294;
Probe 378	chr8	19824279	19824399;
Probe 379	chr8	19824384	19824504;
Probe 380	chr8	19824489	19824609;
Probe 381	chr8	19824594	19824714;
Probe 382	chr8	19824699	19824819;
Probe 383	chr8	144294573	144294693;
Probe 384	chr8	144294678	144294798;
Probe 385	chr8	144294783	144294903;
Probe 386	chr8	144294888	144295008;
Probe 387	chr8	144294993	144295113;
Probe 388	chr8	144295098	144295218;
Probe 389	chr8	144295203	144295323;
Probe 390	chr8	144295308	144295428;
Probe 391	chr8	144295413	144295533;
Probe 392	chr8	144295518	144295638;
Probe 393	chr8	144295623	144295743;
Probe 394	chr8	144295728	144295848;
Probe 395	chr8	144295833	144295953;
Probe 396	chr8	144295938	144296058;
Probe 397	chr8	144296043	144296163;
Probe 398	chr8	144296148	144296268;
Probe 399	chr8	144296253	144296373;
Probe 400	chr8	144296358	144296478;
Probe 401	chr8	144296463	144296583;
Probe 402	chr8	144296568	144296688;
Probe 403	chr8	144296673	144296793;
Probe 404	chr8	144296778	144296898;
Probe 405	chr8	144296883	144297003;
Probe 406	chr8	144296988	144297108;
Probe 407	chr8	144297093	144297213;
Probe 408	chr8	144297198	144297318;
Probe 409	chr8	144297303	144297423;
Probe 410	chr8	144297408	144297528;
Probe 411	chr8	144297513	144297633;
Probe 412	chr8	144297618	144297738;
Probe 413	chr8	144297723	144297843;
Probe 414	chr8	144297828	144297948;
Probe 415	chr8	144297933	144298053;
Probe 416	chr8	144298038	144298158;
Probe 417	chr8	144298143	144298263;

Probe 418	chr8	144298248	144298368;
Probe 419	chr8	144298353	144298473;
Probe 420	chr8	144298458	144298578;
Probe 421	chr8	144298563	144298683;
Probe 422	chr8	144298668	144298788;
Probe 423	chr8	144298773	144298893;
Probe 424	chr8	144298878	144298998;
Probe 425	chr8	144298983	144299103;

The reference genome is Hg19.

In some specific embodiments of the present application, the capture probes comprise a plurality of probe sets selected from a probe set 1 to a probe set 6;

The probe set 1 comprises a plurality of probes selected from the probes 1 to 26;

The probe set 2 comprises a plurality of probes selected from the probes 27 to 64;

The probe set 3 comprises a plurality of probes selected from the probes 65 to 112;

The probe set 4 comprises a plurality of probes selected from the probes 113 to 139;

The probe set 5 comprises a plurality of probes selected from the probes 140 to 382;

The probe set 6 comprises a plurality of probes selected from the probes 383 to 425.

In some specific embodiments of the present application, the capture probes comprise the probe set 1 to the probe set 6;

The probe set 1 comprises the probes 1 to 26;

The probe set 2 comprises the probes 27 to 64;

The probe set 3 comprises the probes 65 to 112;

The probe set 4 comprises the probes 113 to 139;

The probe set 5 comprises the probes 140 to 382;

The probe set 6 comprises the probes 383 to 425.

In another embodiment of the present application, the capture probes are used for preparing a familial chylomicronemia syndrome detection kit.

In still another embodiment of the present application, a familial chylomicronemia syndrome detection kit comprising the capture probes is provided.

In some specific embodiments of the present application, the familial chylomicronemia syndrome detection kit further includes one or more of a nucleic acid extraction reagent, a DNA library construction reagent, a sample and library quantification reagent, a fragment quality control reagent, a hybridization capture reagent, a nucleic acid purification reagent, a target gene fragment amplification reagent, and a sequencing reagent.

In yet another one or more embodiments of the present application, use of the capture probes for constructing a detection library for familial chylomicronemia syndrome-related gene mutations is provided.

In a further one or more embodiments of the present application, use of the detection kit for constructing a detection library for familial chylomicronemia syndrome-related gene mutations is provided.

In a further one or more embodiments of the present application, a method for detecting familial chylomicronemia syndrome-related gene mutations is provided, comprising capturing target gene fragments containing the mutations by using the capture probes or the detection kit, and detecting the captured fragments.

In some specific embodiments of the present application, sequencing is used to detect the captured fragments.

Details of one or more embodiments of the present application are presented in the following description, and other features, objectives, and advantages of the present application will become apparent from the description and the claims.

Specific Embodiments

Below, the present invention is further described in detail in conjunction with embodiments and examples. It should be understood that these embodiments and examples are only used to illustrate the present invention and are not used to limit the scope of the present invention, and the purpose of providing these embodiments and

examples is to make the understanding of the disclosed content of the present invention more thorough and comprehensive. It should also be understood that the present invention can be realized in many different forms and is not limited to the embodiments and examples described herein, and those skilled in the art can make various changes or modifications without departing from the substance of the present invention, and any equivalent forms obtained in a similar way shall fall within the protection scope of the present application. In addition, in the following description, a large number of specific details are given in order to facilitate a more adequate understanding of the present invention, and it should be understood that the present invention may be implemented without one or more of these details.

Unless otherwise defined, all technical and scientific terms used herein have the same meanings as are commonly understood by those skilled in the technical field to which the present invention belongs. The terms used herein in the specification of the present invention are only for the purpose of describing the embodiments and examples, and are not intended to limit the present invention.

Terms

Unless otherwise stated or where there is a contradiction, the terms or phrases used herein have the following meanings:

The scope of selection of the terms “and/or,” “or/and,” and “as well as/or” used herein includes any one item among two or more related listed items, and also includes any and all combinations of the related listed items, wherein the any and all combinations include a combination of any two related listed items, any more than two related listed items, or all related listed items. It should be noted that when at least three items are connected by a combination of at least two conjunctions selected from “and/or,” “or/and,” and “as well as/or,” it should be understood that, in the present application, the technical solution undoubtedly includes the technical solution in which all are connected by “logical AND,” and also undoubtedly includes the technical solution in which all are connected by “logical OR.” For example, “A and/or B” includes three alternatives: A, B, and A+B. For another example, the technical solution of “A, as well as/or, B, as well as/or, C, as well as/or, D” includes any one of A, B, C, and D (that is, the technical solution in which all are connected by “logical OR”), and also includes any and all combinations of A, B, C, and D, that is, includes a combination of any two items or any three items among A, B, C, and D, and further includes the four-item combination of A, B, C, and D (that is, the technical solution in which all are connected by “logical AND”).

In the present invention, terms such as “a plurality of,” “multiple kinds,” “multiple times,” and “multiple elements,” unless otherwise specifically limited, mean greater than 2 or equal to 2 in quantity. For example, “one or more kinds” means one kind or two or more kinds.

“Combination thereof,” “any combination thereof,” “any combination manner thereof,” and the like used herein include all suitable combination manners of any two items or any more than two items among the listed items.

Herein, the term “suitable” as in “suitable combination manner,” “suitable manner,” “any suitable manner,” and the like is based on whether the technical solution of the present invention can be implemented, the technical problem of the present invention can be solved, and the intended technical effect of the present invention can be achieved.

Herein, “preferably,” “better,” “more preferably,” and “as appropriate” are only used to describe embodiments or examples with better effects, and it should be understood that they do not constitute a limitation on the protection scope of the present invention.

In the present invention, “further,” “still further,” “particularly,” and the like are used for descriptive purposes and indicate differences in content, but should not be understood as limitations on the protection scope of the present invention.

In the present invention, “optionally,” “optional,” and “option” mean may or may not be present, that is, mean any one selected from the two parallel solutions of “present” or “absent.” If a technical solution contains

multiple occurrences of “optional,” then, unless otherwise specifically stated and where there is no contradiction or mutually restrictive relationship, each “optional” is independent of the others.

In the present invention, in “a first aspect,” “a second aspect,” “a third aspect,” “a fourth aspect,” and the like, the terms “first,” “second,” “third,” “fourth,” and the like are only used for descriptive purposes, and cannot be understood as indicating or implying relative importance or quantity, nor can they be understood as implicitly indicating the importance or quantity of the indicated technical features. Moreover, “first,” “second,” “third,” “fourth,” and the like only serve the purpose of non-exhaustive enumerative description, and should be understood as not constituting a closed-ended limitation on quantity.

In the present invention, among technical features described in an open-ended manner, included are closed-ended technical solutions composed of the recited features, and also included are open-ended technical solutions comprising the recited features.

In the present invention, where a numerical interval (that is, a numerical range) is involved, unless otherwise specifically stated, the optional numerical values distributed within the above numerical interval are regarded as continuous, and include the two numerical endpoints of the numerical range (that is, the minimum value and the maximum value), as well as each numerical value between the two numerical endpoints. Unless otherwise specifically stated, when a numerical interval refers only to integers within the numerical interval, including the two endpoint integers of the numerical range, as well as each integer between the two endpoints, this is equivalent herein to directly listing each integer, for example, t being an integer selected from 1 to 10 means that t is any one integer selected from the integer group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. In addition, when multiple ranges describe features or characteristics, these ranges may be combined. In other words, unless otherwise indicated, the ranges disclosed herein should be understood as including any and all subranges subsumed therein.

The temperature parameters in the present invention, unless otherwise specifically limited, are allowed to be constant-temperature treatment, and are also allowed to vary within a certain temperature interval. It should be understood that the constant-temperature treatment allows the temperature to fluctuate within the precision range controlled by the instrument. Fluctuation is allowed within a range such as $\pm 5^{\circ}\text{C}$, $\pm 4^{\circ}\text{C}$, $\pm 3^{\circ}\text{C}$, $\pm 2^{\circ}\text{C}$, or $\pm 1^{\circ}\text{C}$.

In the present invention, % (w/w) and wt% both denote weight percentage, % (v/v) denotes volume percentage, and % (w/v) denotes mass/volume percentage.

All literature mentioned in the present invention is incorporated herein by reference, just as if each of the literature were individually incorporated by reference. Unless there is a conflict with the inventive purpose and/or technical solution of the present application, the cited literature involved in the present invention is cited for its entire content and all purposes. When cited literature is involved in the present invention, the definitions of related technical features, terms, nouns, phrases, and the like in the cited literature are also incorporated. When cited literature is involved in the present invention, examples and preferred modes of the cited related technical features may also be incorporated into the present application as reference, but only to the extent that the present invention can be implemented. It should be understood that, when the cited content conflicts with the description in the present application, the present application shall prevail or adaptive correction may be made according to the description of the present application.

The embodiments of the present invention will be described in detail below in conjunction with examples. It should be understood that these examples are only used to illustrate the present invention and are not used to limit the scope of the present invention. For the experimental methods in the following examples for which specific conditions are not indicated, the guidance provided in the present invention shall be consulted first, and they may also be based on experimental manuals or conventional conditions in the art, may also follow the recommendation of the manufacturer, or may be based on experimental methods known in the art.

FCS is caused by one or more gene mutations, and these gene mutations can cause loss of gene functions in lipoprotein lipase (LPL), apolipoprotein CII (APOC2), lipase maturation factor 1 (LMF1), glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1), apolipoprotein AV

(APOA5), and glycerol-3-phosphate dehydrogenase 1 (GPD1), thereby affecting the lipolysis and clearance of chylomicrons. In one example embodiment of the present application, 6 genes closely related to FCS were selected (*LPL*, *APOC2*, *LMF1*, *GPIHBP1*, *APOA5*, and *GPD1*), and a probe panel covering exon and hotspot intron regions of the 6 genes was designed for capture sequencing, aiming to stably and accurately detect gene mutations related to FCS, and to provide a more convenient and accurate FCS detection method for clinical practice. It has important significance for the clinical diagnosis and treatment of FCS.

In a first aspect of the embodiments of the present application

The present application provides a capture probe comprising one or more probe sets selected from a probe set 1 to a probe set 6;

Probe set 1 comprises one or more probes selected from probes 1 to 26;

Probe set 2 comprises one or more probes selected from probes 27 to 64;

Probe set 3 comprises one or more probes selected from probes 65 to 112;

Probe set 4 comprises one or more probes selected from probes 113 to 139;

Probe set 5 comprises one or more probes selected from probes 140 to 382;

Probe set 6 comprises one or more probes selected from probes 383 to 425;

The probes 1 to 425 are constructed for target gene fragments located between different start positions and end positions on the following chromosomes and are complementary to and paired with said target gene fragments:

Probe number	Chromosome	Start position	End position
Probe 1	chr11	116660063	116660183;
Probe 2	chr11	116660168	116660288;
Probe 3	chr11	116660273	116660393;
Probe 4	chr11	116660378	116660498;
Probe 5	chr11	116660483	116660603;
Probe 6	chr11	116660588	116660708;
Probe 7	chr11	116660693	116660813;
Probe 8	chr11	116660798	116660918;
Probe 9	chr11	116660903	116661023;
Probe 10	chr11	116661008	116661128;
Probe 11	chr11	116661113	116661233;
Probe 12	chr11	116661218	116661338;
Probe 13	chr11	116661323	116661443;
Probe 14	chr11	116661428	116661548;
Probe 15	chr11	116661533	116661653;
Probe 16	chr11	116661638	116661758;
Probe 17	chr11	116661743	116661863;
Probe 18	chr11	116662282	116662402;
Probe 19	chr11	116662387	116662507;
Probe 20	chr11	116662508	116662628;
Probe 21	chr11	116663076	116663196;
Probe 22	chr11	116663181	116663301;
Probe 23	chr11	116663286	116663406;
Probe 24	chr11	116663391	116663511;
Probe 25	chr11	116663496	116663616;
Probe 26	chr11	116663601	116663721;
Probe 27	chr12	50497271	50497391;
Probe 28	chr12	50497376	50497496;
Probe 29	chr12	50497481	50497601;

Probe 30	chr12	50497586	50497706;
Probe 31	chr12	50497691	50497811;
Probe 32	chr12	50497796	50497916;
Probe 33	chr12	50498337	50498457;
Probe 34	chr12	50498442	50498562;
Probe 35	chr12	50499311	50499431;
Probe 36	chr12	50499416	50499536;
Probe 37	chr12	50500051	50500171;
Probe 38	chr12	50500156	50500276;
Probe 39	chr12	50500568	50500688;
Probe 40	chr12	50500673	50500793;
Probe 41	chr12	50501330	50501450;
Probe 42	chr12	50501435	50501555;
Probe 43	chr12	50501540	50501660;
Probe 44	chr12	50501787	50501907;
Probe 45	chr12	50501892	50502012;
Probe 46	chr12	50503186	50503306;
Probe 47	chr12	50503291	50503411;
Probe 48	chr12	50503396	50503516;
Probe 49	chr12	50503501	50503621;
Probe 50	chr12	50503606	50503726;
Probe 51	chr12	50503711	50503831;
Probe 52	chr12	50503816	50503936;
Probe 53	chr12	50503921	50504041;
Probe 54	chr12	50504026	50504146;
Probe 55	chr12	50504131	50504251;
Probe 56	chr12	50504236	50504356;
Probe 57	chr12	50504341	50504461;
Probe 58	chr12	50504446	50504566;
Probe 59	chr12	50504551	50504671;
Probe 60	chr12	50504656	50504776;
Probe 61	chr12	50504761	50504881;
Probe 62	chr12	50504866	50504986;
Probe 63	chr12	50504971	50505091;
Probe 64	chr12	50505076	50505196;
Probe 65	chr16	903614	903734;
Probe 66	chr16	903719	903839;
Probe 67	chr16	903824	903944;
Probe 68	chr16	903929	904049;
Probe 69	chr16	904034	904154;
Probe 70	chr16	904139	904259;
Probe 71	chr16	904244	904364;
Probe 72	chr16	904349	904469;
Probe 73	chr16	904454	904574;
Probe 74	chr16	904559	904679;
Probe 75	chr16	904664	904784;
Probe 76	chr16	905087	905207;
Probe 77	chr16	905192	905312;
Probe 78	chr16	918924	919044;
Probe 79	chr16	919029	919149;
Probe 80	chr16	919863	919983;

Probe 81	chr16	919968	920088;
Probe 82	chr16	920709	920829;
Probe 83	chr16	920814	920934;
Probe 84	chr16	921141	921261;
Probe 85	chr16	921246	921366;
Probe 86	chr16	929550	929670;
Probe 87	chr16	929655	929775;
Probe 88	chr16	942987	943107;
Probe 89	chr16	960911	961031;
Probe 90	chr16	961016	961136;
Probe 91	chr16	981622	981742;
Probe 92	chr16	981727	981847;
Probe 93	chr16	983971	984091;
Probe 94	chr16	984076	984196;
Probe 95	chr16	984170	984290;
Probe 96	chr16	1004337	1004457;
Probe 97	chr16	1004442	1004562;
Probe 98	chr16	1004547	1004667;
Probe 99	chr16	1004652	1004772;
Probe 100	chr16	1020768	1020888;
Probe 101	chr16	1020873	1020993;
Probe 102	chr16	1020978	1021098;
Probe 103	chr16	1031125	1031245;
Probe 104	chr16	1031230	1031350;
Probe 105	chr16	1031335	1031455;
Probe 106	chr16	1031440	1031560;
Probe 107	chr16	1031545	1031665;
Probe 108	chr16	1031650	1031770;
Probe 109	chr16	1031755	1031875;
Probe 110	chr16	1031860	1031980;
Probe 111	chr16	1031965	1032085;
Probe 112	chr16	1032070	1032190;
Probe 113	chr19	45448788	45448908;
Probe 114	chr19	45448893	45449013;
Probe 115	chr19	45448998	45449118;
Probe 116	chr19	45449103	45449223;
Probe 117	chr19	45449208	45449328;
Probe 118	chr19	45449313	45449433;
Probe 119	chr19	45449418	45449538;
Probe 120	chr19	45449628	45449748;
Probe 121	chr19	45449733	45449853;
Probe 122	chr19	45450048	45450168;
Probe 123	chr19	45450363	45450483;
Probe 124	chr19	45450468	45450588;
Probe 125	chr19	45450573	45450693;
Probe 126	chr19	45450678	45450798;
Probe 127	chr19	45451518	45451638;
Probe 128	chr19	45451623	45451743;
Probe 129	chr19	45451728	45451848;
Probe 130	chr19	45451833	45451953;
Probe 131	chr19	45451938	45452058;

Probe 132	chr19	45452043	45452163;
Probe 133	chr19	45452148	45452268;
Probe 134	chr19	45452253	45452373;
Probe 135	chr19	45452358	45452478;
Probe 136	chr19	45452463	45452583;
Probe 137	chr19	45452568	45452688;
Probe 138	chr19	45452673	45452793;
Probe 139	chr19	45452778	45452898;
Probe 140	chr8	19796244	19796364;
Probe 141	chr8	19796349	19796469;
Probe 142	chr8	19796454	19796574;
Probe 143	chr8	19796559	19796679;
Probe 144	chr8	19796664	19796784;
Probe 145	chr8	19796769	19796889;
Probe 146	chr8	19796874	19796994;
Probe 147	chr8	19796979	19797099;
Probe 148	chr8	19797084	19797204;
Probe 149	chr8	19797189	19797309;
Probe 150	chr8	19797294	19797414;
Probe 151	chr8	19797399	19797519;
Probe 152	chr8	19797504	19797624;
Probe 153	chr8	19797609	19797729;
Probe 154	chr8	19797714	19797834;
Probe 155	chr8	19797819	19797939;
Probe 156	chr8	19797924	19798044;
Probe 157	chr8	19798029	19798149;
Probe 158	chr8	19798134	19798254;
Probe 159	chr8	19798239	19798359;
Probe 160	chr8	19798344	19798464;
Probe 161	chr8	19798449	19798569;
Probe 162	chr8	19798554	19798674;
Probe 163	chr8	19798659	19798779;
Probe 164	chr8	19798764	19798884;
Probe 165	chr8	19798869	19798989;
Probe 166	chr8	19798974	19799094;
Probe 167	chr8	19799079	19799199;
Probe 168	chr8	19799184	19799304;
Probe 169	chr8	19799289	19799409;
Probe 170	chr8	19799394	19799514;
Probe 171	chr8	19799499	19799619;
Probe 172	chr8	19799604	19799724;
Probe 173	chr8	19799709	19799829;
Probe 174	chr8	19799814	19799934;
Probe 175	chr8	19799919	19800039;
Probe 176	chr8	19800024	19800144;
Probe 177	chr8	19800129	19800249;
Probe 178	chr8	19800234	19800354;
Probe 179	chr8	19800339	19800459;
Probe 180	chr8	19800444	19800564;
Probe 181	chr8	19800549	19800669;
Probe 182	chr8	19800654	19800774;

Probe 183	chr8	19800759	19800879;
Probe 184	chr8	19800864	19800984;
Probe 185	chr8	19800969	19801089;
Probe 186	chr8	19801074	19801194;
Probe 187	chr8	19801179	19801299;
Probe 188	chr8	19801284	19801404;
Probe 189	chr8	19801704	19801824;
Probe 190	chr8	19801809	19801929;
Probe 191	chr8	19801914	19802034;
Probe 192	chr8	19802019	19802139;
Probe 193	chr8	19802124	19802244;
Probe 194	chr8	19802229	19802349;
Probe 195	chr8	19802334	19802454;
Probe 196	chr8	19802439	19802559;
Probe 197	chr8	19802544	19802664;
Probe 198	chr8	19802649	19802769;
Probe 199	chr8	19802754	19802874;
Probe 200	chr8	19802859	19802979;
Probe 201	chr8	19802964	19803084;
Probe 202	chr8	19803069	19803189;
Probe 203	chr8	19803174	19803294;
Probe 204	chr8	19803279	19803399;
Probe 205	chr8	19803384	19803504;
Probe 206	chr8	19803489	19803609;
Probe 207	chr8	19803594	19803714;
Probe 208	chr8	19803699	19803819;
Probe 209	chr8	19803804	19803924;
Probe 210	chr8	19803909	19804029;
Probe 211	chr8	19804014	19804134;
Probe 212	chr8	19804119	19804239;
Probe 213	chr8	19804224	19804344;
Probe 214	chr8	19804329	19804449;
Probe 215	chr8	19804434	19804554;
Probe 216	chr8	19804539	19804659;
Probe 217	chr8	19804644	19804764;
Probe 218	chr8	19805064	19805184;
Probe 219	chr8	19805169	19805289;
Probe 220	chr8	19805274	19805394;
Probe 221	chr8	19805379	19805499;
Probe 222	chr8	19805484	19805604;
Probe 223	chr8	19805589	19805709;
Probe 224	chr8	19805694	19805814;
Probe 225	chr8	19805799	19805919;
Probe 226	chr8	19805904	19806024;
Probe 227	chr8	19806009	19806129;
Probe 228	chr8	19806114	19806234;
Probe 229	chr8	19806219	19806339;
Probe 230	chr8	19806324	19806444;
Probe 231	chr8	19806429	19806549;
Probe 232	chr8	19806534	19806654;
Probe 233	chr8	19806639	19806759;

Probe 234	chr8	19806744	19806864;
Probe 235	chr8	19806849	19806969;
Probe 236	chr8	19807269	19807389;
Probe 237	chr8	19807374	19807494;
Probe 238	chr8	19807479	19807599;
Probe 239	chr8	19807584	19807704;
Probe 240	chr8	19807689	19807809;
Probe 241	chr8	19807794	19807914;
Probe 242	chr8	19807899	19808019;
Probe 243	chr8	19808319	19808439;
Probe 244	chr8	19808424	19808544;
Probe 245	chr8	19808529	19808649;
Probe 246	chr8	19808634	19808754;
Probe 247	chr8	19808739	19808859;
Probe 248	chr8	19808844	19808964;
Probe 249	chr8	19808949	19809069;
Probe 250	chr8	19809054	19809174;
Probe 251	chr8	19809159	19809279;
Probe 252	chr8	19809264	19809384;
Probe 253	chr8	19809369	19809489;
Probe 254	chr8	19809474	19809594;
Probe 255	chr8	19809579	19809699;
Probe 256	chr8	19809684	19809804;
Probe 257	chr8	19809789	19809909;
Probe 258	chr8	19809894	19810014;
Probe 259	chr8	19809999	19810119;
Probe 260	chr8	19810104	19810224;
Probe 261	chr8	19810209	19810329;
Probe 262	chr8	19810314	19810434;
Probe 263	chr8	19810419	19810539;
Probe 264	chr8	19810524	19810644;
Probe 265	chr8	19810629	19810749;
Probe 266	chr8	19810734	19810854;
Probe 267	chr8	19810839	19810959;
Probe 268	chr8	19810944	19811064;
Probe 269	chr8	19811049	19811169;
Probe 270	chr8	19811154	19811274;
Probe 271	chr8	19811259	19811379;
Probe 272	chr8	19811364	19811484;
Probe 273	chr8	19811469	19811589;
Probe 274	chr8	19811574	19811694;
Probe 275	chr8	19811679	19811799;
Probe 276	chr8	19811784	19811904;
Probe 277	chr8	19811889	19812009;
Probe 278	chr8	19811994	19812114;
Probe 279	chr8	19812099	19812219;
Probe 280	chr8	19812204	19812324;
Probe 281	chr8	19812309	19812429;
Probe 282	chr8	19812519	19812639;
Probe 283	chr8	19812624	19812744;
Probe 284	chr8	19812729	19812849;

Probe 285	chr8	19812834	19812954;
Probe 286	chr8	19812939	19813059;
Probe 287	chr8	19813044	19813164;
Probe 288	chr8	19813149	19813269;
Probe 289	chr8	19813254	19813374;
Probe 290	chr8	19813359	19813479;
Probe 291	chr8	19813464	19813584;
Probe 292	chr8	19813569	19813689;
Probe 293	chr8	19813674	19813794;
Probe 294	chr8	19813779	19813899;
Probe 295	chr8	19813884	19814004;
Probe 296	chr8	19814094	19814214;
Probe 297	chr8	19814199	19814319;
Probe 298	chr8	19814304	19814424;
Probe 299	chr8	19814619	19814739;
Probe 300	chr8	19814724	19814844;
Probe 301	chr8	19814829	19814949;
Probe 302	chr8	19814934	19815054;
Probe 303	chr8	19815039	19815159;
Probe 304	chr8	19815144	19815264;
Probe 305	chr8	19815249	19815369;
Probe 306	chr8	19815354	19815474;
Probe 307	chr8	19815459	19815579;
Probe 308	chr8	19815774	19815894;
Probe 309	chr8	19815879	19815999;
Probe 310	chr8	19815984	19816104;
Probe 311	chr8	19816194	19816314;
Probe 312	chr8	19816299	19816419;
Probe 313	chr8	19816404	19816524;
Probe 314	chr8	19816509	19816629;
Probe 315	chr8	19816614	19816734;
Probe 316	chr8	19816719	19816839;
Probe 317	chr8	19816824	19816944;
Probe 318	chr8	19816929	19817049;
Probe 319	chr8	19817034	19817154;
Probe 320	chr8	19817139	19817259;
Probe 321	chr8	19817559	19817679;
Probe 322	chr8	19817664	19817784;
Probe 323	chr8	19817769	19817889;
Probe 324	chr8	19817874	19817994;
Probe 325	chr8	19817979	19818099;
Probe 326	chr8	19818084	19818204;
Probe 327	chr8	19818189	19818309;
Probe 328	chr8	19818294	19818414;
Probe 329	chr8	19818399	19818519;
Probe 330	chr8	19818504	19818624;
Probe 331	chr8	19818609	19818729;
Probe 332	chr8	19818714	19818834;
Probe 333	chr8	19818819	19818939;
Probe 334	chr8	19818924	19819044;
Probe 335	chr8	19819029	19819149;

Probe 336	chr8	19819134	19819254;
Probe 337	chr8	19819239	19819359;
Probe 338	chr8	19819344	19819464;
Probe 339	chr8	19819449	19819569;
Probe 340	chr8	19819554	19819674;
Probe 341	chr8	19819659	19819779;
Probe 342	chr8	19819764	19819884;
Probe 343	chr8	19819869	19819989;
Probe 344	chr8	19819974	19820094;
Probe 345	chr8	19820079	19820199;
Probe 346	chr8	19820184	19820304;
Probe 347	chr8	19820289	19820409;
Probe 348	chr8	19820394	19820514;
Probe 349	chr8	19820499	19820619;
Probe 350	chr8	19820604	19820724;
Probe 351	chr8	19820919	19821039;
Probe 352	chr8	19821024	19821144;
Probe 353	chr8	19821129	19821249;
Probe 354	chr8	19821234	19821354;
Probe 355	chr8	19821339	19821459;
Probe 356	chr8	19821759	19821879;
Probe 357	chr8	19821864	19821984;
Probe 358	chr8	19821969	19822089;
Probe 359	chr8	19822284	19822404;
Probe 360	chr8	19822389	19822509;
Probe 361	chr8	19822494	19822614;
Probe 362	chr8	19822599	19822719;
Probe 363	chr8	19822704	19822824;
Probe 364	chr8	19822809	19822929;
Probe 365	chr8	19822914	19823034;
Probe 366	chr8	19823019	19823139;
Probe 367	chr8	19823124	19823244;
Probe 368	chr8	19823229	19823349;
Probe 369	chr8	19823334	19823454;
Probe 370	chr8	19823439	19823559;
Probe 371	chr8	19823544	19823664;
Probe 372	chr8	19823649	19823769;
Probe 373	chr8	19823754	19823874;
Probe 374	chr8	19823859	19823979;
Probe 375	chr8	19823964	19824084;
Probe 376	chr8	19824069	19824189;
Probe 377	chr8	19824174	19824294;
Probe 378	chr8	19824279	19824399;
Probe 379	chr8	19824384	19824504;
Probe 380	chr8	19824489	19824609;
Probe 381	chr8	19824594	19824714;
Probe 382	chr8	19824699	19824819;
Probe 383	chr8	144294573	144294693;
Probe 384	chr8	144294678	144294798;
Probe 385	chr8	144294783	144294903;
Probe 386	chr8	144294888	144295008;

Probe 387	chr8	144294993	144295113;
Probe 388	chr8	144295098	144295218;
Probe 389	chr8	144295203	144295323;
Probe 390	chr8	144295308	144295428;
Probe 391	chr8	144295413	144295533;
Probe 392	chr8	144295518	144295638;
Probe 393	chr8	144295623	144295743;
Probe 394	chr8	144295728	144295848;
Probe 395	chr8	144295833	144295953;
Probe 396	chr8	144295938	144296058;
Probe 397	chr8	144296043	144296163;
Probe 398	chr8	144296148	144296268;
Probe 399	chr8	144296253	144296373;
Probe 400	chr8	144296358	144296478;
Probe 401	chr8	144296463	144296583;
Probe 402	chr8	144296568	144296688;
Probe 403	chr8	144296673	144296793;
Probe 404	chr8	144296778	144296898;
Probe 405	chr8	144296883	144297003;
Probe 406	chr8	144296988	144297108;
Probe 407	chr8	144297093	144297213;
Probe 408	chr8	144297198	144297318;
Probe 409	chr8	144297303	144297423;
Probe 410	chr8	144297408	144297528;
Probe 411	chr8	144297513	144297633;
Probe 412	chr8	144297618	144297738;
Probe 413	chr8	144297723	144297843;
Probe 414	chr8	144297828	144297948;
Probe 415	chr8	144297933	144298053;
Probe 416	chr8	144298038	144298158;
Probe 417	chr8	144298143	144298263;
Probe 418	chr8	144298248	144298368;
Probe 419	chr8	144298353	144298473;
Probe 420	chr8	144298458	144298578;
Probe 421	chr8	144298563	144298683;
Probe 422	chr8	144298668	144298788;
Probe 423	chr8	144298773	144298893;
Probe 424	chr8	144298878	144298998;
Probe 425	chr8	144298983	144299103;

The reference genome is Hg19.

The capture probes provided in the embodiments of the present application are designed to cover the exons and hotspot intron regions of 6 genes closely related to FCS (*LPL*, *APOC2*, *LMF1*, *GPIHBP1*, *APOA5* and *GPD1*). It should be understood that, according to actual needs, some of the probe sets may be selected to detect some of the target genes, and they may be, for example, any one, two, three, four, or five probe sets selected from the probe sets 1 to 6. In order to meet the detection requirements of certain regions of the target gene, a corresponding number of probes may be selected from the corresponding probe set, for example, selecting 1 probe, 2 probes, 3 probes... 24 probes, 25 probes, and 26 probes from the probe set 1.

Optionally, the capture probes comprise a plurality of probe sets selected from the probe set 1 to probe set 6;

The probe set 1 comprises a plurality of probes selected from probes 1 to 26;

The probe set 2 comprises a plurality of probes selected from the probe 27 to the probe 64;

The probe set 3 comprises a plurality of probes selected from the probe 65 to the probe 112;

The probe set 4 comprises a plurality of probes selected from the probe 113 to the probe 139;

The probe set 5 comprises a plurality of probes selected from the probe 140 to the probe 382;

The probe set 6 comprises a plurality of probes selected from the probe 383 to the probe 425.

Further optionally, the capture probes comprise the probe set 1 to the probe set 6;

The probe set 1 comprises probes 1 to 26;

The probe set 2 comprises the probe 27 to the probe 64;

The probe set 3 comprises the probe 65 to the probe 112;

The probe set 4 comprises the probe 113 to the probe 139;

The probe set 5 comprises the probe 140 to the probe 382;

The probe set 6 comprises the probe 383 to the probe 425.

A second aspect of the embodiments of the present application

The embodiments of the present application provide use of the capture probes in preparing a familial chylomicronemia syndrome detection kit.

A third aspect of the embodiments of the present application

The embodiments of the present application provide a familial chylomicronemia syndrome detection kit comprising the capture probes.

Optionally, the familial chylomicronemia syndrome detection kit further includes one or more of a nucleic acid extraction reagent, a DNA library construction reagent, a sample and library quantification reagent, a fragment quality control reagent, a hybridization capture reagent, a nucleic acid purification reagent, a target gene fragment amplification reagent, and a sequencing reagent.

A fourth aspect of the embodiments of the present application

The embodiments of the present application provide use of the capture probes in constructing a detection library for gene mutations related to familial chylomicronemia syndrome.

A fifth aspect of the embodiments of the present application

The embodiments of the present application provide use of the detection kit in constructing a detection library for gene mutations related to familial chylomicronemia syndrome.

A sixth aspect of the embodiments of the present application

The embodiments of the present application provide a method for detecting familial chylomicronemia syndrome-related gene mutations, comprising using the capture probes or the detection kit to capture target gene fragments containing gene mutations related to familial chylomicronemia syndrome, and detecting the captured fragments.

Optionally, sequencing is used to detect the captured fragments.

In the following specific embodiments, measurement parameters involving raw material components may, unless otherwise specifically stated, have slight deviations within the weighing accuracy range. For the temperature and time parameters involved, deviations caused by instrument testing accuracy or operational accuracy are allowable.

The reagents used in the detection process of this embodiment is listed as follows:

Table 1

No.	Function	Name of reagent consumable	Brand	Specification
1	Nucleic acid extraction	QIAamp DNA Mini Kit(250)	QIAGEN	51306
2	Nucleic acid quantification	Qubit™dsDNA HS Assay Kit	ThermoFisher	Q32854
3	Specifically hydrolyzing cytosine (C) or uracil (U) residues of RNA	RNase A (17,500 U)	QIAGEN	19101
4	Constructing DNA libraries	VAHTS Universal DNA Library Prep Kit for Illumina V3	Vazyme	ND607-02
5	DNA amplification	KAPA HiFi HotStart ReadyMix	Kapa Biosystems	KK2602
6	Library construction adapter	NEXTflex®Dual-Indexed DNA Barcodes(1-96)	Bioo Scientific	NOVA-514160
7	Library construction adapter	NEXTflex®Dual-Indexed DNA Barcodes (97-192)	Bioo Scientific	NOVA-514161

No.	Function	Name of reagent consumable	Brand	Specification
8	Purifying nucleic acid	Agencourt AMPure XP 450mL Kit	Beckman Coulter	A63882
9	Blocking sample adapter sequences	xGen®Universal Blockers-TS Mix,4x96rxn	Integrated DNA Technologies	1075476
10	Binding and capturing nucleic acids complementary to the target sequence	FCS_Probes (Table 4)	Nanodigmbio	customized
11	Targeted capture hybridization and washing	xGen® Hybridization and Wash Kit	Integrated DNA Technologies	1080584
12	Complementarily paired P5 sequence	Illumina P5 Primer	customized	customized
13	Complementarily paired P7 sequence	Illumina P7 Primer	customized	customized
14	DNA molecular weight determination and quantitative analysis	DNA High Sensitivity Reagent Kit	PerkinElmer	CLS760672
15	Microfluidic chip	DNA Extended Range Chip for use with GX Touch/GXII Touch HT	PerkinElmer	760517
16	Buffer component	TWEEN®20	SigmaAldrich	P7949
17	Buffer component	1M Tris pH 7.0	ThermoFisher	AM9851
18	Buffer component	Sodium hydroxide solution	Fluka Analytical	319511-500ML
19	Buffer component	Sodium hypochlorite solution	SigmaAldrich	239305
20	Calibration quality control	PhiX Control v3	Illumina	FC-110-3001
21	Cluster generation and sequencing	NovaSeq 6000 v2 kit (300cycles)	Illumina	FC-404-2004

The equipment used in the detection process of this embodiment is listed as follows:

Table 2

No.	Function	Equipment name	Factory number	Model
1	Vortex oscillation	Vortex-Genie 2	Scientific Industries	SI-0246
2	High-speed centrifugation	Heraeus Pico 21 Centrifuge, Ventilated	ThermoFisher	75002415
3	Dry constant temperature	GL-150B Dry Thermostat	Kylin-Bell	GL-150B
4	Instant rapid centrifugation	TGear Mini centrifuge (OSE-MC8)	TIANGEN BIOTECH (BEIJING)	OSE-MC8
5	Nucleic acid quantification	Qubit 3 Fluorometer	ThermoFisher	Q33216
6	Nucleic acid quantitative analysis and purity assessment	NanoDrop™ 2000 Spectrophotometer	ThermoFisher	ND-2000
7	PCR nucleic acid amplification	GeneAmp® PCR System 9700, 96-Well Aluminum	ThermoFisher	4314879
8	Electrophoresis power supply	PowerPac™ Basic Power Supply	Bio-Rad	1645050
9	Gel imaging analysis	Tanon 2500 Gel Imaging System	Tanon Science & Technology	Tanon-2500
10	Ultrasonic fragmentation of samples	M220 Focused-ultrasonicator™	Covaris	500295
11	PCR nucleic acid amplification	Veriti™ 96-Well Thermal Cycler	ThermoFisher	4375786
12	Vacuum concentration of nucleic acid	Savant™ DNA SpeedVac™ Concentrator	ThermoFisher	DNA120-230
13	Performing	LabChip GX Touch HT Nucleic Acid	PerkinElmer	CLS137031

	electrophoretic separation as well as qualitative and quantitative analysis of nucleic acid	Analyzer		
14	Aspiration, discharge	GL-802 Compact Desktop Vacuum Pump	Kylin-Bell	GL-802
15	Microplate centrifugation	MPS 1000 Mini Plate Spinner Centrifuge	Labnet	C1000
16	Preparation of pure water and ultrapure water	Direct-Q® 3 UV Water Purification System	MerckMillipore	ZRQSV3CN
17	High-throughput sequencing	NovaSeq™ 6000 Dx	Illumina	A00335

Example 1

In this example, the capture sequencing detection process for 6 genes related to FCS is divided into four steps: sample preparation, library construction, target region capture, and sequencing.

1. Panel design

In this embodiment, the region covered by the target capture probe panel for detecting 6 genes related to FCS, namely *LPL*, *APOC2*, *LMF1*, *GPIHBP1*, *APOA5* and *GPD1*, is 18.6 kb, covering all exons and hotspot intron regions of the 6 genes closely related to FCS (Table 3). The high-density probe design ensures that each target region will be covered by at least two probes (see Table 4).

Table 3. Probe coverage ranges for 6 FCS-related genes

Gene	Coverage
<i>APOC2</i>	Full exon+500bp upstream, 49.1% intron.
<i>LPL</i>	Full exon+500bp upstream, 89.3% intron.
<i>GPIHBP1</i>	Full gene+500bp upstream.
<i>APOA5</i>	Full exon+500bp upstream.
<i>GPD1</i>	Full exon+500bp upstream.
<i>LMF1</i>	Full exon+500bp upstream.

Table 4. Capture probes

Number	Chr	Start	End	Number	Chr	Start	End
1	chr11	116660063	116660183	14	chr11	116661428	116661548
2	chr11	116660168	116660288	15	chr11	116661533	116661653
3	chr11	116660273	116660393	16	chr11	116661638	116661758
4	chr11	116660378	116660498	17	chr11	116661743	116661863
5	chr11	116660483	116660603	18	chr11	116662282	116662402
6	chr11	116660588	116660708	19	chr11	116662387	116662507
7	chr11	116660693	116660813	20	chr11	116662508	116662628
8	chr11	116660798	116660918	21	chr11	116663076	116663196
9	chr11	116660903	116661023	22	chr11	116663181	116663301
10	chr11	116661008	116661128	23	chr11	116663286	116663406
11	chr11	116661113	116661233	24	chr11	116663391	116663511
12	chr11	116661218	116661338	25	chr11	116663496	116663616
13	chr11	116661323	116661443	26	chr11	116663601	116663721
27	chr12	50497271	50497391	46	chr12	50503186	50503306
28	chr12	50497376	50497496	47	chr12	50503291	50503411
29	chr12	50497481	50497601	48	chr12	50503396	50503516
30	chr12	50497586	50497706	49	chr12	50503501	50503621

31	chr12	50497691	50497811	50	chr12	50503606	50503726
32	chr12	50497796	50497916	51	chr12	50503711	50503831
33	chr12	50498337	50498457	52	chr12	50503816	50503936
34	chr12	50498442	50498562	53	chr12	50503921	50504041
35	chr12	50499311	50499431	54	chr12	50504026	50504146
36	chr12	50499416	50499536	55	chr12	50504131	50504251
37	chr12	50500051	50500171	56	chr12	50504236	50504356
38	chr12	50500156	50500276	57	chr12	50504341	50504461
39	chr12	50500568	50500688	58	chr12	50504446	50504566
40	chr12	50500673	50500793	59	chr12	50504551	50504671
41	chr12	50501330	50501450	60	chr12	50504656	50504776
42	chr12	50501435	50501555	61	chr12	50504761	50504881
43	chr12	50501540	50501660	62	chr12	50504866	50504986
44	chr12	50501787	50501907	63	chr12	50504971	50505091
45	chr12	50501892	50502012	64	chr12	50505076	50505196
65	chr16	903614	903734	89	chr16	960911	961031
66	chr16	903719	903839	90	chr16	961016	961136
67	chr16	903824	903944	91	chr16	981622	981742
68	chr16	903929	904049	92	chr16	981727	981847
69	chr16	904034	904154	93	chr16	983971	984091
70	chr16	904139	904259	94	chr16	984076	984196
71	chr16	904244	904364	95	chr16	984170	984290
72	chr16	904349	904469	96	chr16	1004337	1004457
73	chr16	904454	904574	97	chr16	1004442	1004562
74	chr16	904559	904679	98	chr16	1004547	1004667
75	chr16	904664	904784	99	chr16	1004652	1004772
76	chr16	905087	905207	100	chr16	1020768	1020888
77	chr16	905192	905312	101	chr16	1020873	1020993
78	chr16	918924	919044	102	chr16	1020978	1021098
79	chr16	919029	919149	103	chr16	1031125	1031245
80	chr16	919863	919983	104	chr16	1031230	1031350
81	chr16	919968	920088	105	chr16	1031335	1031455
82	chr16	920709	920829	106	chr16	1031440	1031560
83	chr16	920814	920934	107	chr16	1031545	1031665
84	chr16	921141	921261	108	chr16	1031650	1031770
85	chr16	921246	921366	109	chr16	1031755	1031875
86	chr16	929550	929670	110	chr16	1031860	1031980
87	chr16	929655	929775	111	chr16	1031965	1032085
88	chr16	942987	943107	112	chr16	1032070	1032190
113	chr19	45448788	45448908	126	chr19	45450678	45450798
114	chr19	45448893	45449013	127	chr19	45451518	45451638
115	chr19	45448998	45449118	128	chr19	45451623	45451743
116	chr19	45449103	45449223	129	chr19	45451728	45451848
117	chr19	45449208	45449328	130	chr19	45451833	45451953
118	chr19	45449313	45449433	131	chr19	45451938	45452058
119	chr19	45449418	45449538	132	chr19	45452043	45452163
120	chr19	45449628	45449748	133	chr19	45452148	45452268
121	chr19	45449733	45449853	134	chr19	45452253	45452373
122	chr19	45450048	45450168	135	chr19	45452358	45452478

123	chr19	45450363	45450483	136	chr19	45452463	45452583
124	chr19	45450468	45450588	137	chr19	45452568	45452688
125	chr19	45450573	45450693	138	chr19	45452673	45452793
140	chr8	19796244	19796364	139	chr19	45452778	45452898
141	chr8	19796349	19796469	262	chr8	19810314	19810434
142	chr8	19796454	19796574	263	chr8	19810419	19810539
143	chr8	19796559	19796679	264	chr8	19810524	19810644
144	chr8	19796664	19796784	265	chr8	19810629	19810749
145	chr8	19796769	19796889	266	chr8	19810734	19810854
146	chr8	19796874	19796994	267	chr8	19810839	19810959
147	chr8	19796979	19797099	268	chr8	19810944	19811064
148	chr8	19797084	19797204	269	chr8	19811049	19811169
149	chr8	19797189	19797309	270	chr8	19811154	19811274
150	chr8	19797294	19797414	271	chr8	19811259	19811379
151	chr8	19797399	19797519	272	chr8	19811364	19811484
152	chr8	19797504	19797624	273	chr8	19811469	19811589
153	chr8	19797609	19797729	274	chr8	19811574	19811694
154	chr8	19797714	19797834	275	chr8	19811679	19811799
155	chr8	19797819	19797939	276	chr8	19811784	19811904
156	chr8	19797924	19798044	277	chr8	19811889	19812009
157	chr8	19798029	19798149	278	chr8	19811994	19812114
158	chr8	19798134	19798254	279	chr8	19812099	19812219
159	chr8	19798239	19798359	280	chr8	19812204	19812324
160	chr8	19798344	19798464	281	chr8	19812309	19812429
161	chr8	19798449	19798569	282	chr8	19812519	19812639
162	chr8	19798554	19798674	283	chr8	19812624	19812744
163	chr8	19798659	19798779	284	chr8	19812729	19812849
164	chr8	19798764	19798884	285	chr8	19812834	19812954
165	chr8	19798869	19798989	286	chr8	19812939	19813059
166	chr8	19798974	19799094	287	chr8	19813044	19813164
167	chr8	19799079	19799199	288	chr8	19813149	19813269
168	chr8	19799184	19799304	289	chr8	19813254	19813374
169	chr8	19799289	19799409	290	chr8	19813359	19813479
170	chr8	19799394	19799514	291	chr8	19813464	19813584
171	chr8	19799499	19799619	292	chr8	19813569	19813689
172	chr8	19799604	19799724	293	chr8	19813674	19813794
173	chr8	19799709	19799829	294	chr8	19813779	19813899
174	chr8	19799814	19799934	295	chr8	19813884	19814004
175	chr8	19799919	19800039	296	chr8	19814094	19814214
176	chr8	19800024	19800144	297	chr8	19814199	19814319
177	chr8	19800129	19800249	298	chr8	19814304	19814424
178	chr8	19800234	19800354	299	chr8	19814619	19814739
179	chr8	19800339	19800459	300	chr8	19814724	19814844
180	chr8	19800444	19800564	301	chr8	19814829	19814949
181	chr8	19800549	19800669	302	chr8	19814934	19815054
182	chr8	19800654	19800774	303	chr8	19815039	19815159
183	chr8	19800759	19800879	304	chr8	19815144	19815264
184	chr8	19800864	19800984	305	chr8	19815249	19815369
185	chr8	19800969	19801089	306	chr8	19815354	19815474

186	chr8	19801074	19801194	307	chr8	19815459	19815579
187	chr8	19801179	19801299	308	chr8	19815774	19815894
188	chr8	19801284	19801404	309	chr8	19815879	19815999
189	chr8	19801704	19801824	310	chr8	19815984	19816104
190	chr8	19801809	19801929	311	chr8	19816194	19816314
191	chr8	19801914	19802034	312	chr8	19816299	19816419
192	chr8	19802019	19802139	313	chr8	19816404	19816524
193	chr8	19802124	19802244	314	chr8	19816509	19816629
194	chr8	19802229	19802349	315	chr8	19816614	19816734
195	chr8	19802334	19802454	316	chr8	19816719	19816839
196	chr8	19802439	19802559	317	chr8	19816824	19816944
197	chr8	19802544	19802664	318	chr8	19816929	19817049
198	chr8	19802649	19802769	319	chr8	19817034	19817154
199	chr8	19802754	19802874	320	chr8	19817139	19817259
200	chr8	19802859	19802979	321	chr8	19817559	19817679
201	chr8	19802964	19803084	322	chr8	19817664	19817784
202	chr8	19803069	19803189	323	chr8	19817769	19817889
203	chr8	19803174	19803294	324	chr8	19817874	19817994
204	chr8	19803279	19803399	325	chr8	19817979	19818099
205	chr8	19803384	19803504	326	chr8	19818084	19818204
206	chr8	19803489	19803609	327	chr8	19818189	19818309
207	chr8	19803594	19803714	328	chr8	19818294	19818414
208	chr8	19803699	19803819	329	chr8	19818399	19818519
209	chr8	19803804	19803924	330	chr8	19818504	19818624
210	chr8	19803909	19804029	331	chr8	19818609	19818729
211	chr8	19804014	19804134	332	chr8	19818714	19818834
212	chr8	19804119	19804239	333	chr8	19818819	19818939
213	chr8	19804224	19804344	334	chr8	19818924	19819044
214	chr8	19804329	19804449	335	chr8	19819029	19819149
215	chr8	19804434	19804554	336	chr8	19819134	19819254
216	chr8	19804539	19804659	337	chr8	19819239	19819359
217	chr8	19804644	19804764	338	chr8	19819344	19819464
218	chr8	19805064	19805184	339	chr8	19819449	19819569
219	chr8	19805169	19805289	340	chr8	19819554	19819674
220	chr8	19805274	19805394	341	chr8	19819659	19819779
221	chr8	19805379	19805499	342	chr8	19819764	19819884
222	chr8	19805484	19805604	343	chr8	19819869	19819989
223	chr8	19805589	19805709	344	chr8	19819974	19820094
224	chr8	19805694	19805814	345	chr8	19820079	19820199
225	chr8	19805799	19805919	346	chr8	19820184	19820304
226	chr8	19805904	19806024	347	chr8	19820289	19820409
227	chr8	19806009	19806129	348	chr8	19820394	19820514
228	chr8	19806114	19806234	349	chr8	19820499	19820619
229	chr8	19806219	19806339	350	chr8	19820604	19820724
230	chr8	19806324	19806444	351	chr8	19820919	19821039
231	chr8	19806429	19806549	352	chr8	19821024	19821144
232	chr8	19806534	19806654	353	chr8	19821129	19821249
233	chr8	19806639	19806759	354	chr8	19821234	19821354
234	chr8	19806744	19806864	355	chr8	19821339	19821459

235	chr8	19806849	19806969	356	chr8	19821759	19821879
236	chr8	19807269	19807389	357	chr8	19821864	19821984
237	chr8	19807374	19807494	358	chr8	19821969	19822089
238	chr8	19807479	19807599	359	chr8	19822284	19822404
239	chr8	19807584	19807704	360	chr8	19822389	19822509
240	chr8	19807689	19807809	361	chr8	19822494	19822614
241	chr8	19807794	19807914	362	chr8	19822599	19822719
242	chr8	19807899	19808019	363	chr8	19822704	19822824
243	chr8	19808319	19808439	364	chr8	19822809	19822929
244	chr8	19808424	19808544	365	chr8	19822914	19823034
245	chr8	19808529	19808649	366	chr8	19823019	19823139
246	chr8	19808634	19808754	367	chr8	19823124	19823244
247	chr8	19808739	19808859	368	chr8	19823229	19823349
248	chr8	19808844	19808964	369	chr8	19823334	19823454
249	chr8	19808949	19809069	370	chr8	19823439	19823559
250	chr8	19809054	19809174	371	chr8	19823544	19823664
251	chr8	19809159	19809279	372	chr8	19823649	19823769
252	chr8	19809264	19809384	373	chr8	19823754	19823874
253	chr8	19809369	19809489	374	chr8	19823859	19823979
254	chr8	19809474	19809594	375	chr8	19823964	19824084
255	chr8	19809579	19809699	376	chr8	19824069	19824189
256	chr8	19809684	19809804	377	chr8	19824174	19824294
257	chr8	19809789	19809909	378	chr8	19824279	19824399
258	chr8	19809894	19810014	379	chr8	19824384	19824504
259	chr8	19809999	19810119	380	chr8	19824489	19824609
260	chr8	19810104	19810224	381	chr8	19824594	19824714
261	chr8	19810209	19810329	382	chr8	19824699	19824819
383	chr8	144294573	144294693	405	chr8	144296883	144297003
384	chr8	144294678	144294798	406	chr8	144296988	144297108
385	chr8	144294783	144294903	407	chr8	144297093	144297213
386	chr8	144294888	144295008	408	chr8	144297198	144297318
387	chr8	144294993	144295113	409	chr8	144297303	144297423
388	chr8	144295098	144295218	410	chr8	144297408	144297528
389	chr8	144295203	144295323	411	chr8	144297513	144297633
390	chr8	144295308	144295428	412	chr8	144297618	144297738
391	chr8	144295413	144295533	413	chr8	144297723	144297843
392	chr8	144295518	144295638	414	chr8	144297828	144297948
393	chr8	144295623	144295743	415	chr8	144297933	144298053
394	chr8	144295728	144295848	416	chr8	144298038	144298158
395	chr8	144295833	144295953	417	chr8	144298143	144298263
396	chr8	144295938	144296058	418	chr8	144298248	144298368
397	chr8	144296043	144296163	419	chr8	144298353	144298473
398	chr8	144296148	144296268	420	chr8	144298458	144298578
399	chr8	144296253	144296373	421	chr8	144298563	144298683
400	chr8	144296358	144296478	422	chr8	144298668	144298788
401	chr8	144296463	144296583	423	chr8	144298773	144298893
402	chr8	144296568	144296688	424	chr8	144298878	144298998
403	chr8	144296673	144296793	425	chr8	144298983	144299103
404	chr8	144296778	144296898				

In this example, target capture probes covered all exons and hotspot intronic regions of the above six genes to ensure accurate and efficient detection of FCS-related gene mutations and to provide a basis for the clinical diagnosis and medication guidance of FCS. The nucleotide sequences of the probes 1 to 425 are shown in SEQ ID NOs. 1 to 425.

2. Detection experiment design

The detection workflow includes four main steps: sample preparation, library construction, target region enrichment, and sequencing. First, about 300 ng of gDNA was taken and fragmented into DNA fragments of about 200 bp by using a Covaris ultrasonic fragmenter (see step 2.1), library preparation was carried out by using an Illumina V3 VAHTS Universal DNA Library Prep Kit (Vazyme ND607-02), and the library was quantified by using a Qubit® dsDNA HS Assay Kit (Thermo Fisher) (see step 2.2). An xGen hybridization and capture kit (Integrated DNA Technologies, 1080584) was used to perform FCS probe capture on the library, and after capture, library quality control (QC) was performed using a Qubit fluorometer (Invitrogen) and LabChip GX Touch HT (Perkin Elmer). Finally, sequencing was carried out on a NovaSeq6000 platform (Illumina) (2×150 bp) (see step 2.4).

The following is a detailed description of each experimental step:

2.1 Sample preparation

Ten mutant gDNA samples containing known variants in six genes (*LPL*, *APOC2*, *LMF1*, *GPIHBP1*, *APOA5*, and *GPD1*) (for specific gene variant types, see attached Table 5), and 10 wild-type gDNA samples not containing any variant type of the above 6 genes (Table 5) were selected. For each gDNA sample, about 300 ng was taken, IDTE buffer (10 mM Tris, 0.1 mM EDTA) was added to make up the volume to 50 μL, and the Covaris ultrasonic fragmenter was set according to the parameters in Table 6 below to fragment the gDNA samples for 180 s.

Table 5. Sample information

Sample number	Gene	Variant information	Sample number	Genotype
PN1	LPL	c.249 + 1G > A	N1	Wild type
PN2	LPL	c.1160_1161insT (p.Lys387fs)	N2	Wild type
PN3	APOC2	c.189C > A (p.Tyr63Ter)	N3	Wild type
PN4	LMF1	c.895C > T (p.Gln299Ter)	N4	Wild type
PN5	GPIHBP1	c.422G > A (p.Trp141Ter)	N5	Wild type
PN6	GPIHBP1	c.417_433del (p.Pro140fs)	N6	Wild type
PN7	APOA5	c.289C > T (p.Gln97Ter)	N7	Wild type
PN8	APOA5	c.990_993del (p.Asp332fs)	N8	Wild type
PN9	GPD1	c.219 + 1_219 + 3del	N9	Wild type

Table 6. Parameter settings of the covaris ultrasonic fragmenter

Peak incident power (W)	Duty factor (%)	Cycles per burst (#)	Treatment time (s)	Temperature (°C)	Sample volume (μL)
450	30	200	180	7	50

2.2 Library construction

2.2.1 End repair and A-tailing

1) transferred the fragmented sample to a 0.2 mL sterilized centrifuge tube, transferred the centrifuge tube onto ice, and then added the following reagents according to the table below.

Table 7

Component	Single reaction system (μL)	Preparation of 11 Mixes (μL)
Fragmented sample	50	550
End Prep Mix 4	15	165
Total volume	65	715

2) After microcentrifugation, collected the liquid to the bottom of the tube for the following reaction.

Table 8

Temperature	Time
Heated lid 105°C	On
20°C	15 min
65°C	15 min
4°C	∞

2.2.2 Adapter ligation

- 1) Thawed the ligase buffer, inverted to mix well, and placed on ice for later use.
- 2) Prepared the reaction system according to the table below, and on ice, dispensed the reagents into the above reaction tubes.

Table 9

Component	Single reaction system (μL)	Preparation of 11 Mixes (μL)
Rapid Ligation buffer 2	25	275
Rapid DNA ligase	5	55
Ultrapure water	3	33
Total volume	33	363

It is recommended that the IDT UDI Adapter Kit be used as the adapter. When the cDNA input amount was ≤ 10 ng, the adapter was diluted 20-fold (diluted with Nuclease-Free Water) before use.

- 3) After carefully confirming the sample number, added 2 μL of Adapter to each sample, gently pipetted to mix well, and after microcentrifugation, collected the liquid to the bottom of the tube. Allowed to react according to the following amplification program.

Table 10

Reaction temperature	Time
Heated lid 105°C	On
20°C	15 min
4°C	∞

2.2.3 Purification of post-ligation products

- 1) Equilibrated the magnetic beads at room temperature for 30 min and vortexed thoroughly to mix well, and took 80 μL into a new 1.5 mL centrifuge tube.
- 2) transferred 100 μL of the ligation product to the 1.5 mL centrifuge tube in step 2.2.2, vortexed to mix well, and incubated at room temperature for 5 min.
- 3) Placed the 1.5 mL centrifuge tube on a magnetic rack, let stand until the solution was completely clear, and discarded the supernatant.
- 4) Added 200 μL of freshly prepared 80% (v/v) ethanol, incubated at room temperature for 30 s, and aspirated and discarded the supernatant.
- 5) Repeated the previous step.
- 6) Microcentrifuged the 1.5 mL centrifuge tube and placed it on the magnetic rack, let stand for 1 min, discarded the residual solution, and air-dried with the lid open at room temperature until the ethanol had completely evaporated.
- 7) Added 22 μL of Nuclease-Free Water, vortexed to mix well, incubated at room temperature for 2 min, microcentrifuged and placed on the magnetic rack, and after the solution was completely clear, transferred 20 μL of the supernatant to a newly labeled 0.2 mL centrifuge tube.

2.2.4 Library amplification

- 1) Thawed the library construction amplification primers and the library construction amplification buffer, and inverted to mix well.
- 2) Prepared the reaction system according to the table below, and dispensed it into the above ligation purification product tubes.

Table 11

Component	Single reaction system	Preparation of 11 Mixes
-----------	------------------------	-------------------------

	(μ L)	(μ L)
Purification products	20	220
PCR Primer Mix 3 for Illumina	5	55
VAHTS HiFi Amplification Mix	25	275
Total volume	50	550

3) Gently pipetted to mix well, and after microcentrifugation, collected the liquid to the bottom of the tube.

Amplification was carried out according to the following program:

Table 12

Temperature	Time	Number of cycles
Heated lid 105°C	On	NA
98°C	3 min	1
98°C	20 s	6
60°C	15 s	
72°C	30 s	
72°C	5 min	1
4°C	∞	1

2.2.5 PCR product purification

1) Equilibrated the magnetic beads at room temperature for 30 min and vortexed thoroughly to mix well, and took 50 μ L into a new 1.5 mL centrifuge tube.

2) transferred 50 μ L of the PCR product to the 1.5 mL centrifuge tube in step 2.2.4, vortexed to mix well, and incubated at room temperature for 5 min.

3) Placed the 1.5 mL centrifuge tube on a magnetic rack, let stand until the solution was completely clear, and discarded the supernatant.

4) Added 200 μ L of freshly prepared 80% ethanol, incubated at room temperature for 30 s, and discarded the supernatant.

5) Repeated the previous step.

6) Microcentrifuged the 1.5 mL centrifuge tube of step 5) and placed it on the magnetic rack, let stand for 1 min and then discarded the residual solution, and air-dried with the lid open at room temperature until the ethanol had completely volatilized.

7) Added 32 μ L of Nuclease-Free Water, vortexed to mix well, incubated at room temperature for 2 min, microcentrifuged and place on the magnetic rack, and after the solution was completely clear, transferred 30 μ L of the supernatant to a newly labeled 1.5 mL centrifuge tube, which was the library product.

2.2.6 Library quality control

1) Used the nucleic acid quantification kit Qubit™ dsDNA HS Assay Kit and its supporting instrument to determine the concentration of the DNA library, and the total amount of the DNA library should be ≥ 500 ng.

2) Used the DNA High Sensitivity Reagent Kit and its supporting instrument to determine the fragment length of the DNA library. The main peak should be within the range of 200-800 bp, and there should be no obvious small-fragment or large-fragment miscellaneous peaks

2.3 Target region enrichment

2.3.1 Library mixing and drying down

1) According to the records in Table 3 or Table 4, after carefully confirming the sample numbers, pooled the DNA libraries into a single tube in a new 1.5 mL LoBind centrifuge tube.

2) In a new 1.5 mL LoBind centrifuge tube, prepared the Blocker Master Mix according to the table below, and when there were multiple samples, prepared an extra 10%.

Table 13

Component	Vol (μ L)	Preparation of 11 Mixes (μ L)
Human Cot DNA	5	55

xGen Universal Blocking Oligo – TS Mix	1	11
Total	6	66

3) After mixing well, added 6 μL of Blocker Master Mix to each pool.

4) After fully vortexing to mix well, centrifuged to collect the Mix to the bottom of the tube, sealed with sealing film, punctured 5 small holes in the film, and placed in a vacuum concentrator to dry down.

2.3.2 Library redissolution, denaturation, and hybridization

1) In a new 1.5 mL LoBind centrifuge tube, prepared the Hybridization Master Mix according to the table below, and when there were multiple samples, prepared an additional amount.

Table 14

Component	Volume (μL)	Preparation of 11 Mixes (μL)
xGen 2 $\times$ Hybridization Buffer	8.5	93.5
xGen Hybridization Buffer Enhancer	2.7	29.7
Ultrapure water	3.8	41.8
Probe	2	22
Total volume	17	187

2) After vortexing to mix well and centrifuging, added 17 μL of Hybridization Master Mix to the dried centrifuge tube (step 2.3.1), fully vortexed to mix well and then microcentrifuged to collect the solution at the bottom of the tube, and let to stand at room temperature for 5-10 min for redissolution. Then transferred all 17 μL of Mix to the pre-prepared 0.2 μL centrifuge tube and placed it in the PCR instrument, and after brief centrifugation, placed it on the PCR instrument to start the HYB program, incubated at 65°C overnight and performed the capture. The reaction system is as follows:

Table 15

HYB program (heated lid set to 100°C)	
95°C	30 s
65°C	Overnight
65°C	∞

2.3.3 Preparation of wash buffers

1) Prepared the 1 $\times$ working solutions according to the table below, and no extra was needed.

Table 16

Component	Buffer (μL)	UPDW (μL)
xGen 2 $\times$ Bead Wash Buffer	160	160
xGen 10 $\times$ Wash Buffer 1	16	144
xGen 10 $\times$ Wash Buffer 1 (metal bath)	11	99
xGen 10 $\times$ Wash Buffer 2	16	144
xGen 10 $\times$ Wash Buffer 3	16	144
xGen 10 $\times$ Stringent Wash Buffer (metal bath)	32	288

2) In a new 1.5 mL LoBind centrifuge tube, prepared the Bead Resuspension Mix according to the table below.

Table 17

Component	Vol (μL)
xGen 2 $\times$ Hybridization Buffer	8.5
xGen Hybridization Buffer Enhancer	2.7
Ultrapure water	5.8
Total	17

2.3.4 Washing streptavidin M270 magnetic beads

1) Took out the magnetic beads at least 30 min in advance and equilibrated to room temperature, and then vortexed thoroughly to mix well for about 15 s.

2) According to the number of samples, respectively took 50 μL /pool into a new 1.5 mL centrifuge tube.

- 3) For each centrifuge tube, added 100 μ L/pool of well-mixed 1 $\times$ Bead Wash Buffer according to the number of CAPs, gently pipetted 10 times to mix well and then let stand on the magnetic rack, and after the solution was completely clear, aspirated and discarded the supernatant (allowed the magnetic beads to separate on the magnetic rack for 1 min).
 - 4) Repeated the previous step 2 times.
 - 5) Added 17 μ L/pool of Bead Resuspension Mix to resuspend the magnetic beads, mixed thoroughly. The resuspension solution may be collected to the bottom of the well by microcentrifugation.
 - 6) Aliquoted the above magnetic bead Mix, and put 17 μ L per tube into new 0.2 μ L centrifuge tubes.
- 2.3.5 Magnetic bead hybridization
- 1) At least 15 min in advance, placed 1 $\times$ Wash Buffer 1 and 1 $\times$ Stringent Wash Buffer on a 65°C metal bath for heating.
 - 2) After the hybridization reaction was carried out overnight, took the sample out of the PCR instrument, and microcentrifuged the sample.
 - 3) Turned off the HYB program, and turned on the WASH program.
 - 4) transferred all 17 μ L of magnetic beads (preheated) into the centrifuge tube for the hybridization reaction, vortexed to mix well, lightly centrifuged, and then placed into the PCR instrument.
 - 5) Incubated for 45 min, and during the incubation process, vortexed to mix well every 12 min, avoiding splashing of the solution as much as possible.

Table 18

WASH program (heated lid set to 70°C)	
65°C	∞

- 2.3.6 Heated washing
- 1) After the 45 min incubation was completed, took the sample out of the PCR instrument.
 - 2) transferred 100 μ L of preheated 1 $\times$ Wash Buffer 1 into the sample, pipetted 10 times to mix well, and avoided generating too many bubbles.
 - 3) transferred all of the above Mix to a new 1.5 mL centrifuge tube, let the sample stand on the magnetic rack for about 1 min, and after the solution was completely clear, aspirated and discarded the supernatant.
 - 4) Removed the sample from the magnetic rack, transferred 150 μ L of preheated 1 $\times$ Stringent Wash Buffer into the sample, and pipetted 10 times to mix well.
 - 5) After placing on the metal bath and incubating at 65°C for 5 min, let the sample stand on the magnetic rack, and after the solution was completely clear, aspirated and discarded the supernatant;
 - 6) Repeated steps 4) to 5).

- 2.3.7 Room-temperature washing
- 1) Added 150 μ L of well-mixed 1 $\times$ Wash Buffer 1, vortexed to mix well and then incubated for 2 min, during which let stand for 30 s and shook for 30 s, and after brief centrifugation, let stand on the magnetic rack (about 1 min), and after the solution was completely clear, aspirated and discarded the supernatant.
 - 2) Added 150 μ L of well-mixed 1 $\times$ Wash Buffer 2, vortexed to mix well and then incubated for 2 min, during which let stand for 30 s and shook for 30 s, and after brief centrifugation, let stand on the magnetic rack (about 1 min), and after the solution was completely clear, aspirated and discarded the supernatant.
 - 3) Added 150 μ L of well-mixed 1 $\times$ Wash Buffer 3, vortexed to mix well and then incubated for 2 min, during which let stand for 30 s and shook for 30 s, and after brief centrifugation, let stand on the magnetic rack (about 1 min), and after the solution was completely clear, aspirated and discarded the supernatant.
 - 4) After centrifuging again, used a 10 μ L pipette tip to aspirate and discarded all residual 1 $\times$ Wash Buffer 3 liquid.

5) Removed the sample from the magnetic rack, added 20 μL of ultrapure water into each centrifuge tube, pipetted 10 times to mix well and resuspended the magnetic beads, then carefully confirmed the sample number, and transferred all resuspension liquid to a newly labeled 0.2 mL centrifuge tube.

2.3.8 PCR amplification

1) In a new LoBind centrifuge tube, prepared the Amplification Reaction Mix, and when there were multiple samples prepared an extra 20%.

Table 19

Component	Vol (μL)
KAPA HiFi HotStart ReadyMix	25
P7 Primer (SEQ ID NO.426: AATGATACGGCGACCACCGA) (10 μM)	2.5
P5 Primer (SEQ ID NO.427: CAAGCAGAAGACGGCATACGA) (10 μM)	2.5
Total	30

2) Transferred 30 μL of Amplification Reaction Mix to the 0.2 mL centrifuge tube (step 2.3.8), vortexed to mix well, microcentrifuged, and then placed into the PCR instrument and allowed to react according to the following program.

Table 20

Reaction temperature	Reaction time	Number of cycles
98°C	45 s	1
98°C	15 s	10
60°C	30 s	
72°C	30 s	
72°C	1 min	1
4°C	∞	1

2.3.9 Post-PCR purification

1) Prepared 400 μL of fresh 80% ethanol for each sample, and when there were multiple samples, prepared an extra 10%.

2) Dispensed the AMPure XP Beads already equilibrated to room temperature into new 1.5 mL centrifuge tubes, 75 μL each.

3) After carefully checking the numbers, transferred all of the amplification product to the 1.5 mL centrifuge tube containing magnetic beads, vortexed to mix well and microcentrifuged, incubated at room temperature for 5-10 min and then let stand on the magnetic rack, and after the solution was completely clear, aspirated and discarded the supernatant.

4) Added 200 μL of freshly prepared 80% ethanol, let stand for 1 min, and then aspirated and discarded the supernatant.

5) Repeated step 4).

6) Kept the sample on the magnetic rack, and air-dried the magnetic beads for 1-3 min.

7) Added 27 μL of ultrapure water to the centrifuge tube, vortexed thoroughly to mix well and microcentrifuged, incubated at room temperature for 5 min, and placed the centrifuge tube on the magnetic rack.

8) After carefully confirming the sample number, transferred 25 μL of the supernatant to a labeled new 1.5 mL centrifuge tube.

2.4 Sequencing

Sequencing of the above 10 samples was performed according to the manufacturer's instructions for the NovaSeq 6000 (Illumina) sequencing system and NovaSeq 6000 v2 kit.

The sequencing data were analyzed by bioinformatics methods, and the detection results are as shown in attached Table 21 and Table 22:

Table 21. Detection results for 10 mutant gDNA samples clearly containing known variant types of the 6 genes

Sample number	Gene	Variant information	Detection result (negative/positive)	Mutation frequency (%)
PN1	LPL	c.249 + 1G > A	Positive	61.52

PN2	LPL	c.1160_1161insT (p.Lys387fs)	Positive	50.84
PN3	APOC2	c.189C > A (p.Tyr63Ter)	Positive	33.04
PN4	LMF1	c.895C > T (p.Gln299Ter)	Positive	45.99
PN5	GPIHBP1	c.422G > A (p.Trp141Ter)	Positive	28.36
PN6	GPIHBP1	c.417_433del (p.Pro140fs)	Positive	42.82
PN7	APOA5	c.289C > T (p.Gln97Ter)	Positive	59.61
PN8	APOA5	c.990_993del (p.Asp332fs)	Positive	56.64
PN9	GPD1	c.219 + 1_219 + 3del	Positive	48.15
PN10	GPD1	c.751dup (p.Thr251fs)	Positive	47.30

Table 22. Detection results for 10 wild-type gDNA samples not containing any variant type of the 6 genes

Sample number	Detection result (negative/positive)
N1	Negative
N2	Negative
N3	Negative
N4	Negative
N5	Negative
N6	Negative
N7	Negative
N8	Negative
N9	Negative
N10	Negative

From the above data, it can be seen that the method of this example showed 100% sensitivity and 100% specificity for detecting variants in the 6 characteristic FCS genes (LPL, APOC2, LMF1, GPIHBP1, APOA5, and GPD1). It has extremely high detection accuracy.

Overall, the embodiments of the present application, through a capture sequencing method, designed target capture probes covering all exons and hotspot intronic regions of 6 FCS-related genes (*LPL*, *APOC2*, *LMF1*, *GPIHBP1*, *APOA5*, and *GPD1*), and through detection of the variant types of the above 6 genes closely related to FCS, achieved precise detection of FCS, which is of great significance to the clinical diagnosis and treatment of FCS.

The technical features of the above-described embodiments and examples may be combined in any suitable manner, and for simplicity of description, not all possible combinations of the technical features in the above embodiments and examples have been described; however, as long as the combinations of these technical features are not contradictory, they shall all be considered to fall within the scope described in this specification.

The above-described examples merely illustrate several embodiments of the present invention, to facilitate concrete and detailed understanding of the technical solution of the present invention, but this shall not therefore be understood as a limitation on the scope of patent protection of the invention. It should be pointed out that, for a person of ordinary skill in the art, without departing from the concept of the present invention, several modifications and improvements may also be made, and these all belong to the protection scope of the present invention. In addition, it should be understood that, after reading the above disclosure of the present invention, a person skilled in the art may make various changes or modifications to the present invention, and any equivalent forms obtained in a similar way fall within the protection scope of the present application. It should also be understood that technical solutions obtained by a person skilled in the art based on the technical solution provided by the present invention, through logical analysis, reasoning, or limited experiments, are all within the protection scope of the claims appended to the present invention. Therefore, the protection scope of the patent of the present invention shall be subject to the content of the appended claims, and the specification may be used to interpret the content of the claims.

Claims

1. A capture probe, which comprises one or more probe sets from a probe set 1 to a probe set 6;
 probe set 1 comprises one or more probes selected from probes 1 to 26;
 probe set 2 comprises one or more probes selected from probes 27 to 64;
 probe set 3 comprises one or more probes selected from probes 65 to 112;
 probe set 4 comprises one or more probes selected from probes 113 to 139;
 probe set 5 comprises one or more probes selected from probes 140 to 382;
 probe set 6 comprises one or more probes selected from probes 383 to 425;
 the probes 1 to 425 are constructed for target gene fragments located between different start positions and end positions on the following chromosomes and are complementary to and paired with said target gene fragments:

Probe number	Chromosome	Start position	End position
Probe 1	chr11	116660063	116660183;
Probe 2	chr11	116660168	116660288;
Probe 3	chr11	116660273	116660393;
Probe 4	chr11	116660378	116660498;
Probe 5	chr11	116660483	116660603;
Probe 6	chr11	116660588	116660708;
Probe 7	chr11	116660693	116660813;
Probe 8	chr11	116660798	116660918;
Probe 9	chr11	116660903	116661023;
Probe 10	chr11	116661008	116661128;
Probe 11	chr11	116661113	116661233;
Probe 12	chr11	116661218	116661338;
Probe 13	chr11	116661323	116661443;
Probe 14	chr11	116661428	116661548;
Probe 15	chr11	116661533	116661653;
Probe 16	chr11	116661638	116661758;
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Probe 422	chr8	144298668	144298788;
Probe 423	chr8	144298773	144298893;
Probe 424	chr8	144298878	144298998;
Probe 425	chr8	144298983	144299103;

the reference genome is Hg19.

2. The capture probe according to claim 1, which comprises a plurality of probe sets selected from a probe set 1 to a probe set 6;

the probe set 1 comprises a plurality of probes selected from the probes 1 to 26;
the probe set 2 comprises a plurality of probes selected from the probes 27 to 64;
the probe set 3 comprises a plurality of probes selected from the probes 65 to 112;
the probe set 4 comprises a plurality of probes selected from the probes 113 to 139;
the probe set 5 comprises a plurality of probes selected from the probes 140 to 382;
the probe set 6 comprises a plurality of probes selected from the probes 383 to 425.

3. The capture probe according to claim 2, which comprises the probe set 1 to the probe set 6;

the probe set 1 comprises the probes 1 to 26;
the probe set 2 comprises the probes 27 to 64;
the probe set 3 comprises the probes 65 to 112;
the probe set 4 comprises the probes 113 to 139;
the probe set 5 comprises the probes 140 to 382;
the probe set 6 comprises the probes 383 to 425.

4. Use of the capture probe according to any one of claims 1 to 3 in preparing a familial chylomicronemia syndrome detection kit.

5. A familial chylomicronemia syndrome detection kit, which comprises the capture probe according to any one of claims 1 to 3.

6. The familial chylomicronemia syndrome detection kit according to claim 5, which further comprises one or more of a nucleic acid extraction reagent, a DNA library construction reagent, a sample and library quantification reagent, a fragment quality control reagent, a hybridization capture reagent, a nucleic acid purification reagent, a target gene fragment amplification reagent, and a sequencing reagent.

7. Use of the capture probe according to any one of claims 1 to 3 in constructing a familial chylomicronemia syndrome-related gene mutation detection library.

8. Use of the detection kit according to claim 5 or 6 in constructing a familial chylomicronemia syndrome-related gene mutation detection library.

9. A method for detecting a familial chylomicronemia syndrome-related gene mutation, which comprises a step of using the capture probe according to any one of claims 1 to 3 or the detection kit according to claim 5 or 6 to capture a target gene fragment containing a familial chylomicronemia syndrome-related gene mutation, and a step of detecting the captured fragment.

10. The method for detecting a familial chylomicronemia syndrome-related gene mutation according to claim 9, wherein the captured fragment is detected by using a sequencing method.