Genotyping the Immune System

# ScisGo-FcR/IGHG-v2

## High resolution genotyping of FcR and IGHG for diagnostics and therapeutics with ScisGo-FcR/IGHG-v2

ScisGo-FcR-IGHG technology utilizes existing data sets at the IMGT and the NCBI genbank repository supplemented with long range sequencing of 1000 genome samples from 25 populations providing a comprehensive database of FcR and IGHG polymorphism. This enhanced database allows the majority of variants detected by the short-read NGS assay to be phased accordingly through mapping back to the database. Our current targeting probes for the FcR genes include a panel of variants that have been previously characterized functionally (Table 1). The four IgG encoding genes are targeted at the CH1, CH2 and CH3 regions collected from 3 corresponding amplicons (Fig. 1) and phase between CH regions is determined through database lookup using enhanced long-read data sets from 1000 genomes samples. This FcR/IGHG short-read NGS multiplexing system uses the same technology as that currently deployed for HLA and post-transplant chimerism now in active use in clinical laboratories (ScisGo-HLA-v6, ScisGo-CHIM-v3).

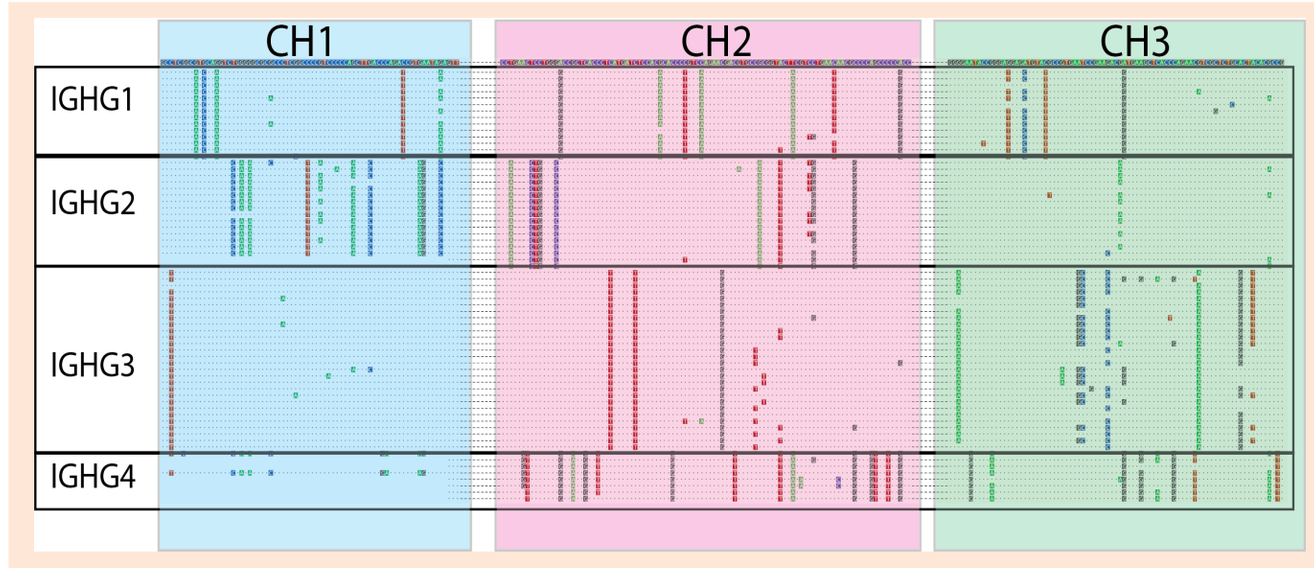


**Figure 1.** Sequence diversity of the Human immunoglobulin constant heavy G chain (IGHG) (Fcγ) (GM) gene C1, C2, C3 regions. The IGHG gene is indicated to the left of each block of listed sequence variants with variable positions indicated.

**Table 1.** FcR polymorphisms detected with **ScisGo-FcR-IGHG-v2**

| Gene | RS | Region | Position | DNA | Ref Seq | Position | Amino Acid | Ref Seq | Effect |
|---|---|---|---|---|---|---|---|---|---|
| **FCGR2A** | rs1801274 | Exon | 500 | A>G | NM_001136219.1 | 167 | His>Arg | NP_001129691.1 | His(H)167: high affinity for IgG2 |
| **FCGR2B** | rs1050501 | Exon | 695 | T>C | NM_001002274.2 | 232 | Ile>Thr | NP_001002274.1 | Thr(T)232: decreased inhibitory activity |
| **FCGR2C** | rs759550223 | Exon | 169 | C>T | NM_201563.5 | 57 | Gln>Ter | NP_963857.3 | Truncated non-functional protein |
| **FCGR2B/C** | rs3219018 | Promoter | -386 | G>C | NM_001002273.2 | | | | -386C: higher promoter activity |
| | rs780467580 | Promoter | -120 | T>A | NM_001002273.2 | | | | -120A: higher promoter activity |
| **FCGR3A** | rs396991 | Exon | 838 | T>G | NM_001127592.2 | 280 | Phe>Val | NP_001121064.2 | Val(V)280: higher affinity for IgG1 and 3, binds IgG4 |
| **FCGR3B** | rs200688856 | Exon | 108 | C>G | NM_000570.4 | 36 | Ser>Arg | NP_000561.3 | |
| | rs527909462 | Exon | 114 | T>C | NM_000570.4 | 38 | Leu>Leu | NP_000561.3 | |
| | rs448740 | Exon | 194 | A>G | NM_000570.4 | 65 | Asn>Ser | NP_000561.3 | |
| | rs5030738 | Exon | 233 | C>A | NM_000570.4 | 78 | Ala>Asp | NP_000561.3 | |
| | rs147574249 | Exon | 244 | A>G | NM_000570.4 | 82 | Asn>Asp | NP_000561.3 | |
| | rs2290834 | Exon | 316 | A>G | NM_000570.4 | 106 | Ile>Val | NP_000561.3 | FCGR3B*01 (NA1): higher affinity for IgG1 and 3 |
| | Haplotype | 108 | 114 | 194 | 233 | 244 | 316 | | |
| | FCGR3B*01 (NA1) | G | C | A | C | G | G | | |
| | FCGR3B*02 (NA2) | C | T | G | C | A | A | | |
| | FCGR3B*03 (SH) | C | T | G | A | A | A | | |
| **FCGRT (FcRn)** | | Intron | Intron1 | VNTR (37bp)*<br>VNTR1 (1 repeat)<br>VNTR2 (2 repeats)<br>VNTR3 (3 repeats)<br>VNTR4 (4 repeats)<br>VNTR5 (5 repeats) | | | | | VNTR3; High expression |
| **FCER1A** | rs2251746 | Promoter | -36 | T>C | NM_002001.3 | | | | -36T: higher promoter activity – additional GATA-1 binding site |
| | rs2427827 | Promoter | -285 | T>C | NM_002001.3 | | | | -285T: increased transcriptional activity – Sp1 site |
| **MS4A2 (FCER1B)** | rs1441586 | Promoter | -211 | T>C | NM_000139.4 | | | | -211T: unknown/higher receptor expression |
| | rs569108 | Exon | 710 | A>G | NM_000139.4 | 237 | Glu>Gly | NP_000130.1 | Gly(G)237: associated with higher expression |
| **FCER2** | rs2228137 | Exon | 181 | C>T | NM_001207019.2 | 61 | Arg>Trp | NP_001193948.2 | Trp(W)62: resistant to proteolytic cleavage |
| **PIGR** | rs291102 | Exon | 1739 | C>T | NM_002644.3 | 580 | Ala>Val | NP_002635.2 | Val(V)580: near endoproteolytic cleavage site/reduced efficiency of IgA release? |
| **FCAR** | rs16986050 | Exon | 739 | A>G | NM_133269.3 | 247 | Ser>Gly | NP_579803.1 | Gly(G)248: enhanced IgA-mediated responses; increased cytokine release |
| | rs3816051 | Promoter | -142 | T>C | NM_133269.3 | | | | -142 C; High expression |
| | rs12462181 | Promoter | -311 | T>C | NM_133269.3 | | | | -311 C; High expression |


Bournazos et al. Clinical and Experimental Immunology. 2009. 157: 244–254, PMID: 19604264

Mkaddem et al. Front Immunol. April 2019. 10:811, PMID: 31057544