ENTREZ PUBMED LITERATURE REVIEW (24 NEW ARTICLE(S))


**Competitive binding of Fe(3+), Cr (3+), and Ni (2+) to transferrin.**

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Competitive binding of Fe(3+), Cr(3+), and Ni(2+) to transferrin (Tf) was investigated at various physiological iron to Tf concentration ratios. Loading percentages for these metal ions are based on a two M( n+) to one Tf (i.e., 100% loading) stoichiometry and were determined using a particle beam/hollow cathode-optical emission spectroscopy (PB/HC-OES) method. Serum iron concentrations typically found in normal, iron-deficient, iron-deficient from chronic disease, iron-deficient from inflammation, and iron-overload conditions were used to determine the effects of iron concentration on iron loading into Tf. The PB/HC-OES method allows the monitoring of metal ions in competition with Fe(3+) for Tf binding. Iron-overload concentrations impeded the ability of chromium (15.0 μM) or nickel (10.3 μM) to load completely into Tf. Low Fe(3+) uptake by Tf under iron-deficient or chronic disease iron concentrations limited Ni(2+) loading into Tf. Competitive binding kinetic studies were performed with Fe(3+), Cr(3+), and Ni(2+) to determine percentages of metal ion uptake into Tf as a function of time. The initial rates of Fe(3+) loading increased in the presence of nickel or chromium, with maximal Fe(3+) loading into Tf in all cases reaching approximately 24%. Addition of Cr(3+) to 50% preloaded Fe(3+)-Tf showed that excess chromium (15.0 μM) displaced roughly 13% of Fe(3+) from Tf, resulting in 7.6 ± 1.3% Cr(3+) loading of Tf. The PB/HC-OES method provides the ability to monitor multiple metal ions competing for Tf binding and will help to understand metal competition for Tf binding.

PMID: 21678080 [PubMed - as supplied by publisher]


**Comparative analysis of the ATRX promoter and 5' regulatory region reveals conserved regulatory elements which are linked to roles in neurodevelopment, alpha-globin regulation and testicular function.**

Tang P, Frankenberg S, Graves JM, Familari M.

Database: PubMed, Embase
Keywords: deferiprone, 30652-11-0, desferrioxamine, deferoxamine, desferal, deferasirox, iron + sickle, iron chelation, iron chelators, iron overload, thalassיה, 1,2 dimethyl-3-hydroxypyridin-4-one, ICL670®, Exjade
ABSTRACT: BACKGROUND: ATRX is a tightly-regulated multifunctional protein with crucial roles in mammalian development. Mutations in the ATRX gene cause ATR-X syndrome, an X-linked recessive developmental disorder resulting in severe mental retardation and mild alpha-thalassemia with facial, skeletal and genital abnormalities. Although ubiquitously expressed the clinical features of the syndrome indicate that ATRX is not likely to be a global regulator of gene expression but involved in regulating specific target genes. The regulation of ATRX expression is not well understood and this is reflected by the current lack of identified upstream regulators. The availability of genomic data from a range of species and the very highly conserved 5' regulatory regions of the ATRX gene has allowed us to investigate putative transcription factor binding sites (TFBSs) in evolutionarily conserved regions of the mammalian ATRX promoter. RESULTS: We identified 12 highly conserved TFBSs of key gene regulators involved in biologically relevant processes such as neural and testis development and alpha-globin regulation. CONCLUSIONS: Our results reveal potentially important regulatory elements in the ATRX gene which may lead to the identification of upstream regulators of ATRX and aid in the understanding of the molecular mechanisms that underlie ATR-X syndrome.

PMID: 21676266 [PubMed - as supplied by publisher]


**Evaluation of ischemia-reperfusion liver injury by near-infrared spectroscopy in an experimental Swine model: the effect of desferoxamine.**


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ABSTRACT Introduction: Ischemia-reperfusion (I-R) injury has long been regarded a primary factor for the physiological dysfunction that can occur following major liver resection performed under vascular control. The aim of our study was to assess the effect of treatment with desferoxamine (DFO), a potent antioxidative agent, monitoring the I-R injury on a porcine model of major hepatectomy. Materials and Methods: Twelve female pigs were allocated to control (n = 6) and DFO groups (n = 6) and underwent 30 min of liver ischemia, during which a ≥30% hepatectomy was performed, followed by six hours of postoperative monitoring. The DFO group animals were preconditioned with a continuous iv solution of DFO to a total dose of 100 mg/kg during their postoperative period. Liver remnants (≈70%
of initial liver volume) were evaluated by means of infrared spectroscopy, serum lactate measurement of the systemic, portal and hepatic vein blood, and by immunohistochemical assessment of apoptosis in consecutive liver biopsies. Results: DFO group demonstrated considerably faster restoration of tissue oxygenation (92.33% vs. 80%, p < .05) and serum lactate values (1.23 mmol/l vs. 2.27 mmol/l, p < .05). Moreover, apoptosis as estimated by TUNEL and caspase-3 staining was significantly lower in the DFO group (0.06% vs. 1.17% and 1.17% vs. 2%, respectively, p < .05). The severity of the I-R injury showed a linear correlation to the restoration of tissue oxygenation, as estimated by infrared-spectroscopy (r(2) = 0.81, p < .01). Conclusion: Iron chelation with DFO appears to attenuate I-R injury of the liver remnant following hepatectomy, as reflected by faster restoration of tissue oxygenation and lower apoptotic activity.

PMID: 21675852 [PubMed - in process]


Noninvasive measurement of liver iron concentration at MRI in children with acute leukemia: initial results.


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BACKGROUND: Routine assessment of body iron load in patients with acute leukemia is usually done by serum ferritin (SF) assay; however, its sensitivity is impaired by different conditions including inflammation and malignancy. OBJECTIVE: To estimate, using MRI, the extent of liver iron overload in children with acute leukemia and receiving blood transfusions, and to examine the association between the degree of hepatic iron overload and clinical parameters including SF and the transfusion iron load (TIL). MATERIAL AND METHODS: A total of 25 MRI measurements of the liver were performed in 15 children with acute leukemia (mean age 9.75 years) using gradient-echo sequences. Signal intensity ratios between the liver and the vertebral muscle (L/M ratio) were calculated and compared with SF-levels. TIL was estimated from the cumulative blood volume received, assuming an amount of 200 mg iron per transfused red blood cell unit. RESULTS: Statistical analysis revealed good correlation between the L/M SI ratio and TIL (r = -0.67, P = 0.002, 95% confidence interval CI = -0.83 to -0.34) in patients with acute leukemia as well as between L/M SI ratio and SF (r = -0.76, P = 0.0003, 95% CI = -0.89 to -0.52). CONCLUSION: SF may reliably reflect liver
iron stores as a routine marker in patients suffering from acute leukemia.

PMID: 21674286  [PubMed - as supplied by publisher]


**ATRX has a critical and conserved role in mammalian sexual differentiation.**

Huyhn K, Renfree MB, Marshall-Graves JA, Pask AJ.

**ABSTRACT:** BACKGROUND: X-linked alpha thalassemia, mental retardation syndrome in humans is a rare recessive disorder caused by mutations in the ATRX gene. The disease is characterised by severe mental retardation, mild alpha-thalassemia, microcephaly, short stature, facial, skeletal, genital and gonadal abnormalities.

RESULTS: We examined the expression of ATRX and ATRY during early development and gonadogenesis in two distantly related mammals: the tammar wallaby (a marsupial) and the mouse (a eutherian). This is the first examination of ATRX and ATRY in the developing mammalian gonad and fetus. ATRX and ATRY were strongly expressed in the developing male and female gonad respectively, of both species. In testes, ATRY expression was detected in the Sertoli cells, germ cells and some interstitial cells. In the developing ovaries, ATRX was initially restricted to the germ cells, but was present in the granulosa cells of mature ovaries from the primary follicle stage onwards and in the corpus luteum. ATRX mRNA expression was also examined outside the gonad in both mouse and tammar wallaby whole embryos. ATRX was detected in the developing limbs, craniofacial elements, neural tissues, tail and phallus. These sites correspond with developmental deficiencies displayed by ATR-X patients

CONCLUSIONS: There is a complex expression pattern throughout development in both mammals, consistent with many of the observed ATR-X syndrome phenotypes in humans. The distribution of ATRX mRNA and protein in the gonads was highly conserved between the tammar and the mouse. The expression profile within the germ cells and somatic cells strikingly overlaps with that of DMRT1, suggesting a possible link between these two genes in gonadal development. Taken together, these data suggest that ATRX has a critical and conserved role in normal development of the testis and ovary in both the somatic and germ cells, and that its broad roles in early mammalian development and gonadal function have remained unchanged for over 148 million years of mammalian evolution.

PMID: 21672208  [PubMed - as supplied by publisher]

**Pancreatic exocrine function and cardiac iron in patients with iron overload and with thalassemia.**


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Patients with β-thalassemia major at risk of cardiac iron overload have to be identified to undergo myocardial iron measurements by magnetic resonance imaging (MRI), especially, in areas and centers with restricted access to MRI. Measurements of heart iron, liver iron, and pancreatic exocrine function were performed in 44 patients by MRI-R2* (the transverse relaxation rate R2* (= 1/T2*) characterizes the magnetic resonance decay from protons not being in phase with each other in contrast to R2 (= 1/T2)), biomagnetic liver susceptometry (LIC), and pancreatic serum amylase (PAM) and lipase (LIP), respectively. ROC analysis (area: 0.88) for detecting patients with cardiac R2* > 50 sec(-1) (T2* < 20 msec) by LIP revealed a cut-off level of 19 U/L. In conclusion, patients at risk of elevated cardiac iron levels could be identified by the exocrine pancreatic lipase and amylase function parameters. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

PMID: 21671371  [PubMed - as supplied by publisher]


**Neurocognitive deficits in children with sickle cell disease are associated with the severity of anemia.**

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**BACKGROUND:** Although neurocognitive deficits in children with sickle cell disease (SCD) have been well documented, the etiology of these deficits has not been completely clarified. The aim of this study was to investigate the association of laboratory markers of disease severity and radiological parameters with
neurocognitive functioning in children with SCD.

**DESIGN AND METHODS:** Participants were 37 children with SCD ((HbSS or HbS-β(0)-thalassemia) aged 6-18 years. All participants underwent extensive neurocognitive assessment. Further data (TCD values, laboratory test results, and MRI data) were obtained from medical charts. Associations were analyzed by hierarchical regression analysis.

**RESULTS:** Hemoglobin was associated with a decrease in verbal short-term memory. There was no association between TCD velocities and neurocognitive functioning, when controlled for age. Children with silent infarcts did not differ from children with normal MRI in neurocognitive functioning. Children with right-left asymmetries in cerebral blood flow as measured by continuous arterial spin labelling (CASL) MRI had better sustained attention than children without asymmetries.

**CONCLUSIONS:** Neurocognitive deficits are associated with the severity of anemia, indicating reduced oxygen delivery to the brain as an etiological mechanism. This implies that children with SCD and normal MRIs may still suffer from neurocognitive impairments, possibly affecting their academic development and full participation in society. Pediatr Blood Cancer 2011; 57: 297-302. © 2010 Wiley-Liss, Inc.

PMID: 21671366 [PubMed - in process]


**Four amino acids guide the assembly or disassembly of Arabidopsis histone H3.3-containing nucleosomes.**

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The histone variant H3.3 and the canonical histone H3.1, which differ in only 4- to 5-aa positions, are coexpressed in complex multicellular eukaryotes from fly to human and plant. H3.3 is mainly associated with active chromatin by replacing H3.1 through chaperones such as histone regulator A, death domain associated protein DAXX, thalassemia/mental retardation syndrome X-linked homolog ATRX, or proto-oncogene protein DEK and plays important roles in the germ line, epigenetic memory, and reprogramming. However, the signals within H3.3 that serve as a guide for its dynamic deposition or depletion in plant chromatin are not clear. Here, we show that Arabidopsis histone H3.3 differs from H3.1 by 4-aa sites: amino acids 31, 41, 87, and 90. Although histone H3.1 is highly enriched in
chromocenters, H3.3 is present in nucleolar foci in addition to being diffusely distributed in the nucleoplasm. We have evaluated the function of the 4 aa that differ between H3.1 and H3.3. We show that amino acid residue 87, and to some extent residue 90, of Arabidopsis histone H3.3 are critical for its deposition into rDNA arrays. When RNA polymerase I-directed nucleolar transcription is inhibited, wild type H3.3, but not H3.3 containing mutations at residues 31 and 41, is depleted from the rDNA arrays. Together, our results are consistent with a model in which amino acids 87 and 90 in the core domain of H3.3 guide nucleosome assembly, whereas amino acids 31 and 41 in the N-terminal tail of Arabidopsis H3.3 guide nucleosome disassembly in nucleolar rDNA.

PMID: 21670303  [PubMed - as supplied by publisher]


Iron overload and HFE gene mutations in Polish patients with liver cirrhosis.

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BACKGROUND: Increased liver iron stores may contribute to the progression of liver injury and fibrosis, and are associated with a higher risk of hepatocellular carcinoma development. Pre-transplant symptoms of iron overload in patients with liver cirrhosis are associated with higher risk of infectious and malignant complications in liver transplant recipients. HFE gene mutations may be involved in the pathogenesis of liver iron overload and influence the progression of chronic liver diseases of different origins. This study was designed to determine the prevalence of iron overload in relation to HFE gene mutations among Polish patients with liver cirrhosis.

METHODS: Sixty-one patients with liver cirrhosis included in the study were compared with a control group of 42 consecutive patients subjected to liver biopsy because of chronic liver diseases. Liver function tests and serum iron markers were assessed in both groups. All patients were screened for HFE mutations (C282Y, H63D, S65C). Thirty-six of 61 patients from the study group and all controls had liver biopsy performed with semiquantitative assessment of iron deposits in hepatocytes.

RESULTS: The biochemical markers of iron overload and iron deposits in the liver were detected with a higher frequency (70% and 47% respectively) in patients with liver cirrhosis. There were no differences in the prevalence of all HFE mutations in both groups. In patients with a diagnosis of hepatocellular carcinoma, no significant associations with iron disorders and HFE gene mutations were found.
CONCLUSIONS: Iron disorders were detected in patients with liver cirrhosis frequently but without significant association with HFE gene mutations. Only the homozygous C282Y mutation seems to occur more frequently in the selected population of patients with liver cirrhosis. As elevated biochemical iron indices accompanied liver iron deposits more frequently in liver cirrhosis compared to controls with chronic liver disease, there is a need for more extensive studies searching for the possible influence of non-HFE iron homeostasis regulators and their modulation on the course of chronic liver disease and liver cirrhosis.

PMID: 21669570 [PubMed - in process]


**Improvement of the cold storage of isolated human hepatocytes.**

Pless G, Sauer IM, Rauen U.

Increasing amounts of human hepatocytes are needed for clinical applications and different fields of research, such as cell transplantation, bioartificial liver support and pharmacological testing. This demand calls for adequate storage options for isolated human liver cells. As cryopreservation results in severe cryoinjury, short term storage is currently performed at 2–8°C in preservation solutions developed for the storage of solid organs. However, besides slowing down cell metabolism, cold also induces cell injury, which is, in many cell types, iron-dependent and not counteracted by current storage solutions. In this study, we aimed to characterize storage injury to human hepatocytes and develop a customized solution for cold storage of these cells. Human hepatocytes were isolated from material obtained from partial liver resections, seeded in monolayer cultures and, after a pre-culture period, stored in the cold in classical and new solutions followed by rewarming in cell culture medium. Human hepatocytes displayed cold-induced injury, resulting in > 80% cell death (LDH release) after one week of cold storage in University of Wisconsin solution or cell culture medium and 3 h of rewarming. Cold-induced injury could be significantly reduced by the addition of the iron chelators deferoxamine and LK 614. Experiments with modified solutions based on the new organ preservation solution Custodiol-N showed that ion-rich variants were better than ion-poor variants, chloride-rich solutions better than chloride-poor solutions, potassium as main cation superior to sodium and pH 7.0 superior to pH 7.4. LDH release after two weeks of cold storage in the thus optimized solution was below 20%, greatly improving cold storage of human hepatocytes. The results were confirmed by the assessment of hepatocellular mitochondrial membrane potential and functional parameters (resazurin reduction, glucacon-stimulated glucose liberation) and thus suggest the use of a customized hepatocyte storage solution.
for the cold storage of these cells.

PMID: 21669032  [PubMed - as supplied by publisher]


**Importance of optimal dosing ≥30 mg/kg/d during deferasirox treatment: 2.7-year follow-up from the ESCALATOR study in patients with β-thalassaemia.**


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Following 1 year’s deferasirox therapy in the ESCALATOR study, 57% of previously chelated patients with β-thalassaemia achieved treatment success (maintenance/reduction of liver iron concentration [LIC] versus baseline LIC). 78% had dose increases at median of 26 wk, suggesting that 1-year results may not have reflected full deferasirox efficacy. Extension data are presented here. Deferasirox starting dose was 20 mg/kg/d (increases to 30/40 mg/kg/d permitted in the core/extension, respectively). Efficacy was primarily assessed by absolute change in LIC and serum ferritin. Overall, 231 patients received deferasirox in the extension; 67.4% (P < 0.0001) achieved treatment success. 66.2% of patients were receiving doses ≥30 mg/kg/d by the end of the extension. By the end of the 1-year extension, mean LIC had decreased by 6.6 ± 9.4 mg Fe/g dw (baseline 19.6 ± 9.2; P < 0.001) and median serum ferritin by 929 ng/mL (baseline 3356; P < 0.0001). There was a concomitant improvement in liver function markers (P < 0.0001). Fewer drug-related adverse events were reported in extension than core study (23.8% vs 44.3%). Doses ≥30 mg/kg/d were generally required because of high transfusional iron intake and high baseline serum ferritin levels, highlighting the importance of administering an adequate dose to achieve net negative iron balance.

PMID: 21668502  [PubMed - as supplied by publisher]

**Achieving treatment goals of reducing or maintaining body iron burden with deferasirox in patients with β-thalassaemia: Results from the ESCALATOR study.**


American University of Beirut Medical Center, Beirut, Lebanon Ain Shams University, Cairo, Egypt National Thalassemia Center, Damascus, Syrian Arab Republic Sultan Qaboos University, Muscat, Oman King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia Novartis Pharmaceuticals, East Hanover, NJ, USA Novartis Pharma AG, Basel, Switzerland Cairo University, Cairo, Egypt.

This analysis evaluated the effects of deferasirox on liver iron concentration in moderate and heavily iron-overloaded patients with β-thalassaemia from the ESCALATOR trial (n = 231). Mean liver iron concentrations (LIC) decreased significantly from $21.1 \pm 8.2$ to $14.2 \pm 12.1$ mg Fe/g dry weight (dw) at 2 yr ($P < 0.001$) in patients with LIC ≥7 mg Fe/g dw at baseline; patients with LIC <7 mg Fe/g dw maintained these levels over the treatment period. The proportion of patients with LIC <7 mg Fe/g dw increased from 9.4% at core baseline to 39.3% by the end of year 2. The results showed that deferasirox enabled therapeutic goals to be achieved, by maintaining LIC in patients with LIC <7 mg Fe/g dw at a mean dose of $22.4 \pm 5.2$ mg/kg/d and significantly reducing LIC in patients with LIC ≥7 mg Fe/g dw at a mean dose of $25.7 \pm 4.2$ mg/kg/d, along with a manageable safety profile.

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**Complications of thalassemia major and their treatment.**

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The life of patients with thalassemia has improved both in duration and in quality in industrialized countries. Complications are still common and include
Heart disease (heart failure and arrhythmias), chronic liver hepatitis, which can evolve in cirrhosis and, rarely, in hepatocellular carcinoma, endocrine problems (hypogonadism, hypothyroidism, diabetes, hypoparathyroidism), stunted growth, osteoporosis, thrombophilia and pseudoxanthoma elasticum. The incidence of complications is decreasing in younger cohorts of patients who have been transfused with blood that has been screened for viruses and thanks to the introduction of new oral iron chelators and imaging methods. The accurate measurement of iron deposits allows better management of iron overload. In addition, therapy for several complications is available. Specialized competence in treating patients with thalassemia is of great importance.

PMID: 21668399  [PubMed - in process]


**Propects for a hepcidin mimic to treat β-thalassemia and hemochromatosis.**

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PMID: 21668388  [PubMed - in process]


**The etiological relation between serum iron level and infection incidence in hemodialysis uremic patients.**


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Through the treatment of anaemia in dialysis patients part of the iron ions remain free in the serum which is at the bacterias disposal for growth and the strengthening of their virulence. The linear relation of the increased serum iron level and tissue iron stores in the body and the infection incidence in dialysed patients has become more emphasised. The need of a clearly defined upper threshold of the serum iron concentration limit has been mentioned in scientific journals intensely, and consequently the demand for more precise professional
instructions for anaemia treatment. For the purpose of participating in these professional and scientific discussions, we have observed the relation between the iron overload of the organism and complication incidence in 120 of our haemodialysis uremic patients, with special emphasis on infections. It has been established that the sepsis incidence is much higher in patients with a serum ferritin concentration above 500 microg/L, than in those patients with a ferritin level lower than the mentioned value (χ² = 7.857, p = 0.005). The incidence of vascular access infection is significantly higher in those patients with a serum ferritin level above 500 microg/L than in those patients with a ferritin level lower than the mentioned value (χ² = 23.186, p = 0.001). Furthermore, it has been determined that the incidence of total infection in patients is 3.8 episodes per 100 patients months, which is in accordance to the referral values of other authors. CONCLUSION--In the analysis of the achieved results, it has been determined that the infection incidence is significantly higher in dialysed patients with a serum level higher than 500 µg/L, than in those patients with lower values.

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Ascorbic acid increases the activity and synthesis of tyrosinase in B16F10 cells through activation of p38 mitogen-activated protein kinase.

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Ascorbic acid, a potential antioxidant, is known to inhibit melanogenesis. However, there are conflicting findings that ascorbic acid has very low stability and acts as a pro-oxidant, eventually increasing proliferation and melanin content in melanoma cells. In the present study, we explored the effects of ascorbic acid on the activity and expression of tyrosinase and melanin pigmentation in the presence and absence of α-melanocyte-stimulating hormone (α-MSH) using B16F10 melanoma cells. The mechanism by which ascorbic acid stimulated the expression of tyrosinase was also investigated. No inhibitory effect on melanin content was observed in ascorbic acid-treated cells, regardless of the presence of α-MSH. Ascorbic acid stimulated the activity and expression of tyrosinase and increased the expression of melanogenic regulatory factors, such as tyrosinase-related protein-1 (TRP-1), dihydroxyphenylaminechrome tautomerase (TRP-2), and microphthalmia-associated transcription factor (MITF). Ascorbic acid also induced phosphorylation of p38 mitogen-activated protein kinase (MAPK). The
inhibition of p38 MAPK pathway by SB203580 led to the suppression of tyrosinase, TRP-1, and TRP-2 expression in cells treated with ascorbic acid. Combined treatment with N-acetyl-L-cysteine and/or desferrioxamine mesylate attenuated the stimulating effect of ascorbic acid on tyrosinase activation in the cells. Collectively, ascorbic acid stimulates tyrosinase activity and expression in B16F10 cells via activation of p38 MAPK signaling and subsequent up-regulation of MITF, tyrosinase, and TRP expression.

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**J Assist Reprod Genet.** 2011 Jun 11. [Epub ahead of print]

**Preimplantation genetic diagnosis for α-and β-double thalassemia.**


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PURPOSE: To evaluate the use of multiple displacement amplification (MDA) for preimplantation genetic diagnosis (PGD) of α- and β-double thalassemia. METHOD: Whole genome of a single cell was directly amplified using MDA and its products were used as templates in fluorescent gap polymerase chain reaction (PCR) analysis of α-thalassemia and in PCR-reverse dot blot analysis, singleplex fluorescent PCR of β-28 and CD17 mutation and HumTH01 for β-thalassemia. RESULTS: 1) MDA from single cell could produce enough DNA templates for the detection of both α and β-thalassemia; 2) The established MDA-PGD protocol for α- and β-double thalassemia was successfully applied in PGD of six embryos, among which, three were transferred, but no pregnancy ensued. CONCLUSIONS: The use of MDA as a universal step allows for the simultaneous diagnosis of two or more hereditary defects.

PMID: 21667101  [PubMed - as supplied by publisher]

**ATRX ADD domain links an atypical histone methylation recognition mechanism to human mental-retardation syndrome.**


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ATR-X (alpha-thalassemia/mental retardation, X-linked) syndrome is a human congenital disorder that causes severe intellectual disabilities. Mutations in the ATRX gene, which encodes an ATP-dependent chromatin-remodeler, are responsible for the syndrome. Approximately 50% of the missense mutations in affected persons are clustered in a cysteine-rich domain termed ADD (ATRX-DNMT3-DNMT3L, ADD(ATRX)), whose function has remained elusive. Here we identify ADD(ATRX) as a previously unknown histone H3-binding module, whose binding is promoted by lysine 9 trimethylation (H3K9me3) but inhibited by lysine 4 trimethylation (H3K4me3). The cocrystal structure of ADD(ATRX) bound to H3(1-15)K9me3 peptide reveals an atypical composite H3K9me3-binding pocket, which is distinct from the conventional trimethyllysine-binding aromatic cage. Notably, H3K9me3-pocket mutants and ATR-X syndrome mutants are defective in both H3K9me3 binding and localization at pericentromeric heterochromatin; thus, we have discovered a unique histone-recognition mechanism underlying the ATR-X etiology.

PMID: 21666679  [PubMed - as supplied by publisher]


**Genotype and phenotype characterizations in a large cohort of β-thalassemia heterozygote with different forms of α-thalassemia in northeast Thailand.**

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In order to update the molecular basis of β-thalassemia and describe hematological features among different mutations and the concurrent of α- and β-thalassemias, 849 unrelated β-thalassemia heterozygotes recruited in northeast Thailand during a prevention and control program were studied. β- and α-thalassemia mutations were investigated using the polymerase chain reaction (PCR)-based technologies and hematological parameters were recorded using standard methods. Seventeen different mutations including both β(0)- and β(+) -thalassemias were identified. Eight of these 17 β-thalassemia alleles accounted for 97.4%, others were found at lower frequencies (<1.0%). Of the 849 cases, 626 were investigated for common α-thalassemia mutations and 155 (24.8%) were found to be co-inherited with different forms of α-thalassemia. Comparison of the hematological parameters among different β-thalassemia mutations revealed an increasing trend of MCV and MCH in a group of heterozygous states for the 3.4kb deletion and the A-G substitution at nucleotide (NT) -28. Hb A(2) and Hb F levels in individuals with the 3.4kb deletion were significantly higher than those with other mutations. Interaction of each β-thalassemia mutation with α-thalassemia did not affect the diagnostic ranges of Hb A(2) and Hb F, though the significantly increased MCV and MCH was noted. These findings underline the heterogeneity of β-thalassemia and the importance of hematological and molecular analyses of both α-and β-thalassemias in the diagnosis and genetic counseling of the couples at-risk of having babies with severe thalassemia diseases in the region.

PMID: 21664157  [PubMed - as supplied by publisher]


Prevalence of HCV among the high risk groups in Khyber Pakhtunkhwa.


ABSTRACT: Hepatitis C is an infectious disease, caused by blood borne pathogen; the Hepatitis C Virus. In this study we analyzed blood samples collected from various risk groups for the prevalence of anti-HCV and active HCV infection with the help of Immunochromtographic tests and nested PCR. The prevalence of active HCV infection among the high risk groups was 15.57% (26/167). The prevalence of HCV in individual risk groups was 15%, 28%, 8%, 14.28% and 14.28% in the case of thalassemics, dialysis, major surgery group, dental surgery group and injection drug users respectively. Our analysis reveals the fact that health care facilities in the Khyber Pakhtunkhwa province of Pakistan are contributing a great deal towards the spread of HCV infection.

Database: PubMed, Embase
Keywords: deferiprone, 30652-11-0, desferrioxamine, deferoxamine, desferal, deferasirox, (iron + sickle) iron chelation, iron chelators, iron overload, thalass*, 1,2 dimethyl-3-hydroxypyridin-4-one, ICL670*, Exjade

Iron Chelation with Deferasirox in Two Patients with HFE Hemochromatosis and Chronic Anemia.

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We present 2 patients with hyperferritinemia, increased liver iron and hemochromatosis-associated HFE genotypes. At diagnosis, both patients had chronic anemia that prevented initiation of phlebotomy. Iron chelation with deferasirox proved to be a safe and effective means of substantially lowering ferritin levels.

PMID: 21659727 [PubMed - as supplied by publisher]


Molecular characterization of a discrete hemoglobinopathy upon investigation for a lung hydatic cyst in an old Tunisian patient.

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We report the case of an old Tunisian patient hospitalized for a complicated hydatic cyst of the right lung. Primary laboratory investigation showed a microcytic hypochromic anemia with an abnormal hemoglobin pattern. Hemoglobin analysis and DNA sequencing of the β-globin gene revealed a compound heterozygote, HbO-Arab/cd 39 β°-thalassemia. This hemoglobinopathy was never diagnosed earlier. It spent undiagnosed until the patient presented with hydatic cyst. Coexistence of the two pathologies complicated the general state of the patient and led to a severe anemia. The patient has undergone a surgical therapy for the hydatic cyst and was advised to start a follow up for her hemoglobinopathy.

PMID: 21659055 [PubMed - in process]

**Bp44mT: An Orally-Active Iron Chelator of the Thiosemicarbazone Class with Potent Anti-Tumour Efficacy.**

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**BACKGROUND AND PURPOSE:** Our previous studies demonstrated that a thiosemicarbazone iron chelator (di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone; Dp44mT) possesses potent and selective anti-cancer activity, but led to cardiotoxicity at non-optimal doses (Whitnall, M. et al. 2006 PNAS USA 103:14901-6). In this study, we examined the in vivo anti-tumour efficacy and tolerability of a new generation 2-benzoylpyridine thiosemicarbazone iron chelator (2-benzoylpyridine-4,4-dimethyl-3-thiosemicarbazone; Bp44mT) administered via the oral or intravenous routes. **EXPERIMENTAL APPROACH:** BpT chelators were tested in vitro against human lung cancer cells (DMS-53) and in vivo in DMS-53 tumour xenografts in mice. The toxicity of Bp44mT in vivo and its effects on the expression of iron-regulated molecules involved in growth and cell cycle control were investigated. **KEY RESULTS:** Administration of Bp44mT by both routes resulted in marked dose-dependent inhibition of tumour growth. When administered at 50 mg.kg(-1) via oral gavage 3 times per week for 23 days, the net xenograft growth was inhibited by 75% as compared to vehicle-treated mice. Toxicological examination showed reversible alterations including slight reduction of RBC count, with a decrease of liver and splenic iron levels which confirmed iron chelation in vivo. Importantly, in contrast to Dp44mT, the chelator-treated mice did not suffer cardiac histological abnormalities. There was also no significant weight loss in mice, suggesting oral administration of Bp44mT was well tolerated. **CONCLUSIONS AND IMPLICATIONS:** This is the first study to show that Bp44mT can be orally administered with potent anti-tumour efficacy. Oral administration of a novel and effective chemotherapeutic provides the benefits of convenience for chronic dosing regimens.

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**Homozygous sickle cell anemia and secondary complications: a ase study.**

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A 26-year-old African-American male presented with chest and back pain, fatigue and a history of the following: homozygous sickle cell anemia, pain crises, stroke, hip replacement following avascular necrosis of the femoral head, priapism, chronic transfusions, iron overload, hypertension, migraine headaches, port infections, depression and type II diabetes.

PMID: 21657139 [PubMed - in process]

**ENTREZ EMBASE LITERATURE REVIEW (2 NEW ARTICLE(S))**


**Response of biochemical markers of bone turnover to oral glucose load in diseases that affect bone metabolism**


Objective: Postprandial suppression of bone resorption is considered one of the main contributors in the circadian rhythm of bone turnover markers. The aim of this study was to investigate this physiological response of bone tissue in diseases that affect bone metabolism. Patients and methods: In this study, 118 patients (45 hypothyroid, 40 hyperthyroid, and 33 β-thalassemic patients) and 78 healthy individuals matched for age and body mass index were included. An oral glucose test (75 g glucose) was performed after overnight fasting. Serum levels of procollagen type-I N-terminal propeptide (P1NP), β-C-terminal telopeptide of type I collagen (β-CTX), and osteocalcin were assayed at 0, 60, and 120 min. Results: Baseline values of bone turnover markers were significantly elevated in hyperthyroid and β-thalassemic patients but not in hypothyroid patients compared with the control group. After oral glucose, the levels of β-CTX but not P1NP or osteocalcin were significantly suppressed in all groups (mean change from baseline is 46.9% for β-CTX, 7.9% for P1NP, and 8% for osteocalcin). The percentage change from baseline for β-CTX was significantly augmented in hypothyroidism (52 vs 42%, P=0.009). Conclusion: The preservation or even augmentation of postprandial suppression of bone resorption in diseases that

*Database: PubMed, Embase*

**Keywords:** deferiprone, 30652-11-0, desferrioxamine, deferoxamine, desferal, deferasirox, (iron + sickle) iron chelation, iron chelators, iron overload, thalass*, 1,2 dimethyl-3-hydroxypyridin-4-one, ICL670*, Exjade
affect bone metabolism through distinct pathogenetic mechanisms suggests the importance of this physiological response to nutrients for the general homeostasis and functional integrity of the skeleton. © 2011 European Society of Endocrinology.


**Recent insights on the medicinal chemistry of sickle cell disease**

Dos Santos J.L., Chin C.M.

Sickle Cell Disease (SCD) is one of the most prevalent hematological diseases in the world. SCD is a genetic disease characterized by punctual mutation that basis on the exchange of glutamic acid to valine in a beta chain of hemoglobin. In deoxygenated state, the interaction among the beta chains leads to hemoglobin polymerization carrying out to deformation of cytoskeleton structure of red blood cells to a sickle shape. Currently, the treatment is performed with the antineoplastic drug hydroxyurea. This review summarizes current knowledge about possible targets and the approaches to discover new compounds to treat the SCD symptoms. Drug design based on therapeutical application and molecular modifications strategies will be discussed. © 2011 Bentham Science Publishers Ltd.