DEVELOPING CURATED RESOURCES FOR RASOPATHIES RESEARCH

By

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Abstract

The RASopathies are a diverse set of genetic diseases that are caused by mutations to the RAS/MAPK signaling pathway, which is crucial in embryonic and early development. Biomedical model studies are important for developing understanding of mechanisms of the RAS/MAPK pathway and their individual effects on disease phenotype, however these studies are hindered by lack of standard nomenclature and functional annotations. We selected chicken as a comparative model, and analyzed a human RAS/MAPK pathway gene set to identify chicken orthologs. These orthologs were then assessed and standardized gene nomenclature, as well as updated ortholog and Ensembl ID mappings. Functional annotations for these genes were assessed for overall functional annotation increases as well as annotation increases related to biological function. This work improved accessibility to existing data in order to allow researchers to more rapidly obtain gene functional data across species when studying RASopathies in chicken.

Acronyms and terms commonly referred to in this text.

Term	Definition
KEGG	Kyoto Encyclopedia of Genes and Genomes; database
HUGO	Human Genome Organization
HGNC	HUGO Genomic Nomenclature Committee; database
CGNC	Chicken Gene Nomenclature Consortium; database
NCBI	National Center for Biotechnology Information; database
LOC	unidentified gene at a particular gene locus
CCDS	Consensus Coding Sequence (Project); database
GO	Gene Ontology project; describes gene products based on functions and attributes
Automatically-Assigned	evidence code for automated annotation assignments, without curatorial judgment
Computational Analysis	evidence code for annotations based on a computational analysis of the gene sequence
Experimental	evidence code based on physical characterizations of a gene or gene product
Author Statement	evidence code based on statements made by the author(s) of the reference being cited
Curatorial Statement	evidence code based on curatorial judgments that do not fall in any other category

Introduction

In the field of microbiology and genetics, new sequencing technologies now allow researchers to rapidly acquire large amounts data. As this data is often generated faster than it can be analyzed and applied, researchers find it more difficult to transform basic experimental data into tangible gains for society at large at a similar rate. This disconnect between data and knowledge is extremely important in terms of medical applications being able to keep up with the current research to develop new understandings and treatments for human diseases. An important aspect for human disease is the use of biomedical models to acquire experimental data on the different functions and interactions of disease genes. Comparative models are useful for identifying important disease stages and development of treatments, by displaying similar or identical disease symptoms while developing much faster than humans, and so are effective for observing disease progression (Jindal, Goyal, Burdine, Rauen, & Shvartsman, 2015; Schmutz & Grimwood, 2004). The translation of experimental data gained from successful comparative animal models into new understanding of human disease is critical in complex genetic diseases that are difficult to treat because of the involvement of multiple signal pathways that target different systems, such as RASopathies.

The RAS/MAPK signaling pathway ('rat sarcoma' protein/mitogen-activated protein kinase pathway) is critical in in embryonic development, as they regulate cell replication, differentiation into various cell types, cell migration, and programmed cell death (Mccubrey et al., 2007; Rauen, 2013; Tidyman & Rauen, 2009). Disruption of the RAS/MAPK pathway can cause a multitude of congenital defects and diseases, collectively known as RASopathies, which affect over 319,000 people in the United States alone (1 in 1000 people) (Rauen, 2013). Genes in the human RAS/MAPK pathway are important Mutated RAS genes can be permanently activated, or otherwise functionally changed, leading to overactive RAS and MAPK protein signaling, causing dangerously increased cell growth and division associated with cancer. RASopathies range from facial dysmorphology (abnormal facial features) to intellectual disability to heart defects, and include diseases such as Noonan syndrome, Costello syndrome, LEOPARD syndrome, cardio-facio-cutaneous syndrome (CFC), and neurofibromatosis type 1 (NF1, von Recklinghausen disease) (Bezniakow Natalia, Gos Monika, 2014). RAS pathologies are hard to study, as comparative studies are hindered because genes in the pathway have poorly defined gene names and functional annotations. There is a *critical need* to improve understanding of the RAS/MAPK pathway, by creating better definitions of standardized gene names and functional annotations such as molecular interactions essential for the pathway, in humans and biomedical models.

For this research project, chicken was used as the comparative biomedical model. Chicken is the model avian species, and principal non-mammalian vertebrate model organism for basic biology and human diseases (Burt et al., 2009). Chicken also occupies a unique evolutionary niche, bridging the gap between mammals and other vertebrates, making the chicken genome useful in comparative genomics for understanding gene regulation, functional elements, and structure in the human genome, and other mammals (Hillier et al., 2004).

We investigated the genes of the RAS/MAPK kinase pathway in humans, and identified functionally similar genes to develop a core set of common orthologous genes in a common biomedical model, chicken (*Gallus gallus*). The chicken gene set was evaluated for similarity of function – what the genes do, how similar the pathways are, and what tissues they are expressed in and then assigned a unique, standardized name for each gene (as there are often several names used for one gene) that reflects the gene's function and similarity to the corresponding human gene. We identified orthologs using publically available phylogenetic resources, assigned standard nomenclature by liaising with gene nomenclature committees (REFs), and assigned evaluated function using the Gene Ontology (Buza, Mccarthy, Wang, Bridges, & Burgess, 2008). To demonstrate my findings and how this annotation improves functional modeling in these biomedical species, I did comparative analyses using this functional information. All of the data produced is publically available via submission to existing biological resources and databases.

The research outcomes from this project include standardized nomenclature for the gene sets, Gene Ontology annotations and a systematic comparative analysis of what is currently known about RAS/MAPK kinase signaling. Quantitative metrics for how I improved understanding of how these gene sets contribute to the RASopathies is based on the number of annotations added, and the number of gene names changed to relate their function. All the resulting data will be made publically available to biocurators at the AgBase database (McCarthy et al., 2011) and the Chicken Gene Nomenclature Consortium (CGNC) (Burt et al., 2009). Educational outcomes of this project will include better understanding of biological databases and resources, how bioinformatics is applied to comparative genomics, and principles of data management and organization using ontologies. By standardizing gene nomenclature and improving gene mappings between databases, as well as increasing functional annotations, this project enables chicken and human gene researchers to more rapidly obtain gene functional data, by increasing ease of access across species and across different databases.

Materials and Methods

Identifying genes involved in RASopathies. The gene set used to define the RAS/MAPK pathway is based off of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (Ogata, Goto, Sato, Fujibuchi, & Bono, 1999) map010410 – MAPK signaling pathway, and map04014 - Ras signaling pathway, downloaded August 28th, 2015. Within the KEGG database, all genes are identified using KEGG IDs. The KEGG gene IDs within the selected pathways were downloaded and manually checked against the Human Genome Organization (HUGO) Genomic Nomenclature Committee (HGNC) database (Gray, Yates, Seal, Wright, & Bruford, 2015) to identify human gene names, gene symbols, and Entrez Gene IDs. Taking these Entrez gene IDs, we mapped these to Ensembl human gene IDs using the Ensembl Biomart tool (Kinsella et al., 2011). The Biomart tool was also used to identify chicken orthologs for this human gene set; since the Biomart tool identifies orthologs by their Ensembl gene IDs, these chicken gene IDs were also mapped to chicken Entrez gene IDs. For chicken genes with no identified human orthologs, I manually reviewed NCBI and Ensembl records to check for additional mapping links between Ensembl IDs and Entrez IDs. To evaluate standardized gene nomenclature for this chicken gene set, I manually reviewed these entries in NCBI, CGNC, and Ensembl databases.

This included updating accession mappings for Ensembl IDs in NCBI and CGNC entries. Any inconsistencies were addressed by proposing gene name, symbol, and/synonyms based on manual review of PubMed articles about the chicken gene, and similarity to their human orthology gene names, as assigned by HGNC. For NCBI and CGNC entries without Ensembl IDs, Ensembl orthologs were confirmed with the Biomart tool.

In cases where no chicken ortholog was identified, human Consensus Coding Sequence (CCDS) gene sequences were analyzed with the Ensembl BLAST/BLAT tool for any sequence matches in the chicken genome. The number of matches, and chromosomal locations were recorded, as well as any possible syntenic regions found using Ensembl syntenic chromosomal comparisons. These matches were reviewed to determine if any of these were possible orthologs that were missed in gene annotation.

Assigning standardized chicken gene nomenclature for chicken orthologs. In evaluating gene nomenclature, the standard for gene names and symbols are assigned by the CGNC, and names of directly corresponding homologs to human genes should have the same name and symbol as the human gene unless there are multiple homologs for a single gene or significant functional or sequential differences (Burt et al., 2009). Using these rules for assigning gene nomenclature, any uncharacterized or "LOC" genes had their names and symbols edited to reflect their function and relation to orthologous human genes.

Evaluating functional annotations for chicken orthologs.
Functional annotations are descriptions of the roles of genes and gene products: their molecular functions, biological processes and cellular components, as determined by experimental studies, or predicted functions (Buza et al., 2008). Existing annotations for the chicken gene products were retrieved from AgBase. Existing GO annotation for the chicken genes orthologous to the Ras and MAPK pathway gene set were then counted and assessed determine mapped biological functions and evidence code types. Since the GO assigns evidence codes to indicate which annotations are assigned based upon direct experimental evidence and which annotations are predicted based upon sequence analyses, these evidence codes were ranked, as designated by the Gene Ontology standards (Buza et al., 2008) and evaluated for improvements made after the initial analysis.

Assessing quantitative and qualitative improvements.
Quantitative assessment of improvements included how many nomenclature standardizations and Ensembl ID mappings were updated within the CGNC database, as well as how many nomenclature inconsistencies and additional Ensembl ID mappings or chicken ortholog mappings were identified within the Ensembl and NCBI database entries for the gene set. GO annotations for the chicken gene set were assessed for quantitative improvements by comparing the number of chicken genes with annotations, number of annotations per gene, number of additions and updated annotations, and total number of annotations before and after this analysis in the UniProtKB database.

Qualitative improvements involved assessing percent improvement of accession mapping between human and chicken RAS genes, to improve ortholog searches when switching between databases. This includes changes made database mappings linking human genes to their chicken orthologs, as well as Ensembl ID and CGNC ID mappings. The next improvement was the potential orthologs identified, particularly those for human genes with BLAST matches on chicken sequence scaffolds, to improve ortholog mappings for gene searches between species. The next level of improvement is increased functional definition, which includes increases in nomenclature standardization, as well as in functional annotations. GO annotations were examined for updates to reflect current gene understanding, by examining the type of annotations that increased, which category had the most additions, and the GO annotation evidence types that were associated with the additions. to gene names and symbols and

Results

Identification of genes involved in RASopathies. 365 unique human genes were identified from KEGG pathways map010410 (Figure 1) and map04014 (Figure 2). Of these human genes, 65 did not have a direct chicken ortholog, as determined using the Ensembl Biomart tool, and manually checking NCBI and Ensembl databases (Supplemental Data Table 1). The 51 that were checked for potential orthologs or orthologous regions using Ensembl BLAST/BLAT and syntenic comparative genomics had no obvious syntenic regions on chicken chromosomes, and 32 had no BLAST matches (Table 1).

Figure 1: KEGG MAPK signaling pathway (map04010). Chicken genes mapped to this pathway are colored blue.

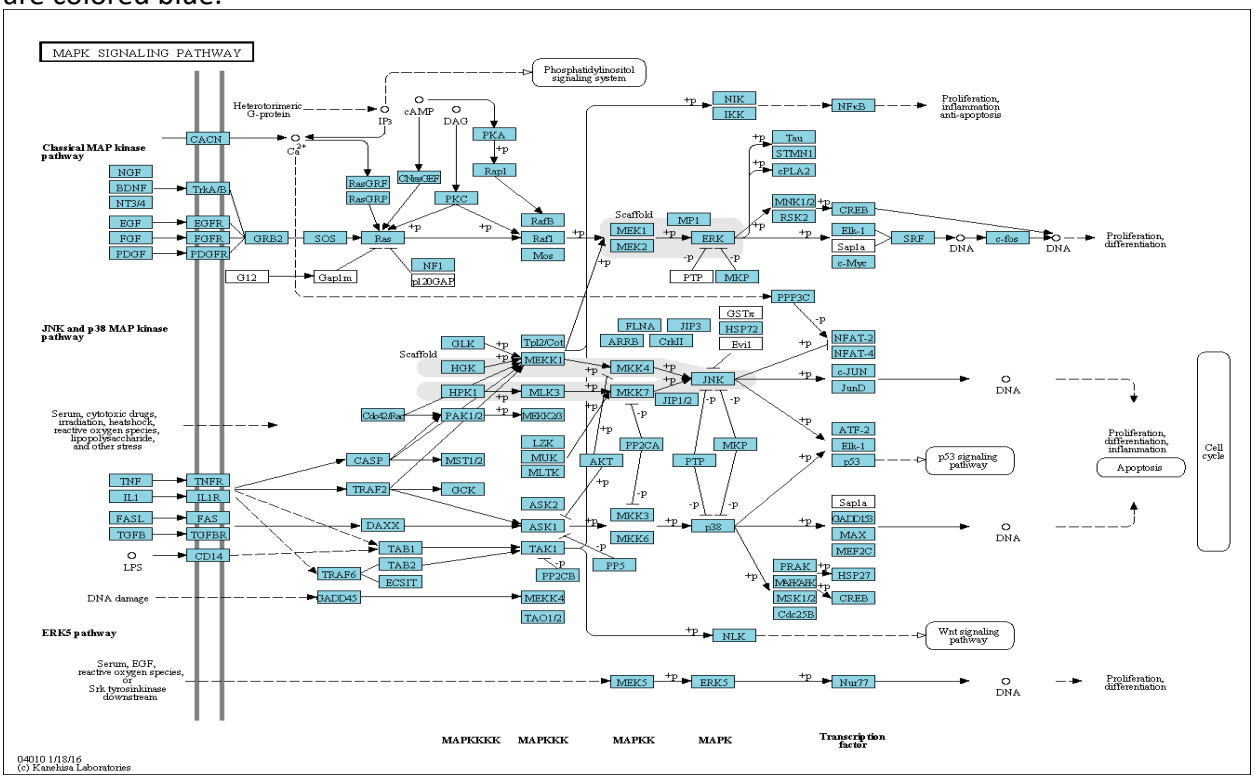


Figure 2: KEGG Ras signaling pathway (map04014.). Chicken genes mapped to this pathway are colored blue.

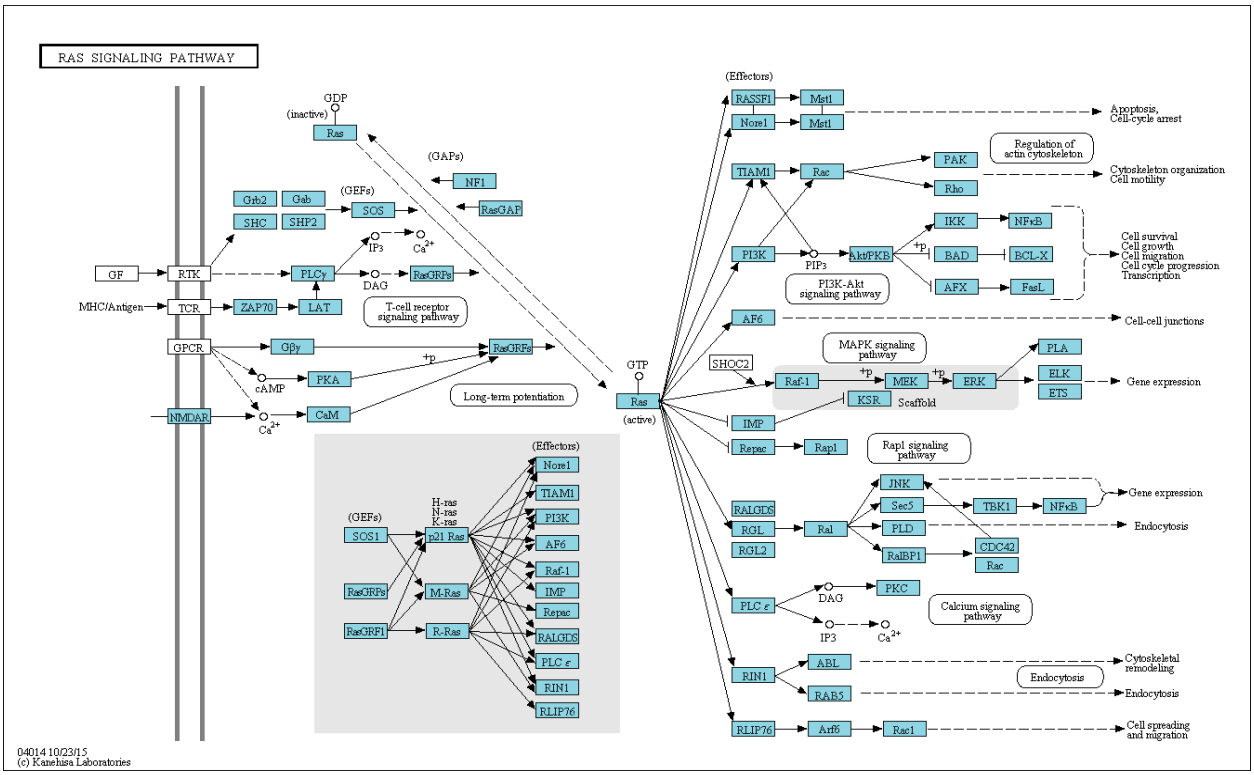


Table 1: Identification of chicken RASopathy orthologs. In instances where there was no clearly identified chicken orthology for a human RASopathy gene, the human gene sequence was searched against the chicken genome, and possible genes are identified below.

Human Gene		Homologous Regions in the Chicken Genome		
Gene Symbol	**Entrez ID**	**Number of Matches**	**Chromosomes**	**Synteny**
DAXX	1616	18	1, 2, 3, 11, 12, 13, 20, 23	No identified syntenic region
PRKCG	5582	8	14, 18, Z	14
TNF	7124	0	_	No identified syntenic region
HSPA1A	3303	2	5	No identified syntenic region
HSPA1B	3304	2	5	No identified syntenic region
HSPA1L	3305	5	5	No identified syntenic region
HSPA6	3310	3	5, 24	25
CACNA1A	773	12	1, 11, 24, 25, Z, AA Scaffold	No identified syntenic region
PRKACA	5566	2	2, AA Scaffold	No identified syntenic region
FGF11	2256	0	_	No identified syntenic region
FGF17	8822	1	6	No identified syntenic region
FGF21	26291	0	_	No identified syntenic region
MAPK3	5595	0	_	No identified syntenic region
IL1A	3552	0	_	Scaffold JH375214.1
MAP4K1	11184	0	_	No identified syntenic region
MAP4K2	5871	0	_	No identified syntenic region
MAP3K11	4296	0	_	No identified syntenic region
ARRB1	408	6	AA Scaffolds	1
ARRB2	409	6	AA Scaffolds	No identified syntenic region
JUND	3727	4	Z	28
TP53	7157	0	_	No identified syntenic region
PPP5C	5536	0	_	No identified syntenic region

MAPK7	5598	1	JH Scaffold	No identified syntenic region
NR4A1	3164	6	2, 7, 17, AA Scaffolds	Scaffold LGE22C19W28_E50C23
CACNA1F	778	46	1, 2, 3, 4, 5, 8, 10, 11, 13, 15, 20, 23, 26, 28, Z, LGE Scaffolds	No identified syntenic region
CACNB3	784	4	27	Scaffold AADN03016594.1
CACNG6	59285	0	_	No identified syntenic region
CACNG8	59283	5	2,6, 14, 23	No identified syntenic region
CDC25B	994	0	_	No identified syntenic region
IKBKG	8517	0	_	No identified syntenic region
RRAS	6237	0	_	No identified syntenic region
RELB	5971	2	4, 21	No identified syntenic region
RASGRP2	10235	0	_	No identified syntenic region
RASGRP4	115727	0	_	No identified syntenic region
TGFB1	7040	1	3	No identified syntenic region
RPS6KA4	8986	2	AA Scaffolds	No identified syntenic region
DUSP9	1852	0	_	No identified syntenic region
PRKACG	5568	1	AA Scaffold	Z or 4
PPP3CC	5533	2	AA Scaffolds	No identified syntenic region
ELK1	2002	0	_	No identified syntenic region
TAOK2	9344	13	1, 2, Z	No identified syntenic region
MAP2K7	5609	0	_	No identified syntenic region
DUSP2	1844	4	4, 13	No identified syntenic region
CACNG7	59284	4	18	No identified syntenic region
NTF4	4909	1	2	No identified syntenic region
PLA2G2C	391013	No clear annotated chicken gene		21

PLA2G2F	64600	0	_	21
PLD2	5338	3	9	No identified syntenic region
BAD	572	0	_	No identified syntenic region
CALM3	808	2	1, 5	No identified syntenic region
CALML5	51806	0	_	1
CALML6	163688	0	_	21
GNB2	2783	5	1, 21	No identified syntenic region
GNG3	2785	1	5	No identified syntenic region
GNG8	94235	0	_	No identified syntenic region
EFNA1	1942	0	_	No identified syntenic region
EFNA3	1944	4	13, Z, AA Scaffold, JH Scaffold	No identified syntenic region
EFNA4	1945	0	_	No identified syntenic region
LAT	27040	0	_	No identified syntenic region
PLA2G16	11145	0	_	No identified syntenic region
VEGFB	7423	0	_	No identified syntenic region
SYNGAP1	8831	13	1, 3, 4, 10, 14, 17, 21, 23, 26, Z, JH Scaffold	No identified syntenic region
RIN1	9610	1	7	No identified syntenic region
PLA2G3	50487	0	_	15
GNGT1	2792	0	_	2

Changes in chicken ortholog nomenclature. To better enable comparative studies, 168 chicken genes from the RASopathy data set were assigned standardized nomenclature, with changes to gene names, gene symbols, gene synonyms (Table 2, Supplemental Data Table 2). 98 chicken genes were assigned updated Ensembl ID mappings, and 35 genes were assigned ortholog mappings on NCBI.

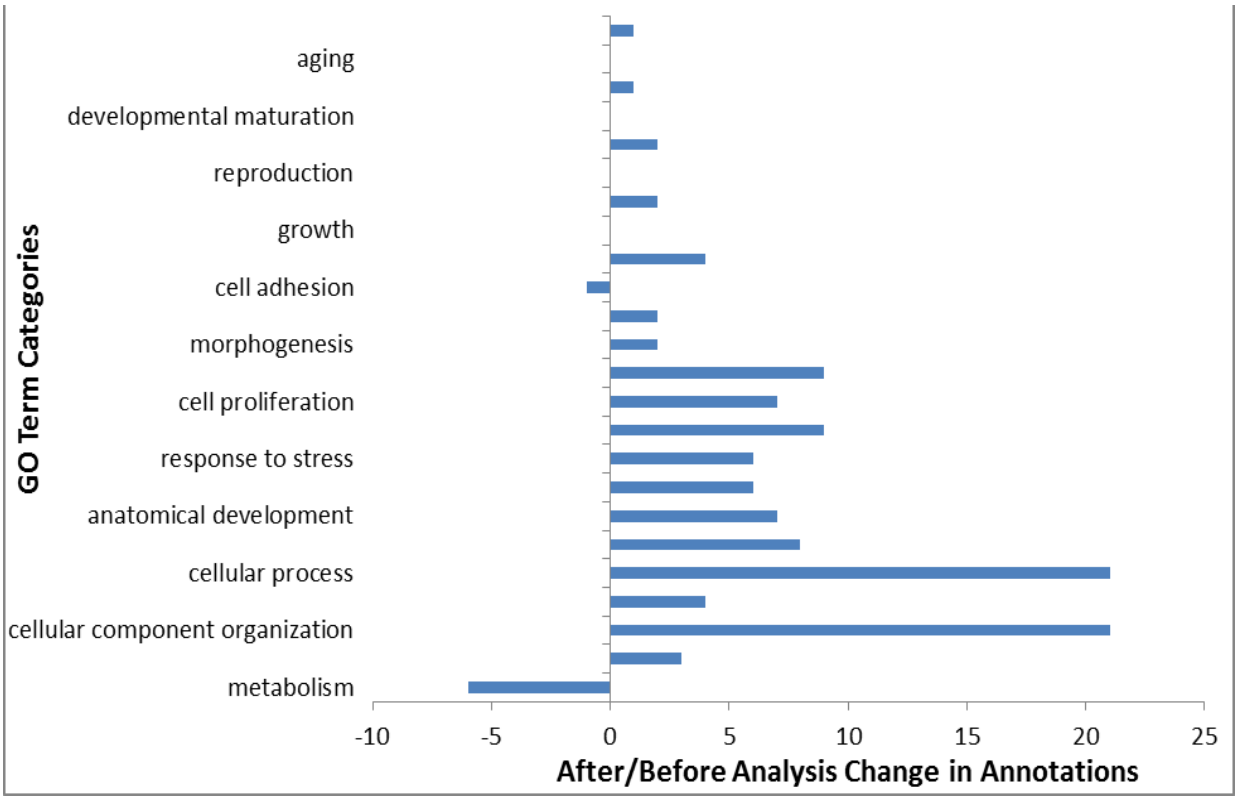
Improving functional annotation of chicken gene products related to RASopathies .
After identifying chicken orthologs for human RASopathy genes, correcting chicken gene nomenclature and mapping these genes to public database accessions, I next looked at the functional information linked to these chicken gene products by examining GO annotations. In total, there were 4553 GO annotations associated with the gene set before the analysis, and

Table 2: Standardization of chicken gene nomenclature and mappings associated with RASopathies.

Gene Entry Changes	Database		
	NCBI	CGNC	Ensembl
Updated Gene Name	8	8	148
Updated Gene Symbol	4	12	33
Added Synonyms	1	49	0
Deleted Synonyms	0	1	0
Incorrect mapping to CGNC	9	N/A	0
Incorrect Entrez ID mapping	0	1	0
Created new entry	1	3	0
Deleted entry	0	2	0
Added Ensembl mappings	79	39	N/A
Updated Ortholog mappings	36	0	0
Total Different Genes	106	46	148

4873 associated with it after the analysis (Table 2, Figure 3). Of the 300 chicken genes, 90.3% initially had assigned GO function. The number of these genes that had GO annotations after assigning standardized gene nomenclature and improving accession mapping did not change. As expected, 68.3% of functional annotations were assigned to Biological Processes, which also had the most additions and overall numerical change. 125 of the genes with annotations were unchanged before and after analysis, while deletions and additions occurred mainly in Biological Process

Figure 3: Functional annotation of chicken gene products associated with RASopathies. The Gene Ontology (GO) annotations for these gene products were compared prior to and just after mapping orthologous chicken genes to their human counterparts. Annotations are reported by relevant Biological Function categories.



annotations (Table 3). Most of the updates involved Inferred from Biological Aspect of Ancestor (IBA) and Inferred from Electronic Annotation (IEA) evidence types, and in every aspect category, the annotation additions outnumbered the deletions (Table 4).

Table 3: Functional annotation of chicken gene products associated with RASopathies. The Gene Ontology (GO) annotations for these gene products were compared prior to and just after mapping orthologous chicken genes to their human counterparts. Annotations are reported by Cellular Component (CC), Molecular Function (MF), and Biological Process (BP).

Annotation Category	Data Set		Changes to GO annotations		
	Before Analysis	After Analysis	Deletions	Additions	No Change [Number of Genes]
CC	835	858	29	52	212
MF	607	618	27	38	220
BP	3,111	3,397	70	356	152
Total	4,553	4,873	126	446	125

Table 4: **Changes in GO annotation before and after analysis.** These changes are categorized based upon GO evidence codes, as described in Guide to GO Evidence Codes [http://geneontology.org/page/guide-go-evidence-codes].

GO Evidence Codes	Annotations		Annotation Changes		
	Before Analysis	After Analysis	Deletions	Additions	Overall Change
Automatically-Assigned	3,310	3,486	96	272	176
Computational Analysis	897	1,010	77	187	113
Experimental	160	191	0	31	31
Author Statement	186	185	2	1	-1
Curatorial Statement	0	1	0	1	1
Total	4,553	4,873	175	492	320

Assessing annotations for chicken RASopathy genes.

There are several steps to improve comparative analysis between chicken and human Rasopathy genes, and I assessed each of these steps. First is to be able to accurately and rapidly identify genes sets across species. Of the 365 human genes involved in RASopathies, we identified 300 orthologus chicken genes. To ensure that comparative mapping between these species is rapid and effective for biomedical researchers, I improved mapping of public database accessions for 38.7% of these chicken genes and provided standardized gene nomenclature for 56%. Taken together this represents a 47.35% improvement to effectively identify these chicken genes.

The second step is to assess the functional information associated with these chicken gene products. Functional annotations are associated with gene products directly by manual curation

of published experimental data and indirectly by transferring functional information from similar or orthologous sequences. As part of this project I identified 12 publications for 7 of these chicken genes that will be manually annotated to provide additional functional information. Moreover, identifying human orthologs allows biocurators to transfer additional functional information. When the GO annotations associated with the chicken RASopathy gene set were compared to GO annotations prior to this project, there was a 7.03% increase. As expected, most GO annotation additions were based upon sequence evidence codes.

Discussion

RASopathies are a diverse set of genetic diseases, and their basis in multiple complex signaling pathways involved in early development, as well as their common occurrence, sets them as a significant set of diseases to model. By gaining more data and improving understanding of the mechanisms of the RAS/MAPK signaling pathway, ubiquitous with its roles in cell function and growth, there will be significant improvement and development of treatments of developmental diseases. Using biomedical models to successfully replicate human disease symptoms through similar mechanisms is one of the most effective ways of quickly producing experimental data for this purpose. Chicken is a practical choice as a biomedical model for RASopathies, due both a biomedical model and the model avian species, which has resulted in a large amount of gene annotation and available ortholog data. We used chicken in this comparative genomics analysis with the intent to improve the ability of researches to effectively use chicken as a model to study RASopathies, as well as other human disease. For this purpose the KEGG pathway maps for the MAPK and Ras pathways were chosen, as they effectively covered a broad gene set that is involved in a vast amount of RAS/MAPK kinase signaling that affects human development and everyday function.

Of the 365 human RAS/MAPK pathway genes, 300 have a listed one-to-one chicken ortholog, which given the status of chicken as a biomedical model, is expected, as it is important for chicken to be able to successfully model human diseases, and therefore should a significant amount of similar or conserved developmental genes. Of those orthologs, a large amount of database entries were found to be below the current standards for nomenclature, and missing ENS entry mappings. Of those human genes that were identified as having BLAST matches to the chicken genome, many had no obvious syntenic regions on chicken chromosomes, but did have BLAST matches to various sequence scaffolds or chromosomes. This suggests missed orthologous sequences on existing gene annotations, likely due to either being located on sequence scaffolds that are not fully assembled and annotated into chicken chromosomes, or from ambiguity in orthology due to expanded chicken gene families with multiple duplicate genes, or from sequence matches identifying sequence motifs common to many genes, which could have implications of chicken gene function, but not as an ortholog of the human gene that was analyzed. Identifying chicken orthologs, potential orthologs, and providing standardized nomenclature to those orthologs allows the improved ability of researches to perform comparative studies between human and chicken by giving greater accessibility to existing gene function data.

Functional annotations were also improved, by the overall increase of total GO annotations, as well as the expansion of annotations related to biological functions in a multicellular system, which are crucial to furthering understanding of the mechanisms of gene products in the RAS/MAPK signaling pathway. Identifying orthologs enables transfer of functional information from chicken to human, as well as sharing potentially applicable GO annotations. This potential is apparent by the majority of the new annotations being based off of computational analysis evidence, which rely on gene sequence analysis or established orthology to infer function based on similarities to sequences with known functions. Sequence based functional annotations provide rapid, genome-wide functional annotation, based on inferences. The complementary approach to this is to acquire detailed experimental data from published papers that physically characterize genes or gene products. I have identified several such papers, which will be used by AgBase biocurators to add to existing functional information, further adding GO annotations to this data set.

Identifying orthologs, potential orthologs, standardizing gene nomenclature, and adding or updating Ensembl ID and ortholog mappings across databases, as well as identifying published papers with experimental data improves functional annotations by increasing accessibility of existing data. These improvements allow for better transfer of gene functional information from chicken to human, and vice versa, which makes it easier for researchers to use chicken as a biomedical model to study RASopathies, and hopefully increase the efficiency of new and existing studies.

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Supplementary Table 1: The RASopathy genes sets used in this study. Human genes from KEGG MAPK signaling (map04010) and Ras signaling pathway (map04014) pathways were mapped to chicken gene accessions, as indicated.

Pathway ID	KEGG ID	Human Entrez ID	Human Ensembl ID	Chicken Ensembl ID	Chicken Entrez ID
map04014	K00922	5290	ENSG00000121879	ENSGALG00000008934	424971
		5291	ENSG00000051382	ENSGALG00000005505	424826
		5293	ENSG00000171608	ENSGALG00000002583	419444
		5294	ENSG00000105851	ENSGALG00000008081	417706
map04014	K01047	81579	ENSG00000123739	ENSGALG00000012185	772082
		84647	ENSG00000138308	ENSGALG00000004332	423705
		5319	ENSG00000170890	ENSGALG00000020989	416980
		5320	ENSG00000188257	ENSGALG00000018981	426748
		391013	ENSG00000187980	_	_
		26279	ENSG00000117215	_	_
		30814	ENSG00000188784	ENSGALG00000014176	426747
		64600	ENSG00000158786	_	_
		50487	ENSG00000100078	_	_
		5322	ENSG00000127472	ENSGALG00000018977	771655
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map04014	K08887	27	ENSG00000143322	ENSGALG00000004213	395410
map04010	K09253	5971	ENSG00000104856	_	_
map04014	K09254	5966	ENSG00000162924	ENSGALG00000007845	396500
map04014	K09593	2549	ENSG00000109458	ENSGALG00000009898	422456
map04014	K09850	11186	ENSG00000068028	_	101750777
map04014	K10632	8315	ENSG00000089234	ENSGALG00000004650	772041
map04010, map04014	K12326	5924	ENSG00000113319	ENSGALG00000015598	100859132
map04014	K12358	4303	ENSG00000184481	ENSGALG00000005658	428703
map04010, map04014	K12361	10235	ENSG00000068831	_	_
map04010, map04014	K12362	25780	ENSG00000152689	ENSGALG00000010435	421460

map04010, map04014	K12363	115727	ENSG00000171777	_	_
map04014	K12380	22821	ENSG00000185989	ENSGALG00000016817	418736
map04010	K12457	4909	ENSG00000225950	_	_
map04010	K13375	7040	ENSG00000105329	_	_
map04010	K13376	7042	ENSG00000092969	ENSGALG00000009612	421352
map04010	K13377	7043	ENSG00000119699	ENSGALG00000010346	396438
map04014	K13618	51365	ENSG00000144837	ENSGALG00000014997	770199
map04014	K14958	8844	ENSG00000141068	ENSGALG00000005685	427839
map04010, map04014	K16342	5321	ENSG00000116711	ENSGALG00000005065	396394
map04014	K16343	8398	ENSG00000184381	ENSGALG00000012281	418028
map04010	K16510	8986	ENSG00000162302	_	_
map04014	K16817	11145	ENSG00000176485	_	_
map04014	K16858	7423	ENSG00000173511	_	_
map04014	K16859	5228	ENSG00000119630	ENSGALG00000026557	_
map04010	K17333	4775	ENSG00000072736	ENSGALG00000003396	415711
map04010, map04014	K17386	5155	ENSG00000100311	ENSGALG00000012178	374128
map04014	K17447	25759	ENSG00000129946	ENSGALG00000001289	770341
map04014	K17448	53358	ENSG00000148082	ENSGALG00000010688	431265
map04014	K17449	399694	ENSG00000185634	ENSGALG00000005011	426482
map04010	K17614	1845	ENSG00000108861	ENSGALG00000029003	425527
map04014	K17630	_	_	ENSGALG00000001861	417513
		10156	ENSG00000105808	ENSGALG00000001876	_
map04014	K17631	8831	ENSG00000197283	_	_
map04014	K17632	8437	ENSG00000111344	ENSGALG00000008150	771057
map04014	K17633	9462	ENSG00000075391	ENSGALG00000004323	429069
map04014	K17634	64926	ENSG00000105122	ENSGALG00000029030	101747651
map04014	K17635	23179	ENSG00000143344	ENSGALG00000004728	424446
map04014	K17636	5863	ENSG00000237441	ENSGALG00000003412	_
map04014	K17637	55770	ENSG00000112685	ENSGALG00000012837	420889
map04014	K17638	9610	ENSG00000174791	_	_
map04010	K18018	84867	ENSG00000110786	ENSGALG00000006368	423085
map04010	K18019	5778	ENSG00000143851	ENSGALG00000000600	770905
map04010, map04014	K18496	2246	ENSG00000113578	ENSGALG00000007343	396094
map04010, map04014	K18497	2247	ENSG00000138685	ENSGALG00000011835	396413
map04010	K18498	1852	ENSG00000130829	_	_
map04014	K18529	283455	ENSG00000171435	ENSGALG00000020905	_

Supplementary Table 2: Accession mapping in orthologous chicken Ensembl ID mappings after manual review.

Pathway ID	KEGG ID	Human Entrez ID	Human Ensembl ID	Chicken Ensembl ID	Chicken Entrez ID
map04014	K00922	5290	ENSG00000121879	ENSGALG00000008934	424971
		5291	ENSG00000051382	ENSGALG00000005505	424826
		5293	ENSG00000171608	ENSGALG00000002583	419444
		5294	ENSG00000105851	ENSGALG00000008081	417706
map04014	K01047	81579	ENSG00000123739	ENSGALG00000012185	772082
		84647	ENSG00000138308	ENSGALG00000004332	423705
		5319	ENSG00000170890	ENSGALG00000020989	416980
		5320	ENSG00000188257	ENSGALG00000018981	426748
		391013	ENSG00000187980	_	_
		26279	ENSG00000117215	_	_
		30814	ENSG00000188784	ENSGALG00000014176	426747
		64600	ENSG00000158786	_	_
		50487	ENSG00000100078	_	_
		5322	ENSG00000127472	ENSGALG00000018977	771655
		8399	ENSG00000069764	ENSGALG00000021314	416425
map04014	K01115	5337	ENSG00000075651	ENSGALG00000009252	424986
		5338	ENSG00000129219	_	_
map04014	K01116	5335	ENSG00000124181	ENSGALG00000003750	419175
map04014	K02158	572	ENSG00000002330	_	_
map04014	K02183	801	ENSG00000198668	ENSGALG00000026445	396523
		805	ENSG00000143933	ENSGALG00000010023	395855
		808	ENSG00000160014	_	_
		810	ENSG00000178363	ENSGALG00000008424	416692
		51806	ENSG00000178372	_	_
		163688	ENSG00000169885	_	_
map04010	K02187	836	ENSG00000164305	ENSGALG00000010638	395476
map04010	K02308	1616	ENSG00000204209	_	_
map04010, map04014	K02580	4790	ENSG00000109320	ENSGALG00000012304	396033
map04010, map04014	K02582	4803	ENSG00000134259	ENSGALG00000002556	396466
map04014	K02583	4804	ENSG00000064300	ENSGALG00000027311	425805
map04014	K02649	5295	ENSG00000145675	ENSGALG00000014786	427171
		5296	ENSG00000105647	ENSGALG00000003428	771142
		8503	ENSG00000117461	ENSGALG00000010335	429096
		23533	ENSG00000141506	ENSGALG00000021573	417319
map04010,	K02677	5578	ENSG00000154229	ENSGALG00000003943	417430

map04014		5579	ENSG00000166501	ENSGALG00000006014	416567
		5582	ENSG00000126583	_	_
map04014	K02678	2113	ENSG00000134954	ENSGALG00000001143	396235
		2114	ENSG00000157557	ENSGALG00000016059	396250
map04010, map04014	K02833	3265	ENSG00000174775	ENSGALG00000006885	396229
map04010, map04014	K03099	6654	ENSG00000115904	ENSGALG00000013224	431192
		6655	ENSG00000100485	ENSGALG00000012273	423572
map04010	K03156	7124	ENSG00000232810	_	_
map04010	K03158	7132	ENSG00000067182	ENSGALG00000014890	418325
map04010	K03173	7186	ENSG00000127191	ENSGALG00000009014	417287
map04010	K03175	7189	ENSG00000175104	ENSGALG00000007932	423163
map04010	K03176	4914	ENSG00000198400	ENSGALG00000019019	396337
map04010	K03283	3303	ENSG00000204389	_	_
		3304	ENSG00000204388	_	_
		3305	ENSG00000204390	_	_
		3306	ENSG00000126803	ENSGALG00000011715	423504
		3310	ENSG00000173110	_	_
		3312	ENSG00000109971	ENSGALG00000006512	395853
map04014	K04163	3363	ENSG00000148680	ENSGALG00000026998	423794
map04010	K04344	773	ENSG00000141837	_	_
map04010, map04014	K04345	5566	ENSG00000072062	_	_
		5567	ENSG00000142875	ENSGALG00000028530	424542
		5568	ENSG00000165059	_	_
		5613	ENSG00000183943	ENSGALG00000016629	418656
map04010	K04346	2768	ENSG00000146535	ENSGALG00000004368	769924
map04010	K04347	55970	ENSG00000172380	ENSGALG00000026591	772239
map04010	K04348	5530	ENSG00000138814	ENSGALG00000012280	395113
		5532	ENSG00000107758	ENSGALG00000005243	378890
		5533	ENSG00000120910	_	_
map04010, map04014	K04349	5923	ENSG00000058335	ENSGALG00000008262	415578
map04010, map04014	K04350	10125	ENSG00000172575	ENSGALG00000009740	423290
map04010, map04014	K04352	5921	ENSG00000145715	ENSGALG00000017706	427327
map04010, map04014	K04353	5906	ENSG00000116473	ENSGALG00000001476	419867
map04010	K04355	627	ENSG00000176697	ENSGALG00000012163	396186
map04010	K04356	4908	ENSG00000185652	ENSGALG00000027299	428099
map04010, map04014	K04357	1950	ENSG00000138798	ENSGALG00000012155	408035
map04010,	K04358	2255	ENSG00000070193	ENSGALG00000014872	395432

map04014		2256	ENSG00000161958	_	_
		2257	ENSG00000114279	ENSGALG00000007219	395704
		2258	ENSG00000129682	ENSGALG00000006508	414831
		2259	ENSG00000102466	ENSGALG00000016866	395554
		8823	ENSG00000196468	ENSGALG00000007806	422330
		8822	ENSG00000158815	_	_
		8817	ENSG00000156427	ENSGALG00000002203	395453
		9965	ENSG00000162344	ENSGALG00000028376	395394
		26281	ENSG00000078579	ENSGALG00000013663	428779
		26291	ENSG00000105550	_	_
		27006	ENSG00000070388	ENSGALG00000001385	100858338
		8074	ENSG00000118972	ENSGALG00000027791	428104
		2248	ENSG00000186895	ENSGALG00000026853	396267
		2249	ENSG00000075388	ENSGALG00000007562	428857
		2250	ENSG00000138675	ENSGALG00000010893	770457
		2251	ENSG00000111241	ENSGALG00000017287	768907
		2252	ENSG00000140285	ENSGALG00000028158	415439
		2253	ENSG00000107831	ENSGALG00000007706	396313
		2254	ENSG00000102678	ENSGALG00000025748	378917
map04010, map04014	K04359	5154	ENSG00000197461	ENSGALG00000003642	374196
map04010	K04360	4915	ENSG00000148053	ENSGALG00000012594	396157
map04010, map04014	K04361	1956	ENSG00000146648	ENSGALG00000012363	396494
map04010, map04014	K04362	2260	ENSG00000077782	ENSGALG00000003311	396516
map04010, map04014	K04363	5156	ENSG00000134853	ENSGALG00000013929	395509
map04010, map04014	K04364	2885	ENSG00000177885	ENSGALG00000008016	386572
map04010	K04365	673	ENSG00000157764	ENSGALG00000012865	396239
map04010, map04014	K04366	5894	ENSG00000132155	ENSGALG00000004998	396245
map04010	K04367	4342	ENSG00000172680	ENSGALG00000015406	428537
map04010, map04014	K04368	5604	ENSG00000169032	ENSGALG00000007687	415549
map04010, map04014	K04369	5605	ENSG00000126934	ENSGALG00000001267	396349
map04010	K04370	8649	ENSG00000109270	ENSGALG00000000055	425210
map04010, map04014	K04371	5594	ENSG00000100030	ENSGALG00000001501	373953
		5595	ENSG00000102882	_	_
map04010	K04372	8569	ENSG00000079277	ENSGALG00000010440	771961
		2872	ENSG00000099875	ENSGALG00000003845	429269

map04010	K04373	6197	ENSG00000177189	ENSGALG00000016406	418605
map04010	K04374	468	ENSG00000128272	ENSGALG00000012135	395693
map04010, map04014	K04375	2002	ENSG00000126767	_	_
map04010	K04376	2005	ENSG00000158711	ENSGALG00000000701	419832
map04010	K04377	4609	ENSG00000136997	ENSGALG00000016308	420332
map04010	K04378	6722	ENSG00000112658	ENSGALG00000013255	396103
map04010	K04379	2353	ENSG00000170345	ENSGALG00000028037	396512
map04010	K04380	4137	ENSG00000186868	ENSGALG00000000625	426737
map04010	K04381	3925	ENSG00000117632	ENSGALG00000001475	396057
map04010	K04383	3552	ENSG00000115008	_	_
map04010	K04386	3554	ENSG00000115594	ENSGALG00000016783	396481
map04010	K04387	7850	ENSG00000115590	ENSGALG00000016782	418715
map04010	K04388	7048	ENSG00000163513	ENSGALG00000011442	477039
map04010, map04014	K04389	356	ENSG00000117560	ENSGALG00000003076	429064
map04010	K04390	355	ENSG00000026103	ENSGALG00000006351	395274
map04010	K04391	929	ENSG00000170458	ENSGALG00000021559	100194427
map04010, map04014	K04392	5879	ENSG00000136238	ENSGALG00000007130	395871
map04010, map04014	K04393	998	ENSG00000070831	ENSGALG00000004796	395917
map04010	K04402	1647	ENSG00000116717	ENSGALG00000025977	693255
map04010	K04403	10454	ENSG00000100324	ENSGALG00000012150	418014
map04010	K04404	23118	ENSG00000055208	ENSGALG00000012356	421622
map04010	K04405	51295	ENSG00000130159	_	100857880
map04010	K04406	8491	ENSG00000011566	ENSGALG00000013227	425965
map04010	K04407	9448	ENSG00000071054	ENSGALG00000016781	418714
map04010	K04408	11184	ENSG00000104814	_	_
map04010, map04014	K04409	5058	ENSG00000149269	ENSGALG00000000681	419083
map04010, map04014	K04410	5062	ENSG00000180370	ENSGALG00000006426	424860
map04010, map04014	K04411	6789	ENSG00000101109	ENSGALG00000004098	419187
map04010	K04412	6788	ENSG00000104375	ENSGALG00000016015	425375
map04010	K04414	5871	ENSG00000168067	_	_
map04010	K04415	1326	ENSG00000107968	ENSGALG00000007356	420479
map04010	K04416	4214	ENSG00000095015	ENSGALG00000014718	427144
map04010	K04419	4296	ENSG00000173327	_	_
map04010	K04420	10746	ENSG00000169967	ENSGALG00000011502	424225
map04010	K04421	4215	ENSG00000198909	ENSGALG00000000525	419954
map04010	K04422	9175	ENSG00000073803	ENSGALG00000006655	424876

map04010	K04423	7786	ENSG00000139625	ENSGALG00000026931	101750914
map04010	K04424	51776	ENSG00000091436	ENSGALG00000009344	424149
map04010	K04425	9064	ENSG00000142733	ENSGALG00000028785	100858193
map04010	K04426	4217	ENSG00000197442	ENSGALG00000013892	421688
map04010	K04427	6885	ENSG00000135341	ENSGALG00000015596	421808
map04010	K04428	4216	ENSG00000085511	ENSGALG00000020003	421579
map04010	K04429	57551	ENSG00000160551	ENSGALG00000004082	417583
		9344	ENSG00000149930	_	_
		51347	ENSG00000135090	ENSGALG00000007396	395499
map04010	K04430	6416	ENSG00000065559	ENSGALG00000001001	417312
map04010	K04431	5609	ENSG00000076984	_	_
map04010	K04432	5606	ENSG00000034152	ENSGALG00000004735	416496
map04010	K04433	5608	ENSG00000108984	ENSGALG00000004370	417445
map04010	K04434	9479	ENSG00000121653	ENSGALG00000008430	423202
map04010	K04435	23542	ENSG00000008735	ENSGALG00000026023	_
map04010	K04436	23162	ENSG00000138834	ENSGALG00000001772	426986
map04010	K04437	2316	ENSG00000196924	_	395261
map04010	K04438	1398	ENSG00000167193	ENSGALG00000002656	417553
map04010	K04439	408	ENSG00000137486	_	_
		409	ENSG00000141480	_	_
map04010, map04014	K04440	5599	ENSG00000107643	ENSGALG00000006109	423778
map04010	K04441	1432	ENSG00000112062	ENSGALG00000019759	421183
map04010	K04442	8550	ENSG00000089022	ENSGALG00000004743	373929
map04010	K04443	9261	ENSG00000162889	ENSGALG00000000883	419847
map04010	K04444	7867	ENSG00000114738	ENSGALG00000002283	415917
map04010	K04445	9252	ENSG00000100784	ENSGALG00000010698	423408
map04010	K04446	4772	ENSG00000131196	ENSGALG00000012654	420815
map04010	K04448	3725	ENSG00000177606	ENSGALG00000010870	424673
map04010	K04449	3727	ENSG00000130522	_	_
map04010	K04450	1386	ENSG00000115966	ENSGALG00000009287	395727
map04010	K04451	7157	ENSG00000141510	_	_
map04010	K04452	1649	ENSG00000175197	_	100857832
map04010	K04453	4149	ENSG00000125952	ENSGALG00000028248	100858676
map04010	K04454	4208	ENSG00000081189	ENSGALG00000014645	769007
map04010	K04455	3315	ENSG00000106211	ENSGALG00000001926	396227
map04010, map04014	K04456	207	ENSG00000142208	ENSGALG00000011620	395928
map04010	K04457	5494	ENSG00000100614	ENSGALG00000011917	423525
map04010	K04458	5801	ENSG00000153233	ENSGALG00000010148	771985
map04010	K04459	1843	ENSG00000120129	ENSGALG00000003706	374192
		11221	ENSG00000143507	ENSGALG00000009450	421340

		80824	ENSG00000111266	ENSGALG00000028155	431336
		1844	ENSG00000158050	_	423890
		1846	ENSG00000120875	ENSGALG00000011419	374272
		1847	ENSG00000138166	ENSGALG00000008581	415891
		1848	ENSG00000139318	ENSGALG00000011207	770435
		1849	ENSG00000164086	ENSGALG00000026085	421340
		1850	ENSG00000184545	ENSGALG00000006647	431336
map04010	K04460	5536	ENSG00000011485	_	_
map04010	K04461	5495	ENSG00000138032	ENSGALG00000009970	421404
map04010	K04462	2122	ENSG00000085276	ENSGALG00000009437	424997
map04010	K04463	5607	ENSG00000137764	ENSGALG00000007930	415557
map04010	K04464	5598	ENSG00000166484	_	_
map04010	K04465	3164	ENSG00000123358	_	_
map04010	K04466	9020	ENSG00000006062	ENSGALG00000000685	419964
map04010, map04014	K04467	1147	ENSG00000213341	ENSGALG00000003289	423669
map04010	K04468	51701	ENSG00000087095	ENSGALG00000005699	417669
map04010	K04469	4791	ENSG00000077150	ENSGALG00000005653	386574
map04014	K04513	387	ENSG00000067560	ENSGALG00000003806	395442
map04010	K04519	3553	ENSG00000125538	ENSGALG00000000534	395196
map04014	K04526	3630	ENSG00000254647	ENSGALG00000006552	396145
map04014	K04527	3643	ENSG00000171105	ENSGALG00000003579	420133
map04014	K04536	2782	ENSG00000078369	ENSGALG00000001334	419402
map04014	K04537	2783	ENSG00000172354	_	_
map04014	K04538	59345	ENSG00000114450	ENSGALG00000008983	424974
map04014	K04539	10681	ENSG00000069966	_	415417
map04014	K04540	2785	ENSG00000162188	_	_
map04014	K04541	2786	ENSG00000168243	ENSGALG00000010986	771582
map04014	K04542	2787	ENSG00000174021	ENSGALG00000027561	424538
map04014	K04543	2788	ENSG00000176533	ENSGALG00000026377	100858976
map04014	K04544	94235	ENSG00000167414	_	_
map04014	K04545	2790	ENSG00000242616	ENSGALG00000015683	769603
map04014	K04546	2791	ENSG00000127920	_	771999
map04014	K04547	51764	ENSG00000127588	ENSGALG00000005293	771014
map04014	K04548	2792	ENSG00000127928	_	_
map04014	K04549	2793	ENSG00000167083	ENSGALG00000026333	100859179
map04014	K04570	598	ENSG00000171552	ENSGALG00000006211	373954
map04010	K04674	7046	ENSG00000106799	ENSGALG00000012617	374094
map04010, map04014	K04735	5970	ENSG00000173039	_	396027
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map04010	K04850	775	ENSG00000151067	ENSGALG00000013022	395891

map04010	K04851	776	ENSG00000157388	ENSGALG00000005332	395895
map04010	K04852	777	ENSG00000198216	ENSGALG00000003833	424412
map04010	K04853	778	ENSG00000102001	_	_
map04010	K04854	8913	ENSG00000006283	ENSGALG00000007623	769385
map04010	K04855	8912	ENSG00000196557	ENSGALG00000005215	416526
map04010	K04856	8911	ENSG00000100346	ENSGALG00000012122	427900
map04010	K04857	779	ENSG00000081248	ENSGALG00000000730	395985
map04010	K04858	781	ENSG00000153956	ENSGALG00000008486	768444
map04010	K04859	9254	ENSG00000007402	ENSGALG00000029021	430150
map04010	K04860	55799	ENSG00000157445	ENSGALG00000005400	415996
map04010	K04861	93589	ENSG00000151062	ENSGALG00000013007	100858946
map04010	K04862	782	ENSG00000067191	ENSGALG00000025788	777366
map04010	K04863	783	ENSG00000165995	ENSGALG00000008591	428420
map04010	K04864	784	ENSG00000167535	_	_
map04010	K04865	785	ENSG00000182389	ENSGALG00000012511	374259
map04010	K04866	786	ENSG00000108878	ENSGALG00000003900	417428
map04010	K04867	10369	ENSG00000166862	ENSGALG00000027830	427909
map04010	K04868	10368	ENSG00000006116	ENSGALG00000026103	395378
map04010	K04869	27092	ENSG00000075461	ENSGALG00000028125	373924
map04010	K04870	27091	ENSG00000075429	ENSGALG00000026628	417429
map04010	K04871	59285	ENSG00000130433	_	_
map04010	K04872	59284	ENSG00000105605	_	_
map04010	K04873	59283	ENSG00000142408	_	_
map04014	K05087	3480	ENSG00000140443	ENSGALG00000007039	395889
map04010, map04014	K05089	5159	ENSG00000113721	ENSGALG00000021313	770488
map04014	K05090	1436	ENSG00000182578	ENSGALG00000005725	396406
map04014	K05091	3815	ENSG00000157404	ENSGALG00000013925	378783
map04010, map04014	K05093	2263	ENSG00000066468	ENSGALG00000009495	396259
map04010, map04014	K05094	2261	ENSG00000068078	ENSGALG00000015708	396515
map04010, map04014	K05095	2264	ENSG00000160867	ENSGALG00000028543	395603
map04014	K05096	2321	ENSG00000102755	ENSGALG00000017091	374100
map04014	K05097	2324	ENSG00000037280	ENSGALG00000005802	395742
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map04014	K05099	4233	ENSG00000105976	ENSGALG00000009390	396134
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