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Genotype List String 1.1: Extending the Genotype List String Grammar for Describing HLA and Killer-cell Immunoglobulin-like Receptor Genotypes

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Abstract

The Genotype List (GL) String grammar for reporting HLA and Killer-cell Immunoglobulin-like Receptor (KIR) genotypes in a text string was described in 2013. Since this initial description, GL Strings have been used to describe HLA and KIR genotypes for more than 40 million subjects, allowing these data to be recorded, stored and transmitted in an easily parsed, text-based format. After a decade of working with HLA and KIR data in GL string format, with advances in HLA and KIR genotyping technologies that have fostered the generation of full-gene sequence data, the need for an extension of the GL String system has become clear. Here, we introduce the new GL

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AUTHOR CONTRIBUTIONS

All authors have read and approved the final manuscript. Jan Hoffman, Jill Hollenbach, Michael Heuer, Loren Gragert, Joel Schneider, Steven Mack, Martin Maiers, Steven Marsh, Robert Milius, Jane Pollack, James Robinson, Jürgen Sauter and Steven Spellman participated in DaSH Hackathon discussions regarding GL String extensions and improvements. Jan Hofmann, Martin Maiers, Robert Milius, Jane Pollack, Jürgen Sauter, Daniel Schefzyk and Alexander Schmidt provided model data. Steven Mack and Jürgen Sauter drafted the paper. Werner Bochtler, Hans-Peter Eberhard, Loren Gragert, Lisbeth Guethlein, Michael Heuer, Jan Hoffman, Jill Hollenbach, Martin Maiers, Steven Marsh, Robert Milius, James Robinson, Daniel Schefzyk, Alexander Schmidt and Steven Spellman made contributions to the final version of the paper.

String delimiter “?”, which addresses the need to describe ambiguity in assigning a gene sequence to gene paralogs. GL Strings that do not include a “?” delimiter continue to be interpreted as originally described. This extension represents version 1.1 of the GL String grammar.

Keywords

genotype list string; killer-cell immunoglobulin-like receptor; HLA

INTRODUCTION

The HLA genes, on chromosome 6p21, are the most polymorphic, medically-relevant loci in the human genome[1–3]. As of January of 2023, 35,820 unique HLA nucleotide sequences, encoding 20,697 unique HLA proteins have been published. HLA genes are key elements of the adaptive immune system, and encode cell-surface antigens that present short, endogenously and exogenously derived peptides for inspection by T cells, permitting the discrimination of self from non-self by the adaptive immune system[4, 5]. The Killer-cell Immunoglobulin-like Receptor (KIR) genes, in the KIR gene cluster of the Leukocyte Receptor Complex on chromosome 19q13.4, expressed on Natural Killer (NK) cells, are key elements of the innate immune system that interact with class I HLA proteins to stimulate or inhibit NK cell activity[6–8]. The KIR region of chromosome 19 displays extensive haplotypic diversity, including many gene duplications and deletions[9]. As of December of 2022, 1617 unique KIR nucleotide sequences, encoding 703 unique proteins, have been published[10]. The key roles played by KIR and HLA molecules in innate and adaptive immunity motivate their routine genotyping for bone-marrow-, peripheral blood- and cord-blood-based hematopoietic progenitor cell therapies, as well as solid-organ transplantation efforts, and donor registries for these therapies store and share HLA and KIR genotypes for millions of potential donors[11–13].

Each unique HLA sequence is assigned a structured name by the World Health Organization Nomenclature Committee for Factors of the HLA System (WHO Nomenclature Committee), and each unique KIR sequence is assigned a similar name by the WHO Nomenclature Committee’s KIR subcommittee[14, 15]. Full-gene HLA and KIR sequencing has historically been difficult, and routine full-gene sequencing is only recently becoming cost-effective[16–19]. Given these historical limitations, HLA and KIR genotyping data have typically been *ambiguous* in that multiple distinct sets and combinations of allele names can be consistent with a pair of nucleotide sequences for a particular gene, when the complete gene sequence has not been determined for a subject. As shown in Table 1, allelic ambiguity occurs when only part of the gene sequence has been determined; alleles with identical nucleotide sequences in this region cannot be distinguished. Until recently, exons 2 and 3 have been commonly sequenced for class I HLA genes, and exon 2 has been commonly sequenced for class II HLA genes. For the KIR genes, though exons 3, 4, 5, 7, 8 and 9 may be sequenced, phase between each exon is not easily established. When the observed pair of allele sequences can appear in multiple pairs of alleles, genotype ambiguity occurs. For example, both the *KIR2DS4*0010101* and *KIR2DS4*002* genotype

and the *KIR2DS4*0040101* and *KIR2DS4*0060102* genotype are consistent with identical sequences of exons 3, 4, 5, 7, 8 and 9, representing different phase options between exons.

To facilitate the lossless storage and transmission of HLA and KIR genotype data, while describing these genotyping ambiguities in a structured manner, the Genotype List (GL) String format was developed to standardize the encoding of genotyping results[20], using a set of case-defined “AND” and “OR” delimiters. While primarily developed for HLA and KIR data, the GL String format can be applied to any genetic system, regardless of its function or application. The Be The Match registry, DKMS, and other registries and donor centers use GL Strings to store and exchange HLA and KIR genotype data for over 40 million patients and volunteer donors[13, 21].

In the decade since the development and initial description of the GL String format, advances in HLA and KIR genotyping technologies have driven discovery and insight into the diversity of the HLA and KIR genes, as well as the large-scale haplotype structure of the KIR gene cluster. Challenges experienced in genotyping the paralogous *KIR2DL5A* and *KIR2DL5B* genes have resulted in the recognition of a new type of ambiguity in which nucleotide sequences cannot be assigned to either the centromeric *KIR2DL5A* gene or the telomeric *KIR2DL5B* gene.

Here, we introduce “?”, a new GL String delimiter that extends the original GL string standard to describe ambiguity in gene location. The extension of the GL String grammar to include the “?” delimiter will require the modification of GL String parsers to allow forward-compatibility, while maintaining backward-compatibility with original GL Strings. We define this extension of the grammar as Genotype List String version 1.1.

METHODS AND RESULTS

The five original GL String delimiters are evaluated in an order of precedence beginning with distinct genes (precedence 1, delimited by “^”), proceeding through ambiguous genotypes (precedence 2, delimited by “|”), gene copies (precedence 3, delimited by “+”), genes for which phase is known (precedence 4, delimited by “~”), and ending with ambiguous alleles (precedence 5, delimited by “/”). These grammatical rules have worked well for the last decade to accurately describe what is known and unknown about an HLA or KIR genotype. The application of these delimiters is further described in Table 2.

The order of delimited elements in a GL String does not inform how that string is parsed. For example, the order of slash-delimited alleles or pipe-delimited genotypes does not indicate the greater likelihood of one allele or one genotype over another. Similarly, the order of loci in a GL String need not correspond to the relative chromosomal position or chromosomal order of those loci. Further, when the “~” delimiter is used to identify chromosomal phase between genes encoding subunits of a heterodimeric protein (e.g., between an HLA-DQA1 allele and an HLA-DQB1 allele), the identified phase does not imply that those alleles will form a heterodimer.

When the examples with precedence 1 to 5 in Table 2 are assembled, the resulting GL String,

“HLA-A*02:01/HLA-A*02:02+HLA-A*03:01|HLA-A*02:07+HLA-A*03:06^HLA-B*08:01+HLA-B*44:02/HLA-B*44:03^HLA-DRB1*03:01~HLA-DRB3*01:01+HLA-DRB1*03:01~HLA-DRB3*01:01”, accurately describes what is known and unknown about this HLA genotype.

It is possible to record the same genotype data with distinct but equivalent GL Strings. For example, “HLA-A*02:01/HLA-A*02:02+HLA-A*03:01” could also be written as “HLA-A*02:01+HLA-A*03:01|HLA-A*02:02+HLA-A*03:01”.

The need for an extension of the GL String grammar was initially raised as part of the ongoing Data Standards Hackathon for Next Generation Sequencing (DaSH for NGS) effort[22]. The advent of long-range, massively-parallel, single molecule sequencing has initiated a sea change in the Histocompatibility and Immunogenetics community, and larger genomics community, expanding and deepening the scope of knowledge of the structure, organization and polymorphism of HLA and KIR genes.

Since the 16th International HLA and Immunogenetics Workshop in 2012, research laboratories, stem cell donor registries, and donor centers have investigated, developed and adopted NGS technologies for routine genotyping[23]. A key outcome of these efforts is the acknowledgement that genotyping results that may once have been dismissed as unusual edge-cases are in fact legitimate polymorphisms that require new approaches for accurate description. Over the course of several DaSH meetings in 2020 and 2021, the extension to the GL String grammar described below was developed.

Describing Gene-Location Ambiguity

While the GL String grammar allows accurate descriptions of what is known and unknown about allele sequences and phasing information between those sequences, it cannot describe what is known or unknown about allele sequences for highly homologous gene paralogues.

As illustrated in Figure 1, the paralogous *KIR2DL5A* and *KIR2DL5B* genes share high sequence homology and are respectively located in the telomeric and centromeric regions of the KIR gene cluster[9, 24]. Recombination between the centromeric and telomeric regions of the KIR gene cluster defines four KIR gene cluster haplotypes by the presence and absence of the *KIR2DL5A* and *KIR2DL5B* genes -- those with *KIR2DL5A* and *KIR2DL5B*, those with only one of either the *KIR2DL5A* or *KIR2DL5B* gene, and those with no *KIR2DL5A* or *KIR2DL5B* gene (Figure 1), so that individuals can have between zero and four alleles of the *KIR2DL5A* and *KIR2DL5B* alleles. This is also the case for the *KIR2DS3* and *KIR2DS5* genes. *KIR2DL5A* and *KIR2DL5B* alleles are similar in sequence, and it can be difficult to distinguish centromeric and telomeric alleles without phased sequence across multiple exons and introns. In these cases, *KIR2DL5A* and *KIR2DL5B* ambiguity cannot be accurately described using the current GL String syntax, which does not permit alleles of paralogous loci to be included in a single “/” delimited string, and does not include an “OR” delimiter for gene location.

To address this, the “?” delimiter describes locus ambiguity where the typing system cannot distinguish paralogous genes, in the same way that the “|” delimiter describes genotype

ambiguity where the typing system cannot distinguish chromosomal phase, and the “/” delimiter describes allele ambiguity where the typing system cannot distinguish between alleles. The “?” delimiter is assigned precedence 0, so that it is evaluated before all other GL String delimiters.

For example, the `KIR2DL5A*0010101+KIR2DL5A*0010201?KIR2DL5A*0010301^KIR2DL5B*0010101?KIR2DL5B*0010201+KIR2DL5B*0010301` string describes three possible relationships between `KIR2DL5` alleles for which partial sequences are known. It cannot be determined which alleles are at the `KIR2DL5A` and `KIRDL5B` loci, so all three possible combinations must be reported. In this case, sequence is known for both alleles, but the corresponding allele name depends on that gene’s location in the telomeric or centromeric section of the `KIR` region.

DISCUSSION AND CONCLUSION

The Histocompatibility and Immunogenetics community is in the “log phase” of the transition from established molecular genotyping methods to so-called third-generation sequencing approaches. The evaluation and application of these technologies is still in process. Extension of the GL String grammar to describe ambiguity in gene-location and gene-copy number will facilitate this transition by fostering more accurate, lossless communication and storage of HLA and `KIR` genotyping results.

Data for other gene systems that assign unique names to the nucleotide sequences of gene variants can be described using GL Strings, and this extension of the format could prove useful for gene systems characterized by large copy-number variation of highly homologous genes (e.g., class I MHC in rhesus macaques), and for describing novel or rare haplotype structures.

It should be noted that GL Strings, while designed to facilitate lossless storage and transmission of genotype data, do not inherently convey all aspects of the typing process itself. For instance, GL Strings of genotypes can be generated by interrogating different numbers of gene features for different subjects (e.g., HLA class I exons 2 and 3 for all subjects, and additionally exons 4 and 5 for a subset of subjects). Consequently, when GL Strings are compared directly, methodological details of a genotyping experiment need to be considered. These details do not typically accompany the reported genotype. DaSH efforts have focused on developing systems and services that formalize the description of immunogenomic genotyping methodologies[25, 26]. With this ongoing effort in mind, we propose that annotations of immunogenomic genotyping experiments include standardized descriptions of genotyping metadata pertinent to gene-feature targets and sequencing technology. As with any data recording format, knowledge of the assumptions and limitations of the format are key for informed data-analysis and application.

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CONFLICT OF INTEREST STATEMENT

Loren Gragert has received research funding from National Marrow Donor Program (NMDP) and United Network for Organ Sharing (UNOS). The remaining authors have no conflicts of interest to declare.

Abbreviations

| | |
|-------------|------------------------------------------|
| DaSH | Data Standards Hackathon |
| GL | Genotype List |
| KIR | Killer-cell Immunoglobulin-like Receptor |
| MHC | Major Histocompatibility Complex |
| NGS | Next Generation Sequencing |
| NK | Natural Killer |
| UTR | Untranslated Region |
| WHO | World Health Organization |

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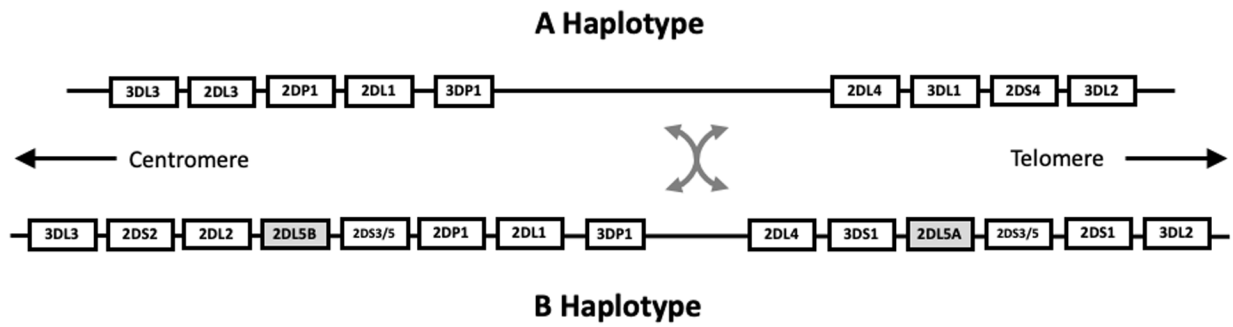


Figure 1.

The KIR2DL5A and KIR2DL5B Genes in the KIR Gene Cluster

The relative organization of the KIR genes on the KIR A and B haplotypes is shown.

Each KIR gene is identified with a rectangular box. Each haplotype can be divided into a centromeric and telomeric segment, between which recombination occurs, resulting in a centromeric A (cenA) haplotype, a centromeric B (cenB) haplotype, a telomeric A (telA) haplotype and a telomeric B (telB) haplotype[24]. The KIR2DL5A and KIR2DL5B genes are indicated in grey.

Table 1.

Examples of Allele Ambiguity for the HLA and KIR Genes

| Locus | Identical Gene Feature ¹ | Ambiguous Alleles | Group ² |
|----------|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| HLA-DRB1 | Exon 2 | DRB1*01:01:01:01, DRB1*01:01:01:02, DRB1*01:01:01:03, DRB1*01:01:01:04, DRB1*01:01:01:05, DRB1*01:01:01:06, DRB1*01:01:01:07, DRB1*01:01:01:08, DRB1*01:01:01:09, DRB1*01:01:01:10, DRB1*01:01:01:11, DRB1*01:01:01:12, DRB1*01:01:01:13, DRB1*01:01:01:14, DRB1*01:01:01:15, DRB1*01:01:01:16, DRB1*01:01:01:17, DRB1*01:01:01:18, DRB1*01:01:01:19, DRB1*01:01:32, DRB1*01:01:33, DRB1*01:01:35, DRB1*01:01:37, DRB1*01:01:39, DRB1*01:01:41, DRB1*01:01:44, DRB1*01:50, DRB1*01:67, DRB1*01:77, DRB1*01:82, DRB1*01:91Q, DRB1*01:95, DRB1*01:98, DRB1*01:100, DRB1*01:103, DRB1*01:104, DRB1*01:107, DRB1*01:115, DRB1*01:117, DRB1*01:119, DRB1*01:120, DRB1*01:121, DRB1*01:128, DRB1*01:129, DRB1*01:132, DRB1*01:137 and DRB1*01:139 | HLA-DRB1*01:01:01G |
| HLA-A | Exons 2 & 3 | A*23:01:01:01, A*23:01:01:02, A*23:01:01:03, A*23:01:01:04, A*23:01:01:05, A*23:01:01:06, A*23:01:01:07, A*23:01:01:08, A*23:01:01:09, A*23:01:01:10, A*23:01:01:11, A*23:01:01:12, A*23:01:01:13, A*23:01:01:14, A*23:01:01:15, A*23:01:01:16, A*23:01:01:17, A*23:01:01:18, A*23:01:01:19, A*23:01:01:20, A*23:01:01:21, A*23:01:01:22, A*23:01:01:23, A*23:01:01:24, A*23:01:01:25, A*23:01:01:26, A*23:01:01:27, A*23:01:01:28, A*23:01:01:29, A*23:01:01:30, A*23:01:05, A*23:01:19, A*23:01:24, A*23:01:25, A*23:01:27, A*23:01:28, A*23:01:31, A*23:01:34, A*23:07N, A*23:17:01:01, A*23:17:01:02, A*23:17:01:03, A*23:17:01:04, A*23:17:02, A*23:18, A*23:20, A*23:58, A*23:85, A*23:86, A*23:87, A*23:88, A*23:91N, A*23:92, A*23:93, A*23:94, A*23:95, A*23:96, A*23:103N, A*23:115, A*23:116, A*23:117, A*23:118, A*23:121, A*23:123 and A*23:125 | HLA-A*23:01:01G |
| KIR2DL5 | Exons 3, 5, 7, 8 & 9 | KIR2DL5A*001, KIR2DL5B*006, KIR2DL5B*008 and KIR2DL5A*012 | KIR2DL5*001 ³ |
| KIR3DL2 | Exons 3, 4, 5, 7, 8 & 9 | KIR3DL2*002, KIR3DL2*101 and KIR3DL2*102 | KIR3DL2*002 ³ |

¹: Gene Features are the structural elements of a gene – Introns, Exons and Untranslated Regions (UTRs)[27].

²: Groups are identifiers that represent sets of alleles sharing a predefined set of gene features. For the HLA alleles, “G groups” (e.g., HLA-DRB1*01:01:01G) represent all of the alleles with identical sequence for exons 2 and 3 for class II HLA alleles, and exon 2 for class II HLA alleles. G group membership described here is specific to IPD-IMGT/HLA Database Release 3.50.0.

³: For KIR alleles, the KIR2DL5*001 and KIR3DL2*002 groups represent all alleles that share identical sequence for KIR exons 3–5 and 7–9 with KIR2DL5A*001 and KIR3DL2*002, respectively[28]. The KIR allele group memberships described here are specific to the KIR typing approach described by Wagner et al., 2018[19]. The use of the KIR2DL5 designation without specifying the A or B ending is not consistent with the official KIR nomenclature.

Table 2.

Genotype List String Delimiters

| Precedence <i>I</i> | Delimiter | Identifies | Example |
|---------------------|-----------|-------------------------|----------------------------------------------------------|
| 0 | ? | Possible Gene Locations | <i>KIR2DL5B*00201?KIR2DL5A*00501</i> |
| 1 | ^ | Unphased Genes | <i>HLA-A*02:07+HLA-A*03:06^HLA-B*08:01+HLA-B*4:02</i> |
| 2 | | Possible Genotypes | <i>HLA-A*02:02:01G+A*03:01:01GHHLA-A*02:881+A*03:303</i> |
| 3 | + | Copies of Genes | <i>HLA-A*02:02+HLA-A*03:01</i> |
| 4 | ~ | Phased Genes | <i>HLA-DRB1*03:01~HLA-DRB3*01:01</i> |
| 5 | / | Possible Alleles | <i>HLA-A*02:01/HLA-A*02:02</i> |

Adapted from (Milius et al., 2013[20]).

I: GL String delimiters are evaluated in the numerical precedence order shown.