dbj|AK151985.1|	Mus musculusribosomal protein 2, full insert s...	643	0.0
gb|AY248756.1|	Mus musculus 18S ribosomal RNA-like mRNA, part...	843	0.0
dbj|AK051610.1|	CCHC type Zn-finger containing protein, full ...	411	9e-114
gb|BC106146.1|	Mus musculus ferritin light chain 1, mRNA (cDN...	250	2e-65
gb|BC096656.1|	eukaryotic translation initiation factor 1, mRN...	715	0.0
dbj|AK146772.1|	ribosomal protein L39, full insert sequence	436	1e-121
dbj|AK011558.1|	mitochondrial ribosomal protein 63, full ins...	418	5e-116
gb|BC086926.1|	Mus musculus transthyretin, mRNA (cDNA clone M...	676	0.0
gb|DQ167195.1|	acupuncture-induced 1-L (Aig1l) mRNA, complete...	313	3e-84
dbj|AK148009.1|	caldesmon 1, full insert sequence	854	0.0
gb|BC106146.1|	Mus musculus ferritin light chain 1, mRNA (cDN...	774	0.0
gb|BC086901.1|	Mus musculus ribosomal protein S17, mRNA (cDNA...	712	0.0
gb|BC012314.1|	Mus musculus ferritin heavy chain 1, mRNA (cDN...	523	1e-147
gb|BC061497.1|	tyrosine 3-monooxygenase/tryptophan 5-monooxyge...	202	6e-51
dbj|AK136262.1|	Cytochrome oxidase subunit 1 (EC 1.9.3.1) (Cy...	401	5e-111
gb|BC003833.1|	Mus musculus ribosomal protein, large, P0, mRN...	710	0.0
gb|AY941793.1|	eIF2 alpha kinase associated protein mRNA ...	680	0.0
dbj|AK151985.1|	ribosomal protein S2, full insert sequence	800	0.0
gb|BC083131.1|	Mus musculus ribosomal protein L19, mRNA (cDNA...	630	6e-180
dbj|AK131579.1|	Cytochrome oxidase sununit 3 (EC 1.9.3.1) (Cy...	730	0.0
gb|BC086926.1|	Mus musculus transthyretin, mRNA (cDNA clone M...	645	0.0
dbj|AK138995.1|	NADH dehydrogenase subunit 1 (EC 1.6.5.3) (NA...	444	9e-124
dbj|AK131586.1|	Cytochrome c oxidase polypeptide II (EC 1.9.3...	658	0.0
gb|BC025600.1|	Mus musculus transmembrane protein 119, mRNA (...	599	2e-170
gb|BC021786.1|	Mus musculus integral membrane protein 2B, mRN...	737	0.0
gb|BC099471.1|	Mus musculus C-type lectin domain family 4, me...	150	2e-35
dbj|AK163440.1|	NADH dehydrogenase subunit 2 homolog [Mus mus...	551	5e-156
gb|BC086926.1|	Mus musculus transthyretin, mRNA (cDNA clone M...	697	0.0
dbj|AK131578.1|	NADH dehydrogenase subunit 1 (EC 1.6.5.3) (NA...	856	0.0
dbj|AK136262.1|	Cytochrome oxidase subunit 1 (EC 1.9.3.1) (Cy...	704	0.0
dbj|AK160039.1|	cDNA 2410018G23 (BBP-like protein 1 homolog)...	695	0.0
gb|BC027412.1|	Mus musculus acyl-Coenzyme A dehydrogenase, lo...	453	1e-126
dbj|AK131579.1|	Cytochrome oxidase sununit 3 (EC 1.9.3.1) (Cy...	545	2e-1

この他、多くの遺伝子が同定され、正常のミクログリアが通常時に転写している遺伝子の概要を得た。

次に結核菌を感染させると

gb|BC082593.1| splicing factor, arginine/serine-rich 5 (SRp40, HRS) 154 2e-36
gb|BC009165.1| thyroid hormone responsive SPOT14 homolog (Rattus), 196 3e-49
gb|BC049955.1| caspase 8, mRNA (cDNA clone MGC:59027 IMAGE:4208824),750 0.0
gb|J04633.1|MUSHSP86A heat shock protein 86 mRNA and 28S ribosomal 259 4e-68
gb|BC046825.1| zinc finger and BTB domain containing 8 opposite str 747 0.0
gb|BC010249.1| coactosin-like 1 (Dictyostelium), mRNA (cDNA clone M 660 0.0
などの遺伝子転写産物が亢進した。
一方、ＣＣＲ５ノックアウトマウスで発現していて野生型マウスで発現があまり認められなかったものは以下のような配列であった。
gb|BC020487.1| vav 1 oncogene, mRNA (cDNA clone MGC:11710 IMAGE:3 63.9 3e-09
gb|BC028437.1| cytotoxic T lymphocyte-associated protein 2 alpha, 156 5e-37
gb|BC028547.1| hepatitis B virus x interacting protein, mRNA (cDNA 774 0.0
gb|BC046766.1|esterase D/formylglutathione hydrolase, mRNA (cDNA c 468 2e-131
dbj|AK009109.1| HUNTINGTIN INTERACTING PROTEIN HYPK (FRAGMENT) hom 424 1e-117
また、CCR5ノックアウトマウスのミクログリアに結核菌が感染して発現が亢進したものは以下のものであった。
dbj|AK145391.1| sperm specific antigen 1, full insert sequence... 344 3e-9
gb|AY036118.1| Mus musculus ETS-related transcription factor ... 466 7e-131
gb|BC049124.1| Mus musculus heat shock protein 90, alpha (cyt... 381 3e-105
gb|BC070415.1| histidine triad nucleotide binding protein 1, mRNA 433 7e-12
dbj|AK030335.1| ATPase,H+ transporting lysosomal (vacuolar proton p 743 0.0
dbj|AK168491.1| Similar to ubiquinol-cytochrome c reductase complex,472 1e-132
dbj|AK081100.1| DBC2 PROTEIN homolog [Mus musculus], full insert se 305 2e-82
dbj|AK150024.1| hypothetical Arginine-rich region profile/Serine-ric 734 0.0
gb|BC039917.1| RNA binding motif protein 42, mRNA (cDNA clone IMAGE: 425 1e-118
gb|BC003707.1| Mus musculus Sec61 alpha 1 subunit (S. cerevisiae), m 455 1e-127
dbj|AK140762.1|macrophage galactose N-acetyl-galactosamine specific 182 3e-45
dbj|AK162423.1|Mus musculus DEAD(Asp-Glu-Ala-Asp)box polypeptide 50,527 3e-149
gb|BC068152.1| Mus musculus stromal cell derived factor 4, mRNA (cD 623 4e-178
gb|BC099479.1| Mus musculus lectin, galactose binding, soluble 1, mR 749 0.0
dbj|AK135348.1|elongation of very long chain fatty acids -like 1, 673 0.0
gb|BC108394.1| Mus musculus tubulin, alpha 1B, mRNA (cDNA clone MGC: 207 5e-53
同1A、同1C。
その他　ribozomal proteins も多数認められた。

これらの遺伝子の中には後の解析の Th1 刺激以外の機械的刺激で上昇した遺伝子も含まれていたため、CCR５が欠損あるいは変異しているヒトの場合でも組織マクロファージの活動が欠損していない組織のマクロファージと同様に周囲の細胞に影響を与えている可能性がある。

また圧力負荷試験では軟骨への負荷が最も高いと考えられる関節面の軟骨細胞のみを試料とした。細胞へ圧力を負荷するためにシリンダ型ポンプで培養液を持続的に培養用チャンバーに注入し、圧制御弁を用いて軟骨細胞に 0.5～3.5 MPa, 0.001 to 1 Hz の変動圧を負荷して転写産物の解析を行った。

Reference	% Unique Matches
chr4	9.41
chr2	9.41
chr3	7.93
chr1	7.69
chr5	7.51
chr6	6.72
chr8	5.86
chr7	5.76
chr12	5.25
chr11	4.64
chr13	4.39
chr10	4.29
chr9	4.17
chr18	3.11
chrX	3.04
chr15	2.63
chr17	1.85
chr16	1.79
chr20	1.43
chr21	1.31
chr19	0.95
chr22	0.44
chrY	0.30
chrUn_gl000220	0.03
chr17_gl000205_random	0.01
chrM	0.01
chr1_gl000192_random	0.01
chr4_gl000193_random	0.01
chr7_gl000195_random	0.01
chr17_ctg5_hap1	0.01
chr9_gl000198_random	0.01
chrUn_gl000214	0.01
chrUn_gl000218	0.01
chrUn_gl000219	0.01
chrUn_gl000224	0.00

Reference	% Unique Matches
chr2	9.10
chr4	8.22
chr1	7.90
chr3	7.38
chr5	7.01
chr6	6.47
chr7	5.51
chr8	5.34
chr12	4.84
chr11	4.36
chr10	4.24
chr13	4.02
chr9	3.89
chr14	3.28
chrX	3.18
chr18	2.94
chr15	2.62
chr16	1.95
chr17	1.93
chr20	1.33
chr21	1.28
chr19	1.11
chr22	0.71
chrY	0.31
chrM	0.04
chrUn_gl000220	0.04
chr7_gl000195_random	0.02
chrUn_gl000219	0.01
chr17_gl000205_random	0.01
chrUn_gl000214	0.01
chrUn_gl000224	0.01
chrUn_gl000218	0.01
chrUn_gl000212	0.01
chr9_gl000198_random	0.01
chr4_gl000194_random	0.01
chrUn_gl000241	0.00
chrUn_gl000230	0.00
chr6_qbl_hap6	0.00
chrUn_gl000223	0.00
chrUn_gl000234	0.00
chrUn_gl000233	0.00
chr6_cox_hap2	0.00
chr6_dbb_hap3	0.00
chr6_mcf_hap5	0.00
chrUn_gl000211	0.00
chr19_gl000208_random	0.00
chr1_gl000192_random	0.00
chr6_mann_hap4	0.00
chrUn_gl000216	0.00
chr6_apd_hap1	0.00
chrUn_gl000232	0.00
chr6_ssto_hap7	0.00
chr4_gl000193_random	0.00
chr17_ctg5_hap1	0.00

たところ、圧負荷により RNA の転写量は急増し、72 時間で約 3 倍程度に上昇することが判明した。チャンバー内に設置された細胞は、5% CO_2, 37℃、細胞培養用インキュベーターで培養され圧力モニター下に外力が負荷された。得られた RNA について cDNA を合成して配列をヒト染色体とのマッピングを行った。コンティグ配列とアノテーションを得て、代表とする非加圧群 22655 本、加圧群 54611 本について解析した。この中でユニークマッチを呈したコンティグ配列の染色体分布を図に示す（左：非加圧、右：加圧群）。リード数で多かったものには成長因子受容体やタンパク輸送関連の遺伝子、転写因子や転写因子制御因子、リン酸化関連遺伝子などが含まれていた。

D:考察

CCR5 の発現を低下させるため、siRNA を細胞に導入して遺伝子の変調を行う方法について当初検討をしたが、脳組織マクロファージではマーカーの siRNA の導入効率が著しく低かったため解析に CCR5 ノックアウトマウスを用いることとした。今回の結果では相同性の高い検索でかかった cDNA のみを表示しており、またマイクロＲＮＡ等については検索の対象に含めていない。刺激されていない状態で転写されていた遺伝子は転写因子やリボゾームＲＮＡ、チトクロームなど代謝に影響する遺伝子など基本的にはミトコンドリアの呼吸等に関与する遺伝子、タンパクや核酸合成の遺伝子、細胞の維持・代謝に関与する遺伝子、中枢神経系機能に関与する遺伝子などが多かった。このようにミクログリアは比較的特徴のな

い細胞で、活性化されていない状態では、あまり遺伝子を発現していないことが判った。この細胞ではまだ機能が不明な遺伝子もいくつか発現していることもわかり、脳内での免疫反応との関係に興味が持たれた。上記リストには載せられていないが配列の中にはミエリンなど希突起膠細胞のみで発現されていると思われるものも含まれていた。これは均一だと思われた細胞集団にわずかに混在していた希突起膠細胞由来のものと考えられる。このポピュレーションの細胞の混入はフローサイトメトリーによる結果から僅かなので、得られた配列は広い範囲の発現遺伝子を網羅していることが期待された。また結核菌の感染では Heat Shock Protein などのストレス関連の遺伝子や caspase などのタンパク分解因子などの発現が上昇した。CCR5 ノックアウトマウスからの細胞でも同様な遺伝子が発現していた。ノックアウトマウスでは正常マウスに比べてリボゾームタンパク関連の転写が多い印象があったが特徴のあるパターンは示していなかった。一方、両者とも各種ケモカインや受容体の転写の亢進は認められず、この結果は半定量 PCR でも支持された。

次に、軟骨にとって圧力の存在の重要性は以前から指摘されており、単純に圧力を負荷するだけでも collagen type-2, keratan sulfate, や integrin 抗体に反応する軟骨基質が増加したり基質の位相が変化したりする。今回の結果からも６時間の生理的範囲内での圧力負荷で転写される RNA の量が上昇することが示された。今回行った RNA-seq 法では定量性に欠けるため、実際に上昇した遺伝子量は非負荷時に転写されている遺伝子のリードなのか新規に転写された遺伝子の数なのかを厳密に区別することはできない。しかしマッピングしたコンティグの数自体が増えていたので新たに転写される遺伝子が多く存在することが窺えた。一般に圧力などの物理的ストレスを細胞に負荷すると多くの細胞で刺激直後からストレス関連の急性相反応タンパクの発現が上昇する。骨代謝に関してこれらの急性相の反応の影響を除くため 72 時間後の時点で転写量が変化している遺伝子に的を絞って解析を行ったが得られた塩基配列についてはリン酸化タンパクや脱リン酸化タンパク、転写因子などが含まれていた。この点について破骨細胞の組織マクロファージとしての役割を含めた時間経過や細胞間刺激を考慮した解析が必要になろう。またリード数が多かった遺伝子の染色体座は非加圧群、加圧群で全体として大きな差が認められなかったが、負荷により第 4 染色体のものが減少するなど若干の変動が認められた。変動するもののなかに Y 染色体のものが少なかったことは圧変動が男女であまり反応に差が無いことを示していると思われる。またミトコンドリアの遺伝子関与が少なかったが影響を及ぼさないようなタイミングを図って実験が計画されて行われたからである。骨芽細胞や破骨細胞への活性化のシグナルについては十分に知ることができなかった点もあるが今回の研究から少なくとも破骨細胞の活性化については軟骨に加わる圧力が影響を及ぼしている可能性が示唆された。関節軟骨が転写する遺伝子が関節の直下にある骨吸収に及ぼす影響について破骨細胞を始めとするケモカインやケモカイン受容体への刺激と共にさらに調べていく必要があろう。

E:結論

進行性下顎頭吸収の病態を解明するにあたり、骨吸収を促進する骨組織マクロファージの活性化のメカニズムや、まず最初にどのような刺激が入って骨吸収に至っているのかという原因を明らかにすることは重要である。CCR5の働きについて影響が知られている脳組織マクロファージと骨組織マクロファージでは同じ炎症でも異なったメカニズムで機能が制御されている可能性があり、一方、顎関節の機能を考慮すると関節軟骨への咀嚼等による日常的な外力刺激が関節軟骨での遺伝子転写を亢進させ、軟骨細胞が骨組織マクロファージの活動に影響を与えている可能性が示唆された。

F:健康危機情報

なし

G:研究発表

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３．　その他の業績

書籍等　なし

H:知的所有権の出願・取得状況（予定を含む）

１．特許取得

なし

２．実用新案登録

なし

３．その他

特記事項なし

平成 22・23 年度厚生労働科学研究費補助金（難治性疾患克服研究事業）
総合分担研究報告書
進行性下顎頭吸収の診断基準策定とその治療に関する研究
（H22-難治-一般-157）

生物統計・臨床データ管理班：進行性下顎頭吸収の診断基準策定を目的とした国際共同研究協力体制基盤整備

Clinical Data Management Group Report: Building a Research Consortium for International Diagnostic Guidelines of Progressive Condylar Resorption

Fumihide Kanaya[1), 2)], Kenji Yamamoto[2)] and Yutaka Maruoka[2), 3), 4)]

Abstract

This group coordinated and facilitated the second-year outcomes of the nation's first Progressive Condylar Resorption research network for clinical guidelines to international dental and oral maxillofacial community. The novel approach investigation both in conventional bone markers and CCR5 related markers communicated well and drew interests from agencies in Europe, North and South America this year. This project summarizes lessons learned and facilitation methods developed in its informatics process.

A: Purpose

In the first year of this project, the Progressive Condylar Resorption (PCR) investigation project obtained new knowledge mainly from a nationwide survey and also from the patients' blood sample analysis in a clinical study, both done for the first time in Japan. For the second year of the project, a main objective was how to translate these study outcomes with each other in order to further compare, interpret, and analyze the data.

This translational communication between clinical information and basic laboratory results for the future

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application in diagnostic and treatment procedures is an integral process for understanding rare disorders with low incidents. In investigating PCR, this project evaluated feasibility for a Japanese clinical facility to become an effective main site of site-participatory global consortium of PCR translational research network to solve the limitation of patient volunteer numbers and research resource.

One key translational item from this project's model mice experiments to the interest for human application was a consideration for genetic variance: Among general Caucasian population, a CCR5 allele, CCR5Δ32 with 32-aminoacid

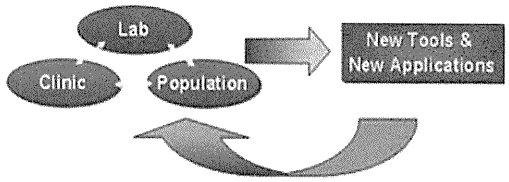


Fig 1. Translational Research Design

deletion, is distributed in a sizable proportion and considered as a non-threat in normal growth and development of the individuals. With results from mice and human cell *in vitro* system and humanized mice *in vivo* system, we investigated whether CCR5 could be a potential candidate for PCR diagnostic biomarkers, which also would open up a possibility for tailor-made treatment for each patients, or not. For that we were interested in a comparison in Japanese population, Caucasian population, and other Asian and Pacific Islander population.

B: Methods

1. Dissemination of NCGM's latest various basic and clinical outcomes. Coordinating basic and clinical researchers' data into internationally communicable format.
2. Taking our approaches to international forums, engaging in proposal facilitation for feasibility investigation to integrate our novel methods into different networks. Communicating our protocols for international regulatory format.
3. Feeding back international input from 1 and 2, bringing the new network into a effectives consortium.

For Step 1, this data management group requested to each investigator to summarize outcomes, disseminated and transformed cumbersome data into analyzable format. With these outcomes the data management group approached to each research population of interest and international agencies to determine the match by a) having PCR case, b) having biomarker testing capacity and c) can participate, and implement the clinical research

protocol, regulated by international agencies?

For Step 2, we proposed a vision for a consortium model to outside agencies, and when an agreement is obtained, we requested the participation in the consortium, facilitate the regulatory process to start the research in respective agencies and coordinated the clinical information and testing procedures for bone metabolism evaluations.

Step 3 entailed active support for Institutional Review Board (IRB), in which each country had different regulation and procedure culture; we gathered help from local embassy, its ministry of foreign affairs and other outside consultant for fine tuning and customizing protocols for each IRB. By allocating our MHLW special research grant for international collaborative works such as inviting top investigators to be a research partner and testing and transporting the study samples, NCGM played a leadership in this consortium and continues to offer strategic support.

<Testing and Evaluation>

1. Basic patient information
   - Age and Sex
   - Main complaint (pain in jaws, discomfort in occlusion, etc.)
   - Intake diagnosis (TMD temporomandibular joint disorder, prognathism and etc.)
   - Medical history (history of autoimmune disorders)
   - Medication (antibiotic, anti-inflammatory, NSAID, anticoagulant, antiplatelet, corticosteroid drugs)
   - Infectious diseases (HIV, HBV, HCV infections)
   - Treatment markers
2. Special values
   - Osteoporosis testing
   - Blood and urine chemokine markers

<Ethics Consideration>

Because of the human subject study phase of the clinical trial, the protocol is regulated by NCGM IRB for human genetics ethics committee. We initiated our involvement in other county's regulatory procedures and international protocol registry process. We continued to stay alert and mindful on the universal ethical features of the study procedures.

C: Results

1. Y. Maruoka, A. Hoshino and F. Kanaya disseminated the outcomes of PCR studies from our group. It consisted of the nationwide clinical survey, CCR5KO model mice experiment, their images, *in vitro* investigation of human macrophages, clinical data of osteoporosis blood markers from 22 NCGM patient volunteers. Clinical

data had some outliners of elevated risks of bone fracture that requires continuous monitoring and following up, and their statistical analysis. We combined these data in a presentable format

2. F. Kanaya registered the clinical study protocol for standardized international registry such as NIH/FDA clinical protocol registry. Fine tuned the disseminated outcomes and tweaked out effective discussion points that should endure international discussion. This group reached out to different networks of key personnel of the field and brought its presentation of these outcomes to those who would be interested in the potential collaboration development in various international regions in
   a) basic research and human genetics
   b) dentistry and oral surgery
   c) foreign diplomacy.
3. As result, the NCGM group developed collaboration with outside agencies, received integral feedbacks for the next phase of both *in vitro* and *in vivo* studies and was invited this group back to the respective agencies. It was essential to secure Czech PCR patient population participation where CCR5Δ32 allele is distributed in 10% ratio and where their CCL5, mutual ligand for CCR5 and CCR1, can newly be added for this project with their participation by our facilitation.
   F. Kanaya continued to work United States Department of Health and Human Services (DHHS) Office of Human Research Protections (OHRP), updated NCGM's regulatory registration for the United States National Institute of Health (NIH) and Food Drug Administration (FDA)'s federalwide assurance (FWA), registered NCGM IRB and its human genetics ethics committee to NIH, obtained NCGM's clinical trial protocol registry network ID on behalf of Dr. Takaaki Kirino, President of NCGM. In 2011, this PCR group's protocol was registered to OHRP.

With the outcome of the two-year research, the study group submitted to Ministry of Health, Labor and Welfare an international proposal for standardized diagnosis and treatment:

[English proposal]
Progressive / Idiopathic Condilar Resorption (diagnostic name of the disease / condition, the number of patients is estimated 1000 patients.)
Definition: Diminishing condylar head volume with changes in condylar shape,

often associated with decreased mandibular ramus height, mandibular retrusion and counter clockwise rotation resulting in progressive Class II basal bone in relation with anterior open bite. Having relatively small and retruded mandible, thus patients often undergo inappropriate treatment or unnecessary orthodontic procedures under misdiagnosis with maxillary protrusion and/or mandibular retrusion.

Discussion for the Cause: As post orthognathic surgery complication, following excessive traumatic burden to the temporomandibular joint known as TMJ.

According to our study, the female/male prevalence rate was approximately 10 times higher for female, indicating the similar results as previous reports from Europe/United States and that at least 1000 patients are estimated to exist in Japan. The patients classified in two groups: idiopathic cases without any systemic complications in their teens and twenties in age and cases with autoimmune diseases above age 50. Biomarkers from our patients' blood and urine tests did not show indications related to inflammation but suggested strong indication of osteoporosis.

For clinical diagnosis, many confused concepts have been mixed and used in dealing with those symptoms, thus appropriate diagnostic criteria need to be established.

No mechanism for cause is yet established, associating with aging and underlying ongoing systemic co-morbidity and host adaptive capacity of the temporo-mandibular joint. Can be initiated by traction compression from joint orthognathic surgery with excessive force load on TMJ. Young onset cases had low mandibular growth rate. Our study strongly indicated non-inflammatory feature could be one significant piece in the entire PCR system.

[Symptoms]

Anterior open bite associated with diminishing volume and changing shape of condylar, decreased mandibular ramus height, mandibular retrusion and counter-clockwise rotation. Patients sometimes present with pain associated with opening/closing jaw. Patients cannot only bite properly, but also malocclusion can have occlusal trauma because periodontal tissues in molar region collects excessive mechanical stress instead.

[Complications]

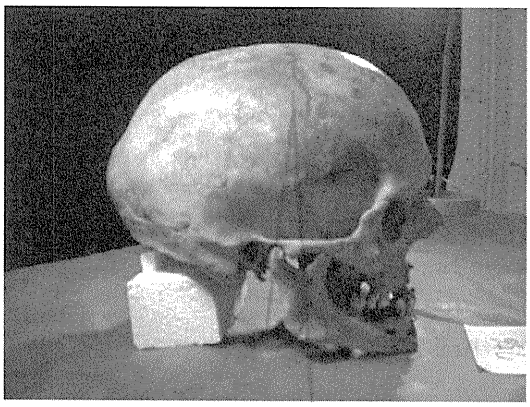
Further severe complications can occur in following order: misdiagnosis as regular maxillary protrusion and/or

mandibular retrusion because patients' mandibular can look smaller and retreated, lead to inappropriate invasive orthodontic procedures and resulting in additional multiple severe complications. Other complication can be progressing malocclusion pain and jaw joint pain because PCR patients have difficulties in biting properly with front teeth, thus their molar region receive excess mechanical stress in periodontal tissues.

[Treatment]

Our surveys found each agency employed in various different ways treating patients presenting these conditions in Japan. There had never been treatment standard guidelines for PCR. There were many reports that supported the effectiveness of stabilizing occlusion. Occlusal splint therapy and orthognathic surgery can be recommended.

International feasibility research:



The study group developed an ongoing

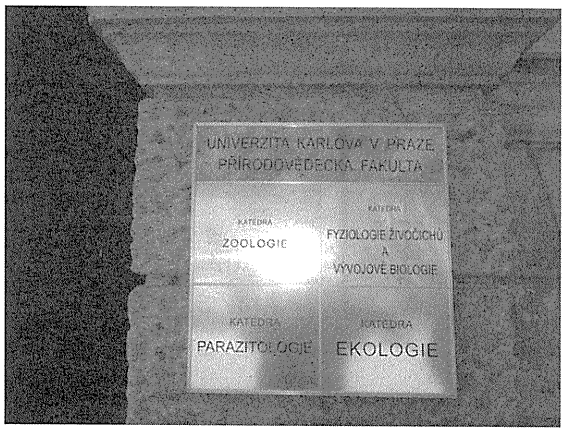


Fig 2. Establishing an International Research Consortium at Institute of Anatomy and Zoology Charles University in Prague

PCR research network with Charles University (Czech), Pascua Community (Chile) and Massachusetts General Hospital Endocrinology Research Unit (USA) by this study. Maruoka contributed to this global facilitation, enabling genetic variant analysis among race subtypes.

One example to cultivate such further collaboration was research facilitation with samples from the counterpart agencies. Maruoka analyzed 64 Czech skull and mandible collections for FMA, Gonial Angle, Condylar Inclination, Skull M-D/A-P, Centric Stop, etc. A few

unpredicted discoveries were that "Alpine" type skull was most prevalent and long midface skulls were rare. Also only one Class III case was observed and FWA was generally small in these samples.

D: Discussion

Through the active facilitation in international community of basic, clinical and translational research and their regulatory process, this group learned valuable lessons:

1. Universal standardized guidelines for evaluation and assessment of PCR diagnosis and treatment are in the starting phase in other countries as well and there has not been much effective networking effort out of Japan other than independent clinical and endocrinal evidences. Because of this study and participating agencies, we captured the global needs for PCR studies for the first time within the international community of clinician and researcher.
2. One very effective way to communicate data for international discussion was to fine-tune our results to make a case and have our effort recognized. As result in this process, we learned our CCR5 related ligands collecting and detecting trials and results were original and unique. Through the new colleagues from our international counterparts, Harvard Medical School AIDS Center proposed to integrate our protocol into their Phase-I clinical trials.
3. It is integral to have *in vitro* data accompanied by *in vivo* validation in order to communicate effectively in international community; an internationally coordinated informatics system would enable realistic analysis of dose-response data for the translation, clinical application and tailor-made treatment for PCR.

E: Conclusion

The current international tendency n clinical research is new, realistic non-invasive testing methods, for mineral metabolism and comparison with not only Caucasian, but also other Asian and Pasific Islander population as control. New informatics on PCR related bone marker candidates would be the next phase of this development and this group should publish these outcomes for international review.

F: Heath Safety Information

Not applicable this year.

G: Publications and presentations

1. Publication

None

2. Conference Presentation

1 Maruoka Y, Kanaya F, *et al.* "Study of Relations between Progressive / Idiopathic Condylar Resorption and Impaired Bone / Cartilage Metabolism Associated with Chemokine Receptor Disorder." *International Convention on Oran and Maxillofacial Surgery 2011,* November 4, 2011. Santiago, Chile.

3. Others

Not applicable

H: 知的所有権の出願・取得状況（予定を含む）

1．特許取得

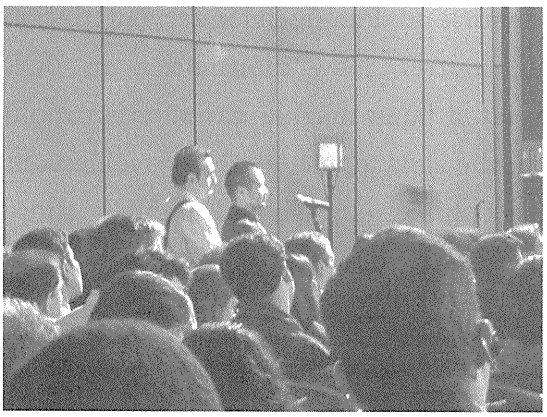
なし

2．実用新案登録

なし

3．その他

なし



Ⅲ. 研究成果の刊行に関する業績一覧

研究成果の刊行に関する一覧表

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