Innate IgG Molecules and Innate B Cells Expressed by Immunoglobulin Constant Heavy G Chain (Fcγ) Genetic Marker Genes Are Involved in the ‘Allergic March’ of IgE Sensitization in Children

Vivi-Anne Oxelius^a Renate Krueger^c Staffan Ahlstedt^b Thomas Keil^d
Susanne Lau^c Ulrich Wahn^c

^aDepartment of Pediatrics and Institute of Laboratory Medicine, Department of Clinical Immunology, University Hospital, Lund University, Lund, and ^bCenter of Allergy Research, National Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; ^cDepartment of Pediatric Pneumology and Immunology and ^dInstitute of Social Medicine, Epidemiology and Health Economics, Charité University Medical Centre, Berlin, Germany

Key Words

Immunoglobulin constant heavy G chain (Fcγ) genetic marker genes · Innate IgG subclass molecules · Innate B cells · IgE sensitization at 1 and 10 years of age

Abstract

Background: Interindividual variations of immunoglobulin constant heavy G chain (*IGHG*) genes on chromosome 14q32.3 are identified by alternative genetic markers (GM) of IgG3, IgG1 and IgG2, respectively. They express structurally and functionally innate IgG molecules and B cells, associated with allergic disease, replicated in several studies. **Materials and Methods:** 1-year-old and 10-year-old, IgE-sensitized and non-sensitized children from the German Multicenter Allergy Study birth cohort were assessed by new serological methods for the mendelian *IGHG* (Fcγ) (GM) genes, as innate IgG molecules and innate B cells. **Results:** Food allergy sensitization in thirty-five 1-year-old children (124 not sensitized) was associated with the *IGHG*bfm* haplotype and B^{*bfm} cells (OR 1.9, 95% CI 1.2–3.1; *p* = 0.010). Aeroallergen sensitization in ninety-nine 10-year-old children (95 not sensitized) was associated with the same genes (OR 1.4, 95% CI 1.02–1.9; *p* = 0.034). The IgE sensitization was most prominent in the

restrictive homozygous *IGHG*bfm/bfm* diplotype, 34% at age 1, increasing to 60% at age 10, rating the highest numbers of positive IgE tests, expressing increased levels of IgE and innate IgG2*n. **Conclusions:** The *IGHG*bfm* haplotype (B^{*bfm} cells) and increased innate IgG2*n levels are predictive factors for IgE sensitization in childhood. *IGHG* genes can be assessed for prognostic and preventive purposes in clinical care.

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Introduction

Several candidate genes have been found associated with the inflammatory response of IgE-mediated allergy [1–3]. Asthma and allergy are linked to the *IGHG* (Fcγ) (genetic marker, GM) genes, replicated in several studies by serological methods [4–7]. Serological *IGHG* gene mapping, based on alternative mendelian GM allotypes of γ3, γ1 and γ2 on chromosome 14q32.3 (5′-μ, δ, γ3, γ1, ψε, α1, γ2, γ4, ε, α2-3′), have identified new innate IgG subclasses and new B cells. There is no genetic marker for IgE but IgG genes are informative. *IGHG* (Fc) (GM) genes are associated with allergen IgE sensitization [8–14]. Ge-

nome-wide association studies have not included GM genes in their genotyping platform [15–17] and have missed *IGHG* as candidate gene.

The alternative GM allotypes are for $\gamma 3$ -chains**b*/5 and/or **g*/21, for $\gamma 1$ -chains **f*/3 and/or **a*/1, and for $\gamma 2$ -chains **n*/23 and/or *-*n*/–23. There are 10 homozygous and heterozygous individual *IGHG* diplotypes, made up by combinations of 4 fixed *IGHG* haplotypes: *IGHG***bfn*, *IGHG***bf-n*, *IGHG***gan* and *IGHG***ga-n*, markers of B-cell variants: B**bfn* (B1), B**bf-n* (B2), B**gan* (B3) and B**ga-n* (B4) [14]. The *IGHG* gene complex, dissected in alleles (allotypes), genotypes, haplotypes and diplotypes and innate IgG subclass levels are registered [18, 19]. A gene map and reference serum levels of healthy Caucasians are given (see online suppl. addendum; for all online suppl. material, see www.karger.com/doi/10.1159/000371351).

The innate alternative IgG subclass variants differ by structure and function, by amino acids [5], by electrophoretic and chromatographic rates [20], by developmental rate during childhood [19], by half-life times [21], by different results on vaccination [22, 23] and treatment with monoclonal humanized antibodies [24]. Allergens, bacteria [22, 23] and virus [25–27] affect *IGHG* genes of individuals differently and relate to the diseases as allergy [7–12], primary immunodeficiency [28], autoimmunity [29, 30] and malignancy [31, 32].

Restrictive *IGHG* genes are found in patients with clinical allergy, increased IgE levels, increased IgG4 levels, with a family history of allergy and in technicians exposed to laboratory animals developing laboratory animal allergy [7–10]. The *IGHG* genes are linked to different phenotypes of childhood asthma: the *IGHG***bfn* to IgE-mediated and the *IGHG***bf-n* and *IGHG***ga-n* to infection-prone asthma, combined with low levels of IgG [7].

The aim of the study was to investigate, if *IGHG* genes can predict the development of atopy in children. The rate of food and aeroallergen IgE sensitization was investigated in *IGHG* diplotypes, *IGHG* haplotypic B cells, *IGHG2* genes and IgG subclass levels of children aged 1 and 10 years, from the Multicenter Allergy Study (MAS). The serum levels of innate IgG subclass molecules were assessed [7] in 10-year-old IgE-sensitized children.

Materials and Methods

Study Population

The study population comprised 194 Caucasian children from the German MAS birth cohort, with case and controls from the same group of patients. Details of recruitment and the study subjects have been reported previously [33]. For the present analyses,

we used data on allergic sensitization from the 1-year and 10-year follow-up assessments. The research protocol was approved by the ethical review board of the coordinating center (Charité University Medical Center, Berlin, Germany).

Assessment of Allergic Sensitization

Specific sensitization to 4 food allergens (hen's egg, cow's milk, soy and wheat) and 5 common indoor and outdoor aeroallergens (house dust mite, cat, dog, birch pollen and timothy grass pollen) was assessed as specific IgE antibodies in blood of 1- and 10-year-old children, respectively, by utilizing ImmunoCAP (Phadia AB, Uppsala, Sweden). Children were regarded as sensitized if the specific IgE to at least 1 allergen was ≥ 0.35 kU/l. The analyses were performed by Phadia Laboratories in Berlin.

IGHG Genotyping and Quantification of Innate IgG Subclass Levels

The *IGHG* genes were assessed by serological *IGHG* (Fc γ) (GM) gene mapping based on alternative GM allotypes for quality and quantity. The GM allotypes are genetic markers on the constant heavy G chains, the Fc part of the molecule. The alternative allotypes of $\gamma 3$, $\gamma 1$ and $\gamma 2$ are distinctive unique entities with different structures and functions. *IGHG* genes and innate IgG subclasses were investigated for quality and quantity with new serological methods: competitive ELISA, double immunodiffusion, Mancini technique [6, 13].

Sera from a hundred and ninety-four 10-year-old and a hundred and fifty-nine 1-year-old children from the MAS were genotyped defining individual *IGHG* diplotypes, *IGHG* haplotypes (B-cell variants), *IGHG* subclass genotypes and alternative *IGHG* allotypes (alleles). The very rare diplotypes (totally <1–2% of Caucasians) were left out. By the tests the quantitative expressions of *IGHG* genes are available. Total IgG subclass levels were measured with the Mancini technique. Innate IgG subclass levels were assessed in IgE-sensitized patients with homozygous *IGHG***bfn*/**bfn* diplotypes and heterozygous *IGHG***bfn*/**bf-n* and compared to not sensitized age- and *IGHG*-matched children from the MAS.

Statistical Analysis

The data were analyzed by the SPSS statistical package, SPSS 11.5, χ^2 test and 2 by 2 tables employing the 'Wald' approximation of the variance of the odds ratios (OR), similar to simple logistic regression with an estimate of the OR for the final model variables and associated 95% confidence intervals (CI). A *p* value <0.05 was considered statistically significant. The serum levels of allelic innate IgG subclasses of IgE-sensitized patients with the *IGHG***bfn*/**bfn* and *IGHG***bfn*/**bf-n* diplotypes were compared to nonsensitized age- and *IGHG*- matched controls with the *z*-test.

Results

The 'Atopic March' in *IGHG* Diplotypes, *IGHG* Haplotypes and *IGHG2* Genotypes

The IgE sensitization rate for children at 1 and 10 years of age, the 'atopic march', was recorded. The atopic march was most prominent within the homozygous *IGHG***bfn*/**bfn* (B1/B1) diplotype, with an increase

from 12/35 = 34% to 27/45 = 60% sensitized (online suppl. table 1). The various specific allergen sensitizations within homozygous *IGHG*bfⁿ/*bfⁿ* were rated from 38 to 60% in 1-year-old and from 25 to 39% in 10-year-old children, respectively. The remaining 2 homozygous diploypes showed lower rates of sensitization, *IGHG*bfⁿ/*bfⁿ* (B2/B2) from 0/7 = 0% to 6/9 = 67% and *IGHG*gaⁿ/*gaⁿ* (B4/B4) from 1/19 = 5% to 9/21 = 43%, respectively. The specific allergen sensitization within *IGHG*bfⁿ/*bfⁿ* was 0% in 1-year-olds and 0–7% in 10-year-olds and within *IGHG*gaⁿ/*gaⁿ* 0–4% in 1-year-olds and 8–15% in 10-year-olds, respectively. Thus, the *IGHG2*ⁿ/*ⁿ* was not involved in the food sensitization but to some degree in aeroallergen sensitization. IgE sensitization was increased within the homozygous *IGHG2*ⁿ/*ⁿ* (*IGHG*bfⁿ/*bfⁿ*) genotype compared to the opposite *IGHG2*ⁿ/*ⁿ*, containing *IGHG*bfⁿ* and *IGHG*gaⁿ* haplotypes (OR 2.9, 95% CI 1.1–7.2; $p = 0.022$). The atopic march for cat allergy was most prominent for *IGHG*bfⁿ/*bfⁿ*: 2 in 1-year-olds and rising to 15 in 10-year-olds, compared to the other homozygous diploypes for *IGHG*bfⁿ/*bfⁿ* from 0 to 1 and for *IGHG*gaⁿ/*gaⁿ* from 0 to 3 in 1- and 10-year-olds, respectively (online suppl. table 1a, b).

*IgE Sensitization in IGHG Haplotypes (Innate B Cells) and IGHG2 Alleles (Innate IgG2*ⁿ and IgG2*ⁿ Molecules)*

Of 35 sensitized (70 *IGHG* haplotypes) 1-year-old children, the *IGHG*bfⁿ* haplotype, B*^{bfⁿ} (B1) cells and the *IGHG2*ⁿ* allele frequencies were significantly increased, in all sensitized ($n = 41$, OR 1.9, 95% CI 1.2–3.1; $p = 0.010$) and in specific hen's egg-sensitized ($n = 32$, OR 2.7, 95% CI 1.4–4.9; $p = 0.001$), in milk-sensitized ($n = 23$, OR 2.0, 95% CI 1.1–4.0; $p = 0.031$) and in wheat-sensitized children ($n = 16$, OR 5.3, 95% CI 1.8–16.0; $p < 0.001$) compared to 124 nonsensitized ones (online suppl. tables 2a, 3a). The opposite *IGHG*gaⁿ* haplotype and B*^{gaⁿ} (B4) cells with the *IGHG2*ⁿ* allele were instead significantly decreased in all sensitized children ($n = 14$, OR 0.5, 95% CI 0.3–0.9; $p = 0.030$).

Of 99 sensitized 10-year-old children (198 *IGHG* haplotypes), the *IGHG*bfⁿ* haplotype, B*^{bfⁿ} (B1) cells and the *IGHG2*ⁿ* allele frequencies were significantly increased in all sensitized ($n = 101$, OR 1.4, 95% CI 1.02–1.9; $p = 0.034$; online suppl. tables 2b, 3b) and in specific birch-sensitized ($n = 61$, OR 2.0, 95% CI 1.3–3.0; $p < 0.001$), in grass-sensitized ($n = 77$, OR 1.4, 95% CI 1.0–2.0; $p = 0.050$), in cat-sensitized ($n = 45$, OR 1.9, 95% CI 1.2–3.1; $p = 0.006$) and in dog-sensitized ($n = 46$, OR 1.4, 95% CI

1.02–1.9; $p = 0.034$) compared to 95 nonsensitized children (online suppl. tables 2b, 3b). In this age group, the frequency of the opposite *IGHG*gaⁿ* haplotype and B*^{gaⁿ} (B4) cells did not differ when compared to nonsensitized children. The *IGHG* gene frequencies of 124 of the 1-year-old and of 95 non-IgE-sensitized 10-year-old children did not deviate from those of a healthy Caucasian population (Hardy-Weinberg equilibrium $p > 0.5$; online suppl. material, gene map).

*Positive IgE Tests Associated with IGHG2*ⁿ Alleles*

Next, we investigated the quality of IgE sensitization by the numbers of positive IgE tests per person, at different ages. We found that carriers of the homozygous *IGHG*bfⁿ/*bfⁿ* including homozygous *IGHG2*ⁿ/*ⁿ* had higher numbers of positive IgE tests than carriers of the alternative *IGHG2*ⁿ/*ⁿ* 2.3 versus 1.0 positive tests per patient in 1-year-olds and 4.5 versus 3.2 positive tests per patient in 10-year-olds.

*Increased Innate IgG2*ⁿ Subclass Levels in IgE-Sensitized Individuals with the Homozygous IGHG*bfⁿ/*bfⁿ and Heterozygous IGHG*bfⁿ/*bfⁿ Diploypes*

Twenty-seven IgE-sensitized 10-year-old children compared to 18 nonsensitized ones, with homozygous *IGHG*bfⁿ/*bfⁿ*, demonstrated significantly increased amounts of the allelic innate IgG2*ⁿ subclass (1.21 ± 0.43 g/l) and IgE (567.29 ± 630.31 kU/l) levels compared to nonsensitized IgG2*ⁿ (0.92 ± 0.44 g/l) and IgE (25.20 ± 20.48 kU/l), respectively (online suppl. table 4). Also 26 IgE-sensitized compared to 26 nonsensitized heterozygous *IGHG*bfⁿ/*bfⁿ* subjects with only 1 *IGHG*bfⁿ* haplotype and 1 *IGHG2*ⁿ* allele demonstrated significantly increased IgG2*ⁿ (0.70 ± 0.24 g/l) and IgE (332.97 ± 314.37 kU/l) levels compared to IgG2*ⁿ (0.55 ± 0.24 g/l) and IgE (45.80 ± 52.95 kU/l), respectively. The level of IgG2*ⁿ was left out.

Discussion

IGHG (γ) genes are in linkage disequilibrium with the *IGHG* (ϵ) gene on chromosome 14q32.3 (5'– μ , δ , γ 3, γ 1, $\psi\epsilon$ α 1, γ 2, γ 4, ϵ , α 2–3'). In the absence of genetic markers for *IGHG*, the *IGHG* genes are informative. The alternative GM allotypes of γ 3-, γ 1- and γ 2-chains, respectively, were identified with a new sensitive competitive ELISA, defining the interindividual variability of innate IgG subclasses and innate B cells [13, 14]. The alternative GM allotypes are markers of the Fc γ part of the IgG molecules

which differ by structures and functions [5]. Specific *IGHG* genes are involved in IgE sensitization of allergy patients [7–12]. Genome-wide association studies and HapMap do not include GM allotypes in their genetic platforms. This has underestimated *IGHG* as candidate gene in immunobiology and allergy [15–17].

We demonstrate a significant association of *IGHG*bf_n* haplotypes with innate IgG3**b*, IgG1**f* and IgG2**n* expressed from the innate B**bf_n* (B1) cells, in 1-year-old children IgE sensitized with food allergens and in 10-year-old children IgE sensitized with aeroallergens (online suppl. tables 2, 3). IgE sensitization was most prominent in the homozygous *IGHG*bf_n/*bf_n* with *IGHG*bf_n* inherited from both parents. The number of IgE sensitized in homozygous *IGHG*bf_n/*bf_n* rose from 12/35 (34%) in 1-year-olds, to 27/45 (60%) in 10-year-olds, demonstrating the ‘atopic march’. Homozygous *IGHG2**n*/**n** contained the dominating numbers of positive IgE tests/individual, compared to the opposite homozygous *IGHG2**n*/**n**. The innate IgG2**n* levels were significantly increased in IgE-sensitized carriers, in homozygous *IGHG*bf_n/*bf_n* and heterozygous *IGHG*bf_n/*bf_n*, compared to age- and *IGHG*-matched nonsensitized children (online suppl. table 4). Increased innate IgG2**n* levels have been recorded in IgE-mediated childhood asthma [7]. The activated *IGHG2**n** allele is probably taking part in the IgE sensitization process. The γ 2-genes are located 18 kb from the γ 4 and another 23 kb from the ϵ -genes on chromosome 14q32.3, which part is activated by IL-4 and IL-13 cytokines from Th2 lymphocytes [34, 35]. Genome-wide association studies have been rather insufficient to capture causal allergy gene variants. However, recently a fine-mapping study of IgE-associated loci confirmed and identified single-nucleotide polymorphisms of chromosome 5q31 regulating the Th2 cytokines IL-4 and IL-13 [36]. The finding of significantly increased IgG2**n* levels in IgE-sensitized children is highlighted and must be compared with the slow rate of increasing IgG2**n* levels during childhood in healthy children [7, 20]. The stimulation by allergens of both the *IGHG2**n** allele and *IGHE* genes, avoiding activation of *IGHG3**b** and *IGHG1**f** alleles upstream, known to be activated by infections in healthy controls, might be in agreement with the hygiene hypothesis. The present paradigm dictates that atopy is accomplished mainly by the effect of *IGHE*, but the whole *IGH* haplotype, where both *IGHG* and *IGHE* genes are involved, gives the particular innate IgG molecules IgG3**b*, IgG1**f* and IgG2**n* a role in allergy, probably in the early sensitization process as the *IGHG* genes are activated before the downstream located *IGHE*. The *IGHG*bf_n* haplotype including the *IGHG2**n**

allele and increased IgG2**n* levels are most prominent risk factors for IgE sensitization.

In 1-year-old children, food allergens had affected individuals with the *IGHG*bf_n* haplotype (B1 cells) more often than those with the other haplotypes. A negative association of the opposite *IGHG2**n** allele with allergen sensitization was observed. The homozygous *IGHG2**n*/**n** genotype demonstrated a weaker sensitization rate (online suppl. tables 1–3). In 10-year-olds, aeroallergens affected mainly the same *IGHG*bf_n*, but the IgE sensitization was found to some degree also in *IGHG*bf_n* and *IGHG*ga_n* haplotypes, with the *IGHG2**n** allele (online suppl. tables 1b, 2b). But when equal numbers of the 6 most common *IGHG* diplotypes of a childhood asthma cohort were investigated, the homozygous *IGHG*bf_n/*bf_n* was linked to atopy and the different homozygous *IGHG*bf_n/*bf_n* and *IGHG*ga_n/*ga_n* were linked to low levels of IgE, low IgE sensitization and low levels of innate IgG subclasses as in IgG subclass deficiencies [7].

B cells are the only cells producing antibodies, and B cells can indirectly be defined by *IGHG* genes [14]. *IGHG* genes of B cells are found in all human somatic cells, also stem cells [34]. All genes constituting the *IGHG* haplotype have an impact on the expressed levels of innate IgG subclasses, as it has been demonstrated in both immunodeficient and healthy individuals [19, 20, 28]. The function of the immunoglobulin G molecule is related to the constant part of the heavy G chains, the Fc γ part of the molecule, in parallel to the function of the variable adaptive antibody binding site. The *IGHG* (Fc γ) (GM) allotypes with epitope differences in the Fc part of the molecule have influence on the outcome of both bacterial and viral infections. Individuals with the *IGHG*bf_n* haplotype are high producers of antibodies against encapsulated bacteria and in vaccination with bacterial polysaccharides [22, 23]. The influence of viral particles acting as Fc γ Rs with preference of binding to different *IGHG* (Fc γ) allotypes [25–27] is important and can be applied also to allergic disease, possibly related to exacerbations. Severe infections in infants with respiratory syncytial virus are associated with the *IGHG*bf_n/*bf_n* diplotype and the *IGHG2**n** alleles [35].

IGHG genes can predict different phenotypes in childhood asthma and must be investigated in other forms of allergy. Active and passive immunotherapy, such as allergy vaccination and treatment with humanized recombinant monoclonal antibodies, affects individuals with different *IGHG* diplotypes with different results. *IGHG* genes must be investigated in relation to other genes and biomarkers with a known association to IgE-mediated allergy.

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Disclosure Statement

Conflict of interest: none declared.

References

- 1 March ME, Sleiman PM, Hakonarson H: The genetics of asthma and allergic disorders. *Discov Med* 2011;11:35–45.
- 2 Cookson WO: Genetics and genomics of asthma and allergic diseases. *Immunol Rev* 2002;190:195–206.
- 3 Ober C: Perspectives on the past decade of asthma genetics. *J Allergy Clin Immunol* 2005;116:274–278.
- 4 Grubb R: The Genetic Markers of Human Immunoglobulins. Berlin, Springer, 1970.
- 5 Grubb R: Human immunoglobulin allotypes and mendelian polymorphism of the human immunoglobulin genes; in Oss CJ, Regemortel MHV (eds): *Immunochemistry*. New York, Dekker, 1994, pp 47–68.
- 6 Oxelius V-A, Pandey JP: Human immunoglobulin constant heavy G chain (*IGHG*) (*Fcγ*) (GM) genes, defining innate variants of IgG molecules and B cells, have impact on disease and therapy. *Clin Immunol* 2013;149:475–486.
- 7 Oxelius V-A: From genotypes of immunoglobulin constant heavy G chain (*IGHG*) (*Fcγ*) (GM) genes to phenotypes in childhood asthma. *Int Arch Allergy Immunol* 2012;159:94–102.
- 8 Oxelius V-A, Hultquist C, Husby S: Gm allotypes as indicators of non-atopic and atopic bronchial asthma. *Int Arch Allergy Appl Immunol* 1993;101:66–71.
- 9 Oxelius V-A, Sjöstedt L, Willers S, Löw B: Development of allergy to laboratory animals is associated with particular Gm and HLA genes. *Int Arch Allergy Immunol* 1996;110:73–78.
- 10 Oxelius V-A: Imbalanced switch of the *IGHG* (immunoglobulin constant heavy G chain) Gm (bfn) genes in atopic childhood asthma. *Allergy* 2000;55:1063–1068.
- 11 Oxelius V-A, Bråbäck L, Ahlstedt S, Björkstén B: Immunoglobulin constant heavy G chain genes as risk factors in childhood allergies. *Clin Exp Allergy* 2006;36:1616–1624.
- 12 Oxelius V-A: Immunoglobulin constant heavy G subclass genes in asthma and allergy. *Immunol Res* 2008;40:179–191.
- 13 Oxelius V-A, Carlsson A-M: Quantitation of Gm allotypes. *Scand J Immunol* 1993;37:143–148.
- 14 Oxelius V-A: Genetic B cell variation based on Immunoglobulin heavy G chain (Gm) genes. *Scand J Immunol* 1999;49:345–346.
- 15 Pandey JP: Genetic polymorphism of Fc. *Science* 2006;311:1376–1377.
- 16 Pandey JP: Genomewide association studies and assessment of risk of disease. *N Engl J Med* 2010;363:2076–2077.
- 17 Pandey JP: Candidate gene approach's missing link. *Science* 2010;329:1148.
- 18 Oxelius V-A: Serum IgG and IgG subclass contents in different GM phenotypes. *Scand J Immunol* 1993;37:149–153.
- 19 Oxelius V-A, Aurivillius M, Carlsson A-M, Musil K: Serum Gm allotype development during childhood. *Scand J Immunol* 1999;50:440–446.
- 20 Oxelius V-A: Preparation of IgG subclass allotypes from polyclonal IgG. *Scand J Immunol* 1999;49:395–398.
- 21 Oxelius V-A, Eibl MM: Different Gm allotype levels in human intravenous immunoglobulin (IVIG) preparations, survival of foreign Gm allotypes in immunodeficient patients. *Clin Exp Immunol* 1996;106:203–207.
- 22 Pandey JP, Fudenberg HH, Virella G, Kyong CU, Lodholt CB, Galbraith RM, Gotschlich EC: Association between immunoglobulin allotypes and immune responses to *Haemophilus influenzae* and *Meningococcus polysaccharides*. *Lancet* 1979;ii:190–192.
- 23 Ambrosino DM, Schiffman G, Gotschlich EC, Schur PH, Rosenberg GA, de Lange GG, van Loghem E, Siber GR: Correlation between G2m(n) immunoglobulin allotype and human antibody response and susceptibility to polysaccharide encapsulated bacteria. *J Clin Invest* 1985;75:1935–1942.
- 24 Jefferis R, Lefranc MP: Human immunoglobulin allotypes: possible implications for immunogenicity. *MAbs* 2009;1:332–338.
- 25 Namboodiri AM, Budkowska A, Nietert PJ, Pandey JP: Fcγ receptor-like hepatitis C virus core protein binds differentially to IgG of discordant Fc (GM) genotypes. *Mol Immunol* 2007;44:3805–3808.
- 26 Atherton A, Armour KL, Bell S, Minson AC, Clark MR: The herpes simplex virus type 1 Fc receptor discrimination between IgG1 allotypes. *Eur J Immunol* 2000;30:2540–2547.
- 27 Pandey JP, Astemborski J, Thomas DL: Epistatic effects of immunoglobulin GM and KM allotypes on outcome of infection with hepatitis C virus. *J Virol* 2004;78:4561–4565.
- 28 Oxelius V-A, Ochs HD, Hammarström L: Restricted immunoglobulin heavy G chain genes in primary immunodeficiencies. *Clin Immunol* 2008;128:190–198.
- 29 Oxelius V-A, Svantesson H, Carlsson A-M: GM phenotype linkage to subsets of juvenile chronic arthritis (JCA). *Scand J Rheum* 1993;22:284–288.
- 30 Jönsson G, Oxelius V-A, Truedsson L, Bracnieri JH, Sturfelt G, Sjöholm AG: Homozygosity for the IgG2 subclass allotype G2M(n) protects against severe infections in hereditary C2 deficiency. *J Immunol* 2006;177:722–728.
- 31 Pandey JP, Nietert PJ, Klaamas K, Kurtenkov O: A genetic variant of immunoglobulin gamma2 is strongly associated with immunity to mucin 1 in patients with breast cancer. *Cancer Immunol Immunother* 2009;58:2025–2029.
- 32 Nakao Y, Matsumoto H, Miyazaki T, Watanabe S, Mukojima T, Kawashima R, Fujita T, Tsuji K: Immunoglobulin G heavy chain allotypes as possible genetic markers for human cancer. *J Natl Cancer Inst* 1981;67:47–50.
- 33 Bergmann RL, Bergmann KE, Lau-Schaden-dorf S, Luck W, Dannemann A, Bauer CP, Dorch W, Foster J, et al: Atopic diseases in infancy. The German Multicenter Atopy Study (MAS-90). *Pediatr Allergy Immunol* 1994;5:19–25.
- 34 Takahashi K, Yamanaka S: Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006;126:663–676.
- 35 Aurivillius M, Oymar K, Oxelius V-A: Immunoglobulin heavy G2 chain (*IGHG2*) gene restriction in the development of severe respiratory syncytial virus infection. *Acta Paediatr* 2005;94:414–418.
- 36 Sharma V, Michel S, Gaertner V, Franke A, Vogelberg C, von Berg A, et al: Fine-mapping of IgE associated loci 1q23, 5q31 and 12q13 using 1,000 Genomes Project data. *Allergy* 2014;69:1077–1084.